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BOOK
OF ABSTRACTS

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Oral Presentations

“From everyday clinical practice”

Comparison of Multiplate analyser measurement and serum thromboxane B2 concentrations to assess the platelet response to low-dose aspirin in Chinese patients with coronary artery disease

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Background: Aspirin resistance is a widely used term for failure of aspirin to prevent the production of platelet COX-1-derived thromboxane (TX) A₂. It can be detected by laboratory tests of platelet TXA₂ production by measurement of its metabolites (e.g. serum TXB₂) or platelet function testing that depends on platelet TX production. This study compared the prevalence of aspirin resistance defined by serum TXB₂ measurement and Multiplate impedance platelet aggregometry, a point-of-care platelet function assay, in Chinese patients with coronary artery disease receiving uncoated low dose aspirin (80 mg daily) antiplatelet monotherapy.

Methods: In Chinese patients with coronary artery disease receiving 80 mg uncoated aspirin antiplatelet monotherapy for at least 7 days, blood samples and urine samples in the morning before and 1 hour after the aspirin dose were collected for the measurement of the trough and peak levels of the anti-platelet effects of aspirin, which were assessed by the measurement of serum TXB₂ (Thromboxane B₂ EIA Kit, Cayman Chemical, MI, USA) and using the Multiplate® analyzer aspirin assay (ASPI test). We used cut-off values of > 300 area under the aggregation curve (AUC) x min for the Multiplate analyzer assay and > 2.2 ng/ml for the serum TXB₂ concentration measurement to classify aspirin resistance on the basis of reports in the literature. An alternative cutoff of > 2 SD above the mean for the serum TXB₂ concentration was also examined, as suggested by some researchers.

Results: Of the 36 patients studied, 27 were males and 21 had diabetes. The mean (±SD) age was 68.6 ± 9.3 years and the mean body mass index was 25.5 ± 2.9 kg/m². The values before and 1 hour after aspirin for the ASPI test were between 96 and 549 AUC and between 110 to 510 AUC, respectively. Serum TXB₂ values before and 1 hour after aspirin ranged between 0.035 and 0.258 ng/ml and between 0.031 and 0.182 ng/ml, respectively. The prevalence of aspirin resistance for the ASPI test was 38.9% (14 out of 36) before the aspirin dose and 27.8% (10 out of 36) 1 hour after aspirin. None of the subjects had serum TXB₂ levels > 2.2 ng/ml. There were 4 patients (11.0%) with serum TXB₂ levels > 2 SD above the mean, which was > 0.204 ng/ml, before the aspirin dose but none of these patients were classified as aspirin resistant by the ASPI test.

Conclusion: In this preliminary analysis, there was poor agreement between the ASPI test and the serum TXB₂ level for identifying aspirin-resistant subjects. A future study with a larger sample size will be conducted to confirm or refute this result. Caution should be used in defining “resistance” to aspirin on the basis of the results of these tests.

Keywords: aspirin resistance

The obesity-mortality paradox in the patients with peripheral artery disease undergoing lower extremity endovascular intervention

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Introduction: Despite evidence of a positive correlation between obesity and increased atherosclerotic cardiovascular morbidity, some authors have described a better clinical outcome in obese patients with coronary artery disease, a phenomenon they coined “obesity paradox”. Also the co-existence of coronary artery disease and peripheral artery disease was described previously. Therefore, we aimed to identify the predictors of all-cause of mortality and to examine the effect of the obesity paradox in the patients with peripheral artery disease, particularly for those undergoing lower extremity endovascular interventions.

Methods: A total of 196 patients who underwent lower extremity endovascular intervention (claudication, n=74; critical limb ischemia, n=122) were retrospectively analyzed. All clinical and angiographic parameters were evaluated to predict the long-term survival. To assess the outcomes according to the body mass index (BMI), patients were classified into 2 groups according to the optimal cut-off value of body mass index (BMI) derived from the area under the receiver operating characteristic analysis of predicting all-cause of death (BMI=21.5 kg/m², the area under the curve value=0.627, sensitivity=67%, specificity=60%); Lower BMI group (≤ 21.5 kg/m², n=72) vs. higher BMI group (> 21.5 kg/m², n=124). All-cause mortality was compared between 2 groups.

Results: During the median follow-up period of 1.2 years, all-cause mortality at 3 year was 16.3%. The independent risk factors for all-cause mortality were old age (HR=1.05, P=0.043) lower BMI (HR=0.83, P=0.016), critical limb ischemia (HR=3.74, P=0.033) and the presence of coronary artery disease defined as angiographically significant $\geq 50\%$ (HR=2.85, P=0.027). Patients with lower BMI had older (74 \pm 11 vs. 71 \pm 10 years, p=0.155) and had higher proportion of critical limb ischemia (68% vs. 59%, p=0.199), although it was not statistically significant. In addition, coronary artery disease was more prevalent in the patients with lower BMI (61% vs. 41%, p=0.007). As for all-cause mortality, patients with lower BMI had significantly higher mortality rate compared to those with higher BMI (28.7% vs. 7.6%, p=0.001).

Conclusion: The lower BMI was associated with severe critical limb ischemia and higher prevalence of coronary artery disease. Furthermore, the obesity paradox was found in these patients undergoing lower extremity endovascular interventions for symptomatic peripheral artery disease, the paradoxical increase in mortality with decreasing BMI.

Keywords: atherosclerotic cardiovascular morbidity, peripheral artery disease, obesity paradox

The elderly with STEMI are more likely to have normal lipid level

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Background: The hypercholesterolemia and dyslipidemia are well known cardiovascular risk factors. It is proved that elevated level of atherogenous lipids is associated with an increase number of complications in STEMI both in young and in the elderly. Advanced age is considered to be an independent predictor of poor outcomes so the elderly are always regarded as a category of high risk. Nevertheless, some trials shows that the elderly with STEMI can be often less committed to a number of factors of cardiovascular risk, such as a dyslipidemia, smoking, male gender. The above mentioned points make relevant the evaluation of prevalence of a hypercholesterolemia in patients of different age with STEMI.

Materials and methods: We enrolled 492 patients with STEMI, with the middle age $64,42 \pm 10,86$ years. Depending on age, patients were divided into 2 groups: I group: till 60 years ($n=187$), the II group – 60 years and over ($n=305$). Patients were compared on prevalence of traditional cardiovascular risk factors.

Table 1 – Cardiovascular risk factors in STEMI patients of different age groups.

Parameters	I group n= 187	II group n= 305	p
Age	51,29±6,53	72,52±8,64	0,0001
Male gender, n (%)	155 (82,88)	158 (51,80)	0,0001
Established dyslipidemia, n (%)	155(82,88)	211 (72,75)	0,0103
Diabetes, n (%)	37 (19,89)	89 (29,37)	0,0200
Current smoking, n (%)	21 (11,22)	86 (28,19)	0,0001
Recent myocardial infarction, n (%)	18 (9,62)	85 (27,96)	0,0001

Results: Patients of advanced age were mostly females. In spite of the fact that among the elderly diabetes and recent myocardial infarction and smoking were significantly more often, these patients significantly rarely had a dyslipidemia.

Conclusion: Elderly patients with STEMI are more severe because of association of multiple risk factors. One the other hand, they are more likely to have normal lipid level.

Keywords: STEMI, dyslipidemia, elderly

Are statins indicated for therapy of resistant hypertension? Lessons of NEMESYS study.

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Introduction: Mild but constant antihypertensive effect of statin therapy was described in several studies. However, its effect in resistant hypertension (RH) patients is unknown.

Methods: Cross-sectional multicentric study NEMESYS screened 10300 consecutive out-ward adult patients of general practitioners. Arterial hypertension (AH) was diagnosed in 6583 pts, of whom 1085 were untreated. Combination of 3+ drugs (including diuretics) was found in 1643 pts (30.0%), RH was present in 492 pts (8.9% of treated). Dyslipidemia exhibit high prevalence (TCH ≥ 5.0 mmol/l – 61.9%, LDL ≥ 3.0 mmol/l – 59.3%, HDL(male) ≤ 1.0 mmol/l – 11.4%, HDL(female) ≤ 1.3 mmol/l – 38.8%, TG ≥ 1.7 mmol/l – 36.2%) with the same proportion between AH and normotensive patients (N).

Results: RH was positively associated with diabetes mellitus (DM) (RR=1.63 [95% CI 1.40-1.91]; p=0.001) and with waist circumference (RR =1.76 [95%CI 1.45-2.17]; p=0.001). Statin therapy acted protectively against resistance to antihypertensives (RR= 0.76 [95%CI 0.68-0.85]; p=0.001).

Lipid spectrum was the same in normotensive, hypertensive and RH groups, however, statin therapy in all AH pts irrespectively of resistance to antihypertensives was associated with lower blood pressure (SBP 137 \pm 16 vs 140 \pm 17 mmHg; p=0.001, DBP 82 \pm 8 vs 84 \pm 8 mmHg; p=0.001) in presence of the same lipid levels (TCH 5.38 \pm 1.15 vs 5.40 \pm 1.13 mmol/l; p=0.684, LDL 3.30 \pm 1.0 vs 3.35 \pm 1.06 mmol/l; p=0.441, TG 1.67 \pm 1.11 vs 1.70 \pm 1.22 mmol/l; p=0.556). Original vs. generic statins caused similar hypotensive effect in all AH pts and RH pts.

The original statins exhibited more pronounced hypotensive effect in AH pts without RH: (SBP 133 \pm 15 vs. 137 \pm 16 mmHg; p=0.055]. Statin therapy was more frequent administered in RH patients (20,6% vs 26,7%; p= 0.001).

Conclusion: in real life medicine we did not observed differences in lipid spectrum comparing statin treated and untreated patients, suggesting low therapeutical effort of general practitioners. Statin therapy exhibited mild hypotensive effect in arterial hypertension patients as well as patients with resistant hypertension, with additional hypotensive effect ranging between 5 mmHg res. 2 mmHg in systolic blood pressure, less expressed in resistant hypertension patients.

Keywords: Arterial hypertension, Resistant arterial hypertension, Statin therapy, Lipid spectrum

Smoking patients in daily practice

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Tobacco dependence, one of the 3 main risk factors of atherosclerosis, is a recognized disease, diagnosis F17 in the WHO International Classification of Diseases, 10th edition. Effective treatment exists: psychobehavioural intervention, and pharmacotherapy to minimize withdrawal symptoms.

As in case of other diseases, also to smokers this treatment should be offered and available. Depending on the time, the intervention can be short or intensive.

In the daily practice, at least the brief intervention should be done with every smoker during each visit. It may take several tens of seconds up to few minutes and it includes 3 main steps: ASK about smoking, clearly ADVISE a smoker to quit, and ASSIST – offer help: at least a leaflet, or brief intervention, or recommendation to intensive treatment possibility. We should ask patients repeatedly – it is a chronic, relapsing disease. To non-smokers, we should point out the importance of no tobacco smoke exposition.

The motivation to stop smoking can be very high especially in patients with atherosclerosis risk, since smoking influences all main risk factors of cardiovascular diseases like dyslipidaemia, hypertension, diabetes mellitus II and insulin resistance, endothelial damage, increased level of erythrocytes, leukocytes as well as thrombocytes, stress hormones (corticoids) or sex hormones, depression and many other. In case of cardiovascular risk even small dose of tobacco smoke can lead to myocardial infarction or sudden cardiac death, mainly in the age under 60. Therefore we should advise patients to avoid any tobacco smoke exposition including passive smoking – diagnosis Z58.7 (passive smoking).

Smoke-free environment, non-smoking health staff and treatment of tobacco dependence should be standard in the daily clinical practice. Furthermore, it is very cost-effective intervention.

Keywords: smoking, treatment

Rationality and immediate results for the use of the Rheolytic thrombectomy (AngioJet) in patients with STEMI.

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Purpose of the study: Evaluation of the immediate results of the application of Rheolytic thrombectomy in patients with acute myocardial infarction-segment elevation ST (STEMI).

Material and methods: The results of PCI in 188 patients (161 (85.6%) men, 27 (14.4%) women) with primary STEMI, to which the Rheolytic thrombectomy. We used two systems Rheolytic-AngioJet thrombectomy 1st generation and AngioJet Ultra. After PCI 178 (94.7%) patients underwent ECHO. All patients received standard medical therapy approved.

Results: The average age of the patients $54,1 \pm 10,7$ years. Smoking history was in 125 (66.5%) patients. The main co-morbidities were hypertension (73.4%) and diabetes mellitus type II (11.2%). In examination group patients: myocardial infarction 32 (17%), 24 (12.8%) previously PCI, 7 (3.7%) – coronary artery bypass grafting. Half of the patients (55.9%) were diagnosed with inferior localization of myocardial infarction. The cardiogenic shock was presented in 22 (12%) patients. The median time from onset of symptoms to arrival at hospital was 222.5 [70; 584] minutes. The single vessel disease was detected in 39.4% of patients, multivessel disease in 32.4% of patients. The infarct-related artery was: LAD (38.3%), RCA (43.6%) arteries. In recently study the complete thrombotic occlusion of the artery was presented in 77.4% of all cases. There are 48.8% drug eluting stents. The time from admission of patients in the hospital to restore coronary blood flow was 41.5 [30, 60] minutes. Angiographic success was achieved in 94.1% of cases. The median duration of PCI was 60 [50; 80] minutes. Complications after PCI were in 3 (1.6%) of cases. Life-threatening cardiac arrhythmias during PCI occurred in 22 (11.7%) patients. The phenomenon of “no-reflow” was the outcome 6 (3,2%) PCI. Hospital mortality rate of 5.9%. The MACCE was 6.9%. In 26% of patients after PCI who was undervented for cardiac ultrasound –not found zones of asynergy. The reduction of myocardial contractile function was observed of 26%. The average ejection fraction was $57.5 \pm 9\%$. The mean duration of hospitalization was $9,5 \pm 0,6$ days.

Conclusion: Rheolytic thrombectomy is reasonable, safe and effective procedure and is characterized by a relatively low in-hospital mortality and low incidence of hospital complications during PCI in patients with STEMI and thrombus burden presented.

Keywords: Rheolytic thrombectomy, acute myocardial infarction-segment elevation ST

High incidence of asymptomatic PAD among unselected patients

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Introduction: Peripheral arterial disease (PAD) represents a manifestation of generalized atherosclerotic disease and also predicts the occurrence of major cardio-vascular events. Studies all over the world suggest a high incidence of asymptomatic PAD. Thus, an adequate management of PAD, right from the asymptomatic stages of the disease, may be useful in prevention of potentially fatal cardio-vascular syndromes (e.g. acute myocardial infarction, stroke).

Aim of the study: The aim of the study was to assess the incidence of PAD among an unselected group of patients admitted in the Internal Diseases, Neurology and Neurosurgery wards of the Emergency Military Hospital "Queen Mary" of Brasov, during the months of October and November 2015.

Methods: In this observational study, a set of 218 random patients were analyzed in order to reveal the presence of PAD. The data we collected was the result of patients' history, full clinical examination focused on signs of PAD and the assessment of the ankle-brachial index (ABI). The patients were included in the study irrespective of the presence or the absence of PAD symptoms. The statistical analysis of the data was performed using Microsoft Excel and MedCalc software.

Results: Among the 218 patients enrolled in the study, there wasn't a significant difference on gender distribution (52.75% men vs. 47.25% women).

In the overall number of patients, there were 32.11% (70 patients) that presented abnormal values of ABI, 44 having an ABI value >1.3 and 26 having an ABI value of <0.9 . Amongst those patients with abnormal ABI values, only 7% (5 patients) accused symptoms of PAD (claudication, pain at rest), all of them having an ABI value of less than 0.9.

Regarding the presence of other cardio-vascular risk factors in the study group, collected data showed that 144 patients were hypertensive, 101 patients had high levels of serum cholesterol, 62 patients declared to be smokers and 51 of them were diabetics. Also, it seemed that smoking was the risk factor most frequently associated with abnormal values of ABI.

Conclusions: The study showed a high incidence of peripheral arterial disease assessed by the abnormal values of ABI. However, most of these patients were asymptomatic for PAD (80.8%), this finding being consisted with other similar studies in the literature.

Keywords: Asymptomatic atherosclerosis, ankle brachial index, cardiovascular risk factors, peripheral arterial disease, smoking

Biomarkers

Antibodies against C-Reactive Protein, CRP peptide and 60-Kilodalton Heat Shock Proteins in patients with Acute coronary atherothrombosis

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Background and aims: C-reactive protein (CRP) is an acute-phase reactant frequently used in histochemistry as a marker of ongoing inflammation and powerful biomarker for the prediction of coronary artery disease risk. Heat-shock protein 60 (Hsp60) and CRP are complement-activating molecules, and the effect of their interactions on the regulation of complement activation was studied.

Aims of the study were to determine presence and possible interrelationship of antibodies (IgG and IgM) against CRP, CRP peptide and Hsp60 in patients with acute atherothrombotic disease, acute coronary syndromes.

Patients and methods: Study included 212 participants divided into two groups: 112 patients with acute coronary atherothrombosis and 100 sex and aged matched controls. Blood samples were taken; sera were frozen and kept in freezer. The samples were sent on dry ice to Immunosciences Lab. Inc Beverly Hills, CA, USA where the analyses were done by using in-house ELISA method.

Results: Our results showed the strong activation of examined antibodies in patients compared to controls. Antibodies against CRP IgM were ranging from 0.06 to 1.47 o.d. in patients compared to 0.105 to 0.805 o.d. in controls, $p < 0.01$. Antibodies against CRP peptide IgM were ranging from 0.052 to 1.103 o.d. compared to 0.086 to 0.633 in controls, $p < 0.01$. Hsp 60 antibodies were ranging from 0.74 to 1.180 o.d. in patients compared to 0.07 to 0.479 o.d. in controls, $p < 0.001$. There was a difference in CRP, CRP peptide and Hsp60 IgG antibodies between groups. Also there was a linear correlation between examined antibodies within the same class, IgG and IgM separately, $p < 0.001$.

Conclusions: In patients with acute coronary syndromes activity of CRP, CRP peptide and Hsp60 IgG and IgM antibodies is high and might represent the autoimmune process which highlights the development and progression of atherosclerosis.

Lipoprotein (a) in acute coronary atherothrombosis

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Atherosclerosis is a complex process in which the several different mechanisms might play a major role. Lipoprotein (a) [Lp(a)] is an independent risk factor for cardiovascular disease. We aimed to investigate presents of lipoprotein a and its possible role in acute coronary atherothrombosis.

Methods and Results: The study included 300 participants; of whom 100 were patients with acute coronary syndromes (ACS), (60.2 ±3.87 years of age, 61% males) and 200 were age and sex matched controls with no known coronary artery disease from Serbia (100) and California (100). Patients with previous infection, surgery, cancer, trauma or concomitant reumathological diseases were excluded from the study. Blood was sampled, frozen and sent on dry ice to Immunosciences Lab. Inc (USA) for analyzes. All traditional risk factors were noted. Lp (a) was determined by using Diamedix Is-Apo Tek Lp(a) tests.

Results: Patients with acute coronary atherothrombosis had significantly higher levels of Lp compared to controls from Serbia and California (177.05 [108.9 – 245.12] nmol/l vs 66.6 [54.9 – 78.4] nmol/l, p

In conclusion, The Lp(a) level is highly elevated in acute coronary atherothrombosis Since it is usually not affected by lifestyle changes or by most drugs, it is not the target of therapy. Instead, when Lp(a) is high, the presence of this added risk factor may suggest the need for more aggressive treatment of other, more treatable risk factors such as an elevated low-density lipoprotein (LDL).

Two measurements of brain natriuretic peptide levels in acute myocardial infarction improve risk prediction of recurrent events in the short-term compared to grace score: A Brasilia heart study subanalysis

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Introduction: Available clinical scores for risk prediction after acute myocardial infarction (AMI) have a limited potential to discriminate high-risk patients. Although BNP levels at admission can predict the chance of adverse outcomes after AMI, there is no information regarding the changes in BNP levels in risk prediction of patients with AMI and normal ventricular function at admission (Killip I).

Methods: Consecutive patients with ST-elevation AMI and Killip I (n=167) were followed for 12 months. We evaluated plasma levels of BNP in the first 24h after symptoms onset (D1) and at the 5th day (D5) and calculated the GRACE score based on admission data.

Results: Independent risk factors were selected using bootstrapping based on Cox-regression analysis. Sex, age, dose of statin and diagnosis of diabetes were selected as significant predictors of sudden death and AMI for the final multivariable model. Both in crude and adjusted Cox-regressions, a Delta BNP above the median (80pg/dL) and a BNP at D1 above 100pg/dL (median) were associated with higher incidence of sudden death and AMI at 30 days (OR:10.88, 95%CI: 1.10-108, p=0.038; OR:1.91, 95%CI: 1.01-4.11, p=0.049, respectively). GRACE score alone showed a moderate C-statistic=0.709 (p=0.029), but adding DeltaBNP improved risk discrimination (C-statistic=0.831, p=0.001), with significant differences between AUCs (p=0.046). Net reclassification (*category-free* NRI) confirmed a significant improvement in individual risk prediction by 33.4% (95%CI: 8-61%) compared with GRACE alone (p=0.034), with adequate calibration according Bayes information criterion and Likelihood ratio test. DeltaBNP+GRACE improved reclassification especially in intermediate risk patients [by 62.5% (p=0.0231)]. However, considering only the first measurement, BNP at D1 did not improve risk reclassification at 30 days compared to GRACE score (cfNRI p=0.8).

Conclusions: Both high BNP levels in the first 24h after AMI and increasing levels of BNP levels in the days following were associated with poorer short-term outcomes in Killip I patients. However, only Delta BNP improves risk reclassification in the short-term, compared to GRACE score as well compared to GRACE + BNP at D1.

Keywords: Acute myocardial infarction, Brain natriuretic peptide, GRACE score, Net reclassification improvement, BNP

What do we know about Lp(a) arteriogenicity? Moscow experience since 1987

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Discovered in 1963 by K. Berg, lipoprotein(a) [Lp(a)] is now well established cardiovascular risk factor. Its association with atherosclerosis and thrombosis is independent of traditional risk factors. Since 1994 In the Russian Cardiology Research Center we have started the evaluation of a cohort of 2120 patients with known Lp(a) level. Most of the participants in the PRELUDE study – **P**rospective **R**ussian **E**valuation of **Lp(a)** role in cardiovascular **D**iseas**E** (NCT02515747) had CHD verified by angiography. We showed that in patients with coronary atherosclerosis the prevalence of Lp(a) more than 30 mg/dl was 39%. There was a positive correlation between Lp(a) level and presence and severity of coronary and carotid atherosclerosis. During follow-up period up to 20 years the risk of coronary events in patients with Lp(a) level above 30 mg/dl was significantly higher than in subjects with lower Lp(a) level irrespective type of treatment of ischemic heart disease: conservative or endovascular treatment or bypass surgery. We found that Lp(a) excess is associated with lower patency of vein grafts within one year after CABG. We demonstrated that low-molecular weight apo(a) isoforms are related with higher risk of cardiovascular events that high-molecular weight apo(a) isoforms despite Lp(a) level. Moreover, niacin treatment in subjects with Lp(a) excess was more effective in diminishing Lp(a) level in the presence of low-molecular weight apo(a) isoforms. Therefore, current evidence shows that pathogenicity of Lp(a) particle could be explained by its structure and number of repeats kringle IV domains of apo(a) molecule. Data about relation of Lp(a) to lower extremities arterial disease and abdominal aortic aneurysm are lacking. However, in accordance with Lp(a) level of more than 50 mg/dl it should be considered as a target for therapeutic apheresis.

Keywords: lipoprotein(a), atherosclerosis, therapeutic apheresis

Inhibition of apoB+DGAT2 synthesis using antisense oligonucleotides rescues liver steatosis

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Targeting the synthesis of apolipoprotein B (apoB) leads to significant reductions of both triglyceride (TG) and LDL-C levels in plasma, but at the cost of hepatic steatosis in some individuals. To gain insight into potential ways to avoid this adverse outcome, we investigated the effect of antisense oligonucleotide (ASO)-mediated knockdown of apoB alone or in combination with DGAT1 or DGAT2, on lipid metabolism in livers of apobec-1 knockout (apoB100 only) mice fed high fat diets. Although significantly increased levels of hepatic TG were detected in mice on apoB ASO for 3 weeks, hepatic TG had returned to levels present in mice receiving control ASO by 6 weeks of treatment. To determine why hepatic steatosis decreased between 3 and 6 weeks of apoB ASO treatment, we measured fatty acid (FA) uptake, FA secretion, *de novo* lipogenesis, and FA oxidation, the latter after a 2-hr, ¹⁴C oleic acid incubation of primary hepatocytes isolated from control ASO- and apoB ASO-treated mice. There were no differences in any of these parameters. Transmission electron and immunofluorescence microscopy showed an increase in the number of autophagosome-like structures in the cytoplasm of hepatocytes after 6 weeks of apoB ASO treatment. Importantly, measurements of FA oxidation over a 16-hr time course in primary hepatocytes from mice treated for 6 weeks with apoB ASO had delayed but significant increases in FA oxidation. The delay was consistent with the need for the tracer to be transported, after incorporation into TG, through the autophagic pathway to lysosomes and finally to mitochondria. Mass spectrometric analysis of microsomal fractions showed that TG levels were at maximum at 3-weeks and decreased by 6-weeks of apoB ASO treatment. Immunoblotting indicated activation of ER-stress in apoB ASO treated mice at 3 weeks and upregulation of autophagy at 6 weeks of treatment. Interestingly, combinatorial injection of mice with apoB+DGAT2 ASO resulted in even greater reduction of TG levels after 6 weeks of treatment than apoB ASO alone. FA oxidation during 16-hr time course was also delayed, but was increased with apoB+DGAT2 ASO treatment compared to apoB ASO alone. Analysis of electron micrographs revealed accumulation of autolysosomes with engulfed ER-like structures in livers of mice treated with apoB+DGAT2 ASO's. These changes were not seen in livers treated with apoB+DGAT1 ASOs. Our results support a model in which knockdown of apoB synthesis results in accumulation of TG in the ER that initially triggers ER stress and later, ER autophagy, with delivery of the accumulated TG to the lysosome and then to the mitochondria where they are oxidized, thus maintaining hepatic lipid homeostasis. Our findings also suggest that ASO-inhibition of the synthesis of both apoB and DGAT2 increases the role of DGAT1 in synthesis of TG that is targeted to the ER, increasing the accumulation of ER-TG that, in turn, increases ER autophagy.

Integrated biomarkers and coronary atherosclerosis: which path to take?

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Purpose: To examine a wide set of clinical and metabolic parameters and their combinations which with high probability would indicate the early development of atherosclerotic lesions of coronary arteries and predict coronary atherosclerosis severity.

Methods: Patients admitted to the National Research Centre for Preventive Medicine for coronary angiography and ultrasound carotid dopplerography were enrolled into the study (n=205; M 66%; 62,8±9,0 yrs). Location and extent of coronary artery lesion were assessed by Gensini Score (GS). Biochemical parameters were determined by routine methods. Multivariate logistic regression analysis was used to screen predictors of coronary atherosclerosis detection and severity.

Results: Total cohort was split into patients with unaffected coronary arteries (GS=0; n=39), and those with coronary atherosclerosis (GS>0; n=166). The extent of coronary lesion was also estimated by GS with distribution of patients into groups: no/subclinical (GS<35; n=112) and severe coronary atherosclerosis (GS≥35; n=93). Preliminary analysis of a number of mathematical models including a wide range of biochemical markers, major structure parameters of arterial wall and their combinations allowed us to select the most significant variables that composed a combined index named an integrated biomarker (i-BIO). The i-BIO included intima-media thickness (≤0.9; >0.9 mm), the number of atherosclerotic carotid plaques (<3; ≥3), the degree of carotid stenosis (≤45; >45 %), the levels of triglycerides (≤1.7; >1.7 mmol/l), glucose (≤5.5; 5.6-6.0; 6.1-6.9; ≥7.0 mmol/l), fibrinogen (≤4.0; >4.0 g/l), hsCRP (<1.0; 1.0-3.0; ≥3.0 mg/l) and adiponectin (≥8.0; <8.0 µg/ml). Patients were divided into three groups according to i-BIO: ≤4 points, 5-8 points, ≥9 points. i-BIO ≤4 points with a probability 83.8% indicated no/subclinical coronary atherosclerosis (GS<35); i-BIO=5-8 with a probability 83.3% detected patients with GS>0; i-BIO ≥9 with a probability 95% demonstrated the presence of coronary atherosclerosis (GS>0), meanwhile 68% of patients had severe coronary damage (GS≥35). Risk of coronary atherosclerosis (GS>0) among those with i-BIO=5-8 points was in 5.1 times (95% CI 2.2-12.0, p=0.002) higher than for patients with i-BIO ≤4 points, while risk of severe coronary atherosclerosis (GS≥35) at i-BIO=5-8 points was in 4.4 times (95% CI 1.7-11.5, p=0.003) higher than for patients with i-BIO ≤4 points.

Conclusion: i-BIO, composed of biochemical and visual parameters, with values of >4 points with a sensitivity of 87.8% detected patients with coronary atherosclerosis (GS>0), values ≥9 points with a specificity of 79.8% allowed to exclude patients free of severe coronary atherosclerosis (GS<35). Application of integrated biomarkers for subclinical and severe coronary atherosclerosis detection might improve risk predictions and reclassification as compared with conventional risk factors.

Keywords: integrated biomarker, coronary atherosclerosis subclinical, coronary atherosclerosis manifested, carotid ultrasound, Gensini score

Low cytochrome oxidase in monocytes and monocyte-derived exosomes links mitochondrial dysfunction to incident cardiovascular diseases

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Introduction: Impaired cytochrome oxidase (COX) complex is associated with mitochondrial dysfunction and metabolic disorders. We hypothesized that low expression of COX genes is related with incident CAD. Extracellular vesicles are being recognized as key players in atherosclerosis. Hence, we tested the hypothesis that low COX in monocyte-derived extracellular vesicles is related with incident CAD.

Methods: We studied 114 consecutive high risk patients: 84 with CAD (cases) and 30 without CAD (controls). Three year follow-up was completed in 81 CAD patients (96%) of which 43 had a new event. CD14+ monocytes and extracellular vesicles were isolated from plasma by MACS (Miltenyi). CD14+ monocytes were also obtained from 10 patients with unstable CAD at three time points. Size distribution and concentration of extracellular vesicles were determined by NanoSight analysis. Blinded RNA analysis was performed using TaqMan RNA assays by Biogazelle (Gent, Belgium). RT-PCR data were analyzed in Biogazelle's qbase+, normalizing for B2M, PPIA, RPL13A, RPS18 and YWHAZ, which we identified as stable housekeeping genes. Second, the relation between COX expression and atherosclerosis was assessed in obese diabetic mice. Third, we determined the effect of their silencing on phenotypic switch of mouse bone-marrow-derived macrophages.

Results: Low mitochondrial *MT-COI* and nucleus-encoded *COX10*, but not nucleus-encoded *COX4I1*, in monocytes were associated with the presence of CAD. Only low *MT-COI* was associated with an increased risk of future events (HR: 2.99; 95% CI: 1.46-6.13), independent of age, gender, smoking, lipids, and occurrence of type 2 diabetes and metabolic syndrome, and number of stenosed arteries. At the onset of an acute event *MT-COI* was low, but higher at day 3 and 30. Peak size of CD14+ extracellular vesicles of controls and CAD patients was ~ 110nm, suggesting that they were exosomes which were positive for Annexin A5 (V). Size was not different between CAD patients with and without new event. Number of exosomes per ml (~ 6.5x. 10⁸) was not different between groups. Expression of *MT-COI*, but not of nucleus encoded *COX4I1* was lower in patients with coronary stenosis. *COX10* was not detected. In addition, Kaplan–Meier analysis revealed that CAD patients with low *MT-COI* more quickly developed a new event. Cox proportional-hazards regression analysis revealed that low *MT-COI* was associated with increased risk of future event (HR, 4.42; 95% CI: 1.57-12) adjusting for age, gender, smoking, lipids, and occurrence of type 2 diabetes and metabolic syndrome, and number of stenosed arteries.

In obese diabetic mice, low aortic *Mt-co1* was associated with M1 phenotype of macrophages and higher oxidized LDL in atherosclerotic plaques in aortic sinus. Caloric restriction increased *Mt-co1*, and reduced M1 macrophages and oxidized LDL. In macrophages, direct RNA silencing of *Mt-co1* and indirect reduction of *Mt-co1* by silencing of the mitochondrial transcription factor *TFAM* in presence of high palmitate increased the inflammatory phenotype.

Conclusions: Low *MT-COI* in monocytes and monocyte-derived exosomes is related to worse cardiovascular outcomes. Low *MT-COI* is related to oxidative stress and inflammation in atherosclerosis.

Keywords: coronary artery disease, monocytes, exosomes, mitochondrial dysfunction, cytochrome oxidase

Association of osteopontin level with coronary atherosclerosis and osteoporosis in man with stable coronary artery disease

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Objective: To measure plasma levels of osteopontin in patients with stable coronary artery disease depending on the severity of osteoporosis, coronary atherosclerosis and coronary artery calcification.

Material and Methods: 111 male patients with verified stable coronary artery disease undergoing coronary artery bypass grafting were included in the study. The mean age of the patients was 59.8 (55; 70) years. The inclusion criteria were as follows: age < 75 years; stable angina I- III functional class. The exclusion criteria were as follows: severe comorbidities, angina IV functional class, severe heart failure, prior coronary revascularization. All patients underwent coronary angiography, multislice computed tomography (MSCT), densitometry, echocardiography, blood sampling to measure osteopontin levels.

Results: 14.4% of patients had single-vessel coronary artery disease (CAD), 24.3% – two-vessel CAD, 61.3% – three-vessel CAD. Mild coronary artery (CA) lesions quantified by the Syntax score were found in 44.2% of patients, moderate – in 30.6% of patients, and severe – in 25.2% of patients. Minor coronary artery calcification (CAC) was detected in 9.9% of patients, mild CAC- in 7.2% of patients, moderate – in 25.2% of patients, severe – in 57.7% of patients. 52.2% of patients had osteopenia, 27.9% of patients – osteoporosis, and 19.8% of patients had normal bone mineral density. Plasma osteopontin levels were 50% higher in patients with the Syntax score above 22 compared to those patients who had the Syntax score below 22 [7.75 (5.14-8.97) vs 5.14 (4.30-7.96) ng / ml, $p = 0.01$]. Osteopontin levels were two times higher in patients with left ventricular ejection fraction (LVEF) < 40% compared to patients with higher LVEF [8.5 (7.65-10.32) vs. 4.6 (4.48 – 7.12), $p < 0.001$]. Osteopontin levels were 48% higher in patients >60 years with the Syntax score of >22, than in those with less severe lesions. A direct correlation between osteopontin levels and left ventricular end systolic and diastolic volumes ($r = 0.22$; $p = 0.02$; $r = 0.21$; $p = 0.03$) and interventricular septum and left ventricular posterior wall ($r = 0.24$; $p = 0.02$; $r = 0.31$; $p < 0.001$) thickness has been identified.

Conclusion: Osteopontin levels in patients with coronary artery disease correlate with the severity of coronary atherosclerosis, particularly in patients over 60 years, as well as with the parameters of left ventricular remodeling.

Keywords: osteopontin, calcification, coronary atherosclerosis, osteoporosis, myocardial remodeling

New peptide-based radiotracer for atherosclerosis PET imaging

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Introduction: Atherosclerosis is a chronic inflammatory disease of the arterial wall, most triggered by modified low-density lipoprotein (LDL) including the electronegative LDL subfraction, LDL(-). Epitopes of LDL(-) reactive to anti-LDL(-) mAbs were mapped by phage display and conformationally restricted mimotope peptides were synthesized. Here, one of these mimotope peptides (P1) was investigated as a new Positron Emission Tomography (PET) molecular imaging agent for atherosclerosis.

Methods: ^{64}Cu was produced by Washington University Cyclotron Facility. The DOTA-P1 and NOTA-P1 peptides were radiolabeled with ^{64}Cu (37 MBq) using ammonium acetate buffer pH 5.5 and 1 nmol of the peptide. Both peptides were challenged with EDTA and analyzed by radio-HPLC. Animal studies were approved by the Washington University Animal Studies Committee. ApoE^{-/-} mice (male, 6-8 weeks old, 7-8 weeks fed on hypercholesterolemic diet, n=4) and C57Bl/6 as control mice (male, 6-8 weeks old, n=2) were injected with 0.37 MBq of ^{64}Cu -DOTA-P1 or ^{64}Cu -NOTA-P1 and dynamic images were acquired (30-60 minutes). The atherosclerotic lesions progression was followed by PET imaging for 3 weeks by using ^{64}Cu -NOTA-P1 as radiotracer. After the acquisition of all PET images, aortas were dissected for autoradiography analysis. Statistical analysis was performed using one-way ANOVA with Bonferroni posttest, with significance level considered as $P < 0.05$.

Results: Radiochemical purity was more than 95% and specific activity was 37 MBq/nmol for both peptides. Semi-quantification of standardized uptake value (SUV) of the PET images demonstrated higher uptake in the aortic arch region from apoE^{-/-} than C57Bl/6 mice for both ^{64}Cu -DOTA-P1 (0.18±0.02 in apoE^{-/-} mice compared to 0.12±0.003 in C57Bl/6 mice) and ^{64}Cu -NOTA-P1 (0.22±0.02 in apoE^{-/-} mice compared to 0.11±0.005 in C57Bl/6 mice). Since ^{64}Cu -NOTA-P1 demonstrated higher uptake, the atherosclerosis follow-up was performed using this radiotracer, with significant higher uptake (0.22±0.02 in apoE^{-/-} mice vs 0.14±0.02 in C57Bl/6 mice). Also, the autoradiography images showed higher signal in the aortic arch from apoE^{-/-} mice compared to the control C57Bl/6 mice.

Conclusions: Our results show that ^{64}Cu -NOTA-P1 has a high uptake in the aortic arch of atherosclerotic apoE^{-/-} mice indicating its potential use as a tool for atherosclerosis PET imaging in pre-clinical studies.

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Keywords: Positron Emission Tomography, Molecular imaging, Electronegative LDL, Atherosclerosis, Mimotopes

Is lipoprotein associated phospholipase A2 an early markers of cardiac damage in rheumatoid arthritis patients without ischemic heart disease?

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Introduction: Rheumatoid arthritis (RA) patients are endangered by precocious ischemic heart disease (IHD), however, identification of high risk population is delayed. Increased (Lp-PLA₂) is considered as marker of instable atherosclerotic plaque in IHD, but its occurrence in RA was not studied.

Method: We examined 56 RA pts and 31 controls matched for age (44±8 vs 44±10 yrs; p=.824), sex (M:F – 20:80 vs 26:84; p=0.824) and smoking habit (Y/N – 20:80 vs 26:74; p=.593) (pre-test requirement at least 21 pairs) without known IHD, diabetes mellitus, CHRI using noninvasive cardiological examination (echocardiography, Doppler examination, ventricular late potentials (VLP) and arterial stiffness. Beside classic risk factors we analysed Lp-PLA₂ (both activity and mass; diaDexus Inc, USA; Microtitrate) and NT-pro-BNP.

Results: RA pts exhibited same level of Lp-PLA₂ mass (423±112 vs 416±75 ng/ml) and higher level of NT-pro-BNP (80.6 ±62 vs 51.9±35 ng/l, p=.008). RA pts exhibited larger aortic diameter (29.3±3.4 vs 25.8±3.6 mm; p=.001), lower value of TAPSE (20.8±2.9 vs 22.0±2.5 mm; p=.053) diastolic dysfunction, and VLP characteristics, but not of arterial stiffness. We did not find association of Lp-PLA₂ with age, duration of RA or clinical markers (HAQ and DAS28 score). As independent predictors of upper quartil of Lp-PLA₂ mass were identified hemoglobin (beta= .40; p=.001), LDL cholesterol (beta=.42; p=.001), E/A peak (beta=-.25; p=.007) and uric acid (beta=.29; p=.004). Correlation with NT-pro-BNP was missing (r=-.20; p=.141).

RA pts exhibited same of Lp-PLA₂ activity (152±31 vs 149±21 nmol/min/ml; p=.786) and higher level of NT-pro-BNP (80.6 ±62 vs 51.9±35 ng/l; p=.008). However, critical values of Lp-PLA₂ activity ≥250 nmol/min/ml were presents in 20.4% of RA pts vs. none in controls (20.4% vs 0%, statistically NA). We again did not find association of Lp-PLA₂ with age, duration of RA or clinical markers or arterial stiffness, ventricular late potential, diastolic dysfunction as well as biomarkers (CRP, NT-pro-BNP). The only identified risk factor was smoking RR = 9.6 [95% CI 0.85-108.7]; p=0.043. Smokers had higher level of (381.6± 335.6 vs 191.0± 65.6 nmol/min/ml) (p=0.004) despite of significantly shorter duration of RA: 7.0±2.9 vs 15.8±6.8 yrs (p=0.012).

As expected, in controls a Lp-PLA₂ was directly correlated to LDL cholesterol (r=.64; p=.003), indirectly to HDL cholesterol (r=-.55; p=.012), but no correlation with other biomarkers or noninvasive examinations method was found. Independent predictors were total and LDL cholesterol.

Conclusion: Lp-PLA₂ activity or mass failed to identified cardiovascularly endangered patients with rheumatoid arthritis a compare to controls. Increased aortic diameter and markers diastolic dysfunction were associated with high Lp-PLA₂. However, Lp-PLA₂ activity over critical values of Lp-LpA2 ≥250 nmol/min/ml were present only in RA patients in proportion (cca 20%) correlating to the empirically observed of high risk RA patients. As explaining factor was identified smoking.

Keywords: Rheumatoid arthritis, Cardiovascular risk biomarkers, Lipoprotein associated phospholipase

Alterations in lipid transfers to High Density Lipoprotein (HDL) in patients with Heart Failure

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WHO estimated that there were twenty-three million subjects worldwide suffering from heart failure (HF) in 2015, with mortality rates equivalent to those of cancer. Higher HDL-cholesterol levels have been associated with longer survival in HF. It is now consensual that the various protective functions of HDL should be explored and transfer of lipids from the other lipoproteins to HDL, mediated by transfer proteins CETP and PLTP is an important step in HDL function in reverse cholesterol transfer. Previously, we showed that the *in vitro* transfer of lipids to HDL is altered in several conditions, such as coronary artery disease, diabetes and sedentary life-style. The aim was to investigate the lipid transfers to HDL in HF patients with NYHA functional assessment I and II (HF I/II), NYHA III and IV (HF III/IV), all with ejection fraction $\leq 40\%$, and in patients with coronary artery disease but without HF (non-HF). Twenty-five HF I/II, 23 HF III/IV and 50 non-HF volunteer patients matched for gender, age and BMI were included in the study. Transfers of radioactive unesterified and esterified cholesterol, triglycerides and phospholipids from a donor artificial emulsion to HDL was determined by an *in vitro* assay in which the emulsion was incubated for 1 h with whole plasma and transfer of lipids was measured in the HDL fraction after chemical precipitation of apo B-containing lipoproteins and the emulsion. Total, LDL and HDL cholesterol, triglycerides, and apo A-I did not differ among the 3 groups, but apo B was lower in both HF groups compared to non-HF ($p < 0.001$). Transfer of esterified and unesterified cholesterol and of phospholipids (in %) was lower in HF-III/IV than in non-HF (HF-III/IV: 5.44 ± 1.76 , 6.29 ± 2.05 , 19.05 ± 2.5 ; non-HF: 6.24 ± 0.85 , 7.33 ± 1.48 , 20.21 ± 1.43 , respectively, $p < 0.05$). Transfers of those three lipids were not different between HF-I/II and non-HF. No differences in triglyceride transfer were observed among the groups. In conclusion, lipid transfers become clearly disturbed in severe HF. In future studies, the possibility that disturbances of lipid transfers to HDL could be involved in the evolution and prognosis of HF should be examined.

Keywords: cholesterol, high density lipoprotein, lipid transfer, heart failure

High neutrophil and basophil blood counts are associated with an increased factor II plasma coagulant activity and may predict total and cardiovascular mortality in patients with stable coronary artery disease

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Background: white blood cell (WBC) count is widely available in clinical practice and has been proposed to provide prognostic information in coronary artery disease (CAD), with elevated levels of WBC predicting adverse cardiovascular outcomes. Recently, the link between leukocytes and coagulation has been emphasized and neutrophil extracellular traps (NETs) have been demonstrated to be a scaffold and stimulus for thrombus formation. The aims of the present study were to investigate i) the correlation between WBC counts and factor II plasma coagulant activity (FII:c), and ii) WBC prognostic significance in the setting of secondary prevention of CAD.

Materials and Methods: WBC count and FII:c were analyzed in 750 subjects (554 CAD and 196 CAD-free, 77.6% males, mean age 60.0±10.5 years) not taking anticoagulant drugs within the angiographically-controlled Verona Heart Study. Moreover, WBC count was assessed as predictor of total and cardiovascular mortality in 823 stable CAD patients (80.2% males, mean age 61.8±9.7 years). Subjects with overt leukocytosis (>10,000/ μ L) or leukopenia (<4,000/ μ L) were excluded.

Results: Neutrophils ($\beta=0.085$; $P=0.021$) and basophils ($\beta=0.073$; $P=0.042$) were significant predictor of FII:c variability in a linear regression model adjusted for all blood cell counts, age, sex, hs-CRP, and CAD diagnosis. In the longitudinal study, after a median follow-up of 61 months, 160 (19.4%) subjects died, 107 (13%) of whom for cardiovascular causes. High levels of neutrophils, monocytes, eosinophils, and basophils were associated with an increased mortality rate in the CAD population. However, in Cox regression models adjusted for all the traditional cardiovascular risk factors, including hs-CRP, only neutrophils and basophils remained predictors of total (the highest *versus* the lowest quartile HRs: 2.87 (1.54-5.34) and 1.71 (1.06-2.75), respectively) and cardiovascular mortality (HRs: 3.31 (1.42-7.71) and 1.85 (1.02-3.35), respectively).

Conclusions: high neutrophil and basophil blood counts are associated with an enhanced FII:c and may be independent predictors of total and cardiovascular mortality in patients with stable CAD.

Keywords: neutrophils, basophils, white cell blood count, factor II plasma coagulant activity, secondary prevention of coronary artery disease

Leukocyte telomere length in peripheral blood as ageing marker and risk factors for age-related diseases in humans

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Objective: to study the relationship between leukocyte telomere length (LTL) in peripheral blood, age and prevalence of risk factors of age-related diseases in population (Novosibirsk, Russia).

Materials and methods: Genomic DNA was isolated from venous blood by phenol-chloroform extraction. The study of telomere length is performed using quantitative real-time PCR-based method by Cawthon (2002) with modifications by Hovatta et al (2012). The study sample included 398 men (mean age $56,3 \pm 7,2$ years) and 365 women (mean age $56,6 \pm 7,1$ years) who were randomly selected from participants of a population-based study of residents of Novosibirsk (9,630 subjects) who were examined at baseline in the frame of the international HAPIEE project.

Results: The mean LTL was 1.24 ± 0.40 in men and 1.33 ± 0.36 in women ($p=0.002$). We found an inverse correlation of LTL with age ($r = -0,159$, $p < 0.001$) and waist/hips ratio ($r = -0.107$, $p = 0.003$) both in men and women. In males, LTL correlated with height ($r = 0.107$, $p = 0.032$), weight ($r = 0.140$, $p = 0.005$), body mass index ($r = 0.109$, $p = 0.030$), waist ($r = 0.111$, $p = 0.027$) and hips ($r = 0.143$, $p = 0.004$). In women, there was an inverse correlation between LTL and waist circumference ($r = -0.127$, $p = 0.015$), waist/hips ratio ($r = -0.141$, $p = 0.007$). The average length of telomeres among non-smokers was the highest compared to smokers and former smokers ($p = 0.016$) and it was inversely correlated with the number of cigarettes smoked ($r = -0.121$, $p = 0.024$). Women with a waist above 88 cm has shorter telomeres than women with lower waist ($p = 0.040$). The average LTL in subjects with “definite” ischemic heart disease (IHD) was significantly shorter than in those without IHD ($p = 0.038$). We did not detect the difference in the length of telomeres in people with self-reported hypertension (HT) but there was a significant difference in LTL between women who were aware of history of elevated blood pressure compared to their counterparts ($p = 0.013$).

Conclusions: In this population sample of middle aged and older Russian men and women, LTL was correlated with age, smoking, and a number of phenotypic traits of age-related chronic diseases and risk factors. The association with awareness of high blood pressure may reflecting the duration of hypertension; and their health deterioration may be present at both the “somatic” and cellular level, including a shortening of leukocyte telomere length.

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Keywords: leukocyte telomere length, ageing, age-related diseases, risk factors

Plasmatic and Urinary microRNAs as Biomarkers in Cardiovascular Diseases

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microRNAs (miRs) belong to the group of small non-coding RNAs with the length of about 22-24 nucleotides. They participate in the post-transcriptional regulation of gene expression however, their effects are not limited only to the cells of origin as they are transferred outside the cells into the interstitial fluid and blood circulation, where they function as intercellular messengers. Their levels in plasma and urine may be determined by molecular biology methods and were shown to be stable, reproducible and to reflect presence of various diseases similarly to commonly available biomarkers.

One of the first studies in the cardiovascular field were revealing the roles of circulating miRNAs in patients with coronary artery disease and in patients after myocardial infarction; so called cardio-miRNAs, such as miR-1, miR-133, miR-208 or miR-499, were repeatedly shown to be increased in plasma of myocardial infarction patients; levels of other miRNAs have shown prognostic significance by predicting cardiovascular death (miR-328 or 134), left ventricle remodeling (e.g. miR-146) or early development of heart failure within one year after myocardial infarction (e.g. p53 responsive miR-34a, miR-192 and miR-194). Subsequently, other miRNAs were shown to be altered in plasma or urine of patients with other cardiovascular diseases such as pulmonary hypertension (e.g. miR-130a or miR-191), pulmonary embolism (e.g. miR-28-3p), atrial fibrillation (e.g. miR-328), deep vein thrombosis (e.g. miR-582 or miR-195) or hypertension (e.g. miR-505). All in all, these results show promising role of miRNAs as the tools for the differential diagnosis and the development of universal serum diagnostic and even prognostic biomarkers.

Nowadays, most of the studies focus on the circulating miRNAs in plasma, serum or even in peripheral blood mononuclear cells (PBMC) or thrombocytes (e.g. miR-223 associated with platelet function and high-density lipoprotein protective properties). Intriguing is determination of miRNA levels in urine – currently most of the studies are being conducted in the nephrology field studying miRNAs as non-invasive markers for prediction of renal transplant rejection or for the differential diagnosis of glomerulonephritis. Whether even urinary miRNAs may reflect the presence of cardiovascular diseases is still to be determined.

Within our presentation, complex overview of the potential use of circulating miRNAs for the diagnosis, prognostic stratification and even differential diagnosis of cardiovascular diseases will be presented. In the end of the presentation, preliminary data focusing on the potential diagnostic role of circulating miRNAs in patients with myocardial infarction and hypertension will be introduced.

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Keywords: microRNA, cardiovascular diseases, myocardial infarction, hypertension, biomarkers

Multiple modification of LDL

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It is commonly accepted that oxidative modification of LDL is atherogenic modification responsible for the onset and progression of atherosclerotic lesions. However, other atherogenic modifications of LDL, namely: small dense, electronegative and desialylated, that undeservedly are paid much less attention have been found in the blood of atherosclerotic patients. More electronegative LDL (LDL-) isolated from patients' blood by ion exchange chromatography possesses chemical composition and physical properties similar to desialylated LDL obtained by lectin chromatography. The sialic acid content of the LDL is 2- to 6-fold lower than that of native LDL and close to that of desialylated LDL. In the native

LDL subfraction, 83% of lipoprotein particles are normally sialylated. By contrast, a major proportion of human LDL- (81%) was desialylated. We also found that the desialylated LDL subfraction consists of 88% LDL-. We have found that a particle of desialylated LDL is smaller and denser than that of native LDL, i.e., desialylated LDL is a small dense lipoprotein. On the other hand, it was reported that small dense LDL has a low content of sialic acid, i.e., is desialylated. In addition, desialylated LDL possesses higher degree of oxidation and oxidizability because of decreased contents of the major fat-soluble antioxidants in lipoprotein particles. Therefore, we believe that all forms of modified LDL isolated by different methods are represented by the same lipoprotein particles that had undergone multiple modification. Supported by Ministry of Education and Sciences of Russia (Project # RFMEFI61614X0010).

Keywords: Desialylation, Electronegativity, Intracellular Lipid Accumulation, Oxidation, Small Dense

Association of circulating endothelial cells and flow-dependent vasodilatation with recurrent cardiovascular events after acute myocardial infarction

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Aim: to study prognostic significance of some markers of endothelial dysfunction in the risk assessment of recurrent cardiovascular events in patients undergoing acute myocardial infarction (AMI).

Materials and Methods: 180 AMI patients have been involved into 3-year prospective study. Recurrent cardiovascular events (RCE) – cardiovascular death, nonfatal myocardial infarction, stroke, pulmonary embolism, life-threatening cardiac arrhythmias and surgery coronary revascularization registered for the entire period of observation in 62 patients. The number of circulating endothelial cells (CEC) was determined by flow cytophotometry. Flow-dependent vasodilation (FDV) investigated at rest using a B-mode ultrasound system during a 2-min period of reactive hyperemia. Lipid levels and activity of von Willebrand factor (vWF) in the blood samples were evaluated using standard biochemical tests.

Results: There was a significant increase of FDV, CEC and vWF in patients with RCE compared with patients without RCE ($p < 0.05$, $p < 0.05$, $p < 0.01$, respectively). A positive correlation between FDV and “main” risk factors (mRF): LDL-C ($r = 0.37$), hypertension ($r = 0.58$) and age ($r = 0.32$) was found. Signs of endothelial damage in combination with an increase in vWF recorded significantly more frequently in patients with RCE in comparison with those without RCE (71% and 43%, respectively, $p < 0.01$). Based on FDV, CEC, vWF and mRF data the linear discriminant function model was developed, which allowed to determine the RCE risk with an accuracy of 87.9%.

Conclusion: The number of CEC and FDV can serve as additional predictors of RCE. Our findings confirm the need of control endothelial dysfunction markers to prevent RCE in patients after AMI.

Keywords: acute myocardial infarction, circulating endothelial cells, flow dependent vasodilatation, von Willebrand factor, low density lipoproteins

New biomarkers in risk stratification of kidney injury in patients with acute coronary syndrome

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The development of renal dysfunction in patient with acute myocardial infarction, especially in those who underwent angiography, is an actual problem, because it worsens the prognosis for those patients. In order to diagnose this condition in time the search for biomarkers is going. One of them is the Growth differentiation factor 15 (GDF 15).

Purpose: estimate the role of various markers in the development of cardiorenal syndrome in patients with acute coronary syndrome (ACS).

Methods. 73 patients were screened with different forms of ACS (55 male and 18 female), mean age was $61, 8 \pm 1, 3$ years. In anamnesis patients had: 23% – previous myocardial infarction, 51% – stable angina, 84% – hypertension, 16% – diabetes mellitus, 6 % – chronic kidney disease. Based on the results of the examination glomerular filtration rate (GFR) was calculated by Modified diet renal disease method (MDRD). A group of patients has been selected ($n= 54$), their creatinine level was determined during the first 24 hours and after 48 hours. All patients were divided into two groups according to acute kidney injury network classification (AKIN): 21 patients in the first group with negative dynamic (1st stage AKIN and higher), 33 patients in the second group without creatinine dynamic. For risk stratification was used global registry of acute coronary events (GRACE) score. In addition, the levels of GDF 15, N terminal-pro B-type natriuretic peptide (NT-pro BNP) were determined during the first day of hospitalization (normal range of GDF 15 < 1200 pg / ml, NT pro-BNP < 200 ng/ml). The follow-up period was 6 months.

Results. By comparing selected groups significant difference was found in GFR estimated after 48 hours ($p<0.001$). GRACE score (prediction of 6 months death) was significantly higher in the group with negative creatinine dynamic ($p<0.01$). The analyses of biomarkers interconnection (GDF 15) and GFR showed significant difference of estimated parameters between two groups as well ($p \leq 0.02$). Also, correlation of high and medium strength was found between GDF 15 and GFR ($p \leq 0.0001$).

Conclusions: The biomarker GDF 15 can be used for risk stratification in development of acute kidney injury in patients with ACS. For high prognostic possibility we can use combination of biomarkers.

Keywords: stratification, biomarkers, acute coronary syndrome, growth differentiation factor 15, kidney

Cardiology/Hypertension

Plasma renin activity and serum aldosterone concentration in patients with different types of renovascular hypertension

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Purpose: Renovascular disease is an important cause of secondary hypertension and has been linked to increased cardiovascular risk. The pathogenesis of renovascular hypertension is complex, though excess activation of renin-angiotensin-aldosterone system (RAAS) is considered to be one of the leading factors. The evaluation of the RAAS activity remains an unsolved issue in the clinical assessment of different forms of renovascular hypertension. We decided to investigate if there are any differences in renin and aldosterone levels in hypertensive patients with different origin of renal artery stenosis (fibromuscular dysplasia or atherosclerotic process) and normal anatomy of the renal artery in order to understand whether these simple screening methods can be useful in distinguishing different forms of renovascular hypertension.

Methods: The patients with uncontrolled hypertension and equivocal result of ultrasound doppler sonography of renal artery were referred to interventional cardiology department for angiography. Before this aldosterone plasma concentration (normal limits 10-105 pg/ml) and plasma renin activity (0.5-1.9 ng/ml/hour) were determined by immunofluorescence method according to standard recommendations after discontinuation of all medications which are known to have an impact on RAAS.

Results: The study included 36 hypertensive patients. According to results of angiography we formed 3 groups: first consisted of hypertensive patients with normal renal artery anatomy [15 (42%), 6 males, 9 females; mean age 49±12.4 years], the second group involved patients with fibromuscular dysplasia [9 (25%) females, mean age 31±9.6 years], and patients with atherosclerotic renovascular stenosis formed the third group [12 (33%); 5 males, 7 females; mean age 54.3±10.4 years]. Mean plasma renin activity and mean serum aldosterone concentration were: 1.7±0.9 and 132.7±92.4; 7.3±6.1 and 349.3±119.1; 9.4±7.2 and 114.4±62.7 in first, second and third groups, respectively. Plasma renin activity was markedly higher and above normal limits in both groups of patients with renovascular hypertension ($p=0.03$), but aldosterone level was significantly increased only in patients with fibromuscular dysplasia and was higher compared to other two groups ($p=0.02$).

Conclusions: Patients with different forms of renovascular hypertension are characterized by plasma renin activity above normal limits, but subsequent marked increase in aldosterone level is present only in patients with fibromuscular dysplasia. Due to high variability of results of RAAS system assessment this finding needs to be further investigated.

Keywords: renovascular hypertension, RAAS system, aldosterone plasma concentration, plasma renin activity

Lipid profile in patients with diabetes with a left main coronary artery stenosis

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The purpose of our research was a studying of a lipid profile in patients with coronary heart disease (CHD) with arterial hypertension (AH) and diabetes mellitus (DM) type 2 depending on the degree of a left main coronary artery (LMCA) stenosis.

Materials and methods. The study included 138 patients with CHD with AH and DM. Patients were divided into 4 groups: 1) CHD with AH (37 pts), 2) CHD with AH and DM (11 pts) 3) CHD with old myocardial infarction (57 pts) 4) CHD with old myocardial infarction and DM (33 pts). We measured degree of LMCA stenosis by coronary angiography (including criterion was stenosis more than 50%). Left ventricle ejection fraction were measured by echocardiography. The lipid profile including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides was assessed by conventional method.

Results. 1 and 2 groups didn't differ among themselves on the compared indicators. Group 4 patients (with DM and old myocardial infarction) had lower cholesterol, LDL-C, HDL-C levels by 10%, 18,4% and 18,2% respectively than the group 3 patients (5.2 ± 1.5 mmol/l and 5.8 ± 1.3 mmol/l, $r=0.03$, 3.1 ± 1.2 mmol/l and 3.8 ± 1.3 mmol/l, $r=0.03$, 3.1 ± 1.2 mmol/l and 3.8 ± 1.3 mmol/l, $r=0.05$ respectively).

Negative significant correlation was found between the degree of LMCA stenosis and total cholesterol ($r=-0.31$, $p=0.04$) and the degree of LMCA stenosis and LDL-C ($r=-0.45$ $p=0.007$) in DM patients.

Conclusion. DM patients with old myocardial infarction compared to DM patients without myocardial infarction and patients without DM at equal degrees of a LMCA stenosis have lower levels of total cholesterol and LDL-C. The greater the degree of LMCA stenosis in DM patients, the lower levels of total cholesterol and LDL-C.

Keywords: coronary heart disease, left main coronary artery stenosis, cholesterol

Risk factors of coronary artery stenosis in patients with rheumatoid arthritis.

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Background: Rheumatoid arthritis (RA) associate with an increased risk of atherosclerotic events and premature coronary artery disease (CAD). Coronary angiography is the gold standard to identify and assess the degree of CA involvement.

Objective: To estimate the CA stenosis in RA pts with suspected CAD and to investigate its association with traditional risk factors (TRFs) and inflammatory markers.

Methods: The investigation enrolled 65 RA pts with suspected CAD, 27 men and 38 women, mean age 57 [52; 62] years, with a long history of the disease (10 [7; 22] years), seropositive for RF (82%) and anti-CCP (58%), with moderate disease activity DAS 28 = 4,6[3,3; 5,6]. All pts underwent CA angiography.

Results: CA stenosis was detected in 23 (35%) of the 65 RA pts, men/women 15/8 (Group I), including single vessel involvement – in 15 (65%) pts, three-vessel damage – in 8 (35%) pts, without cases of documented two vessels lesions. In 42 (65%) out of 65 pts hemodynamically insignificant stenoses (<50%) or intact CA was documented, men/women 10/31 (Group II). Groups were comparable in terms of age, disease duration and DAS 28 scores. Males prevailed in Group 1: 15/23 (65%) vs 10/42 (22%) in Group 2 ($p<0,05$). CAD incidence was higher in Group 1 pts, i.e. history of myocardial infarction – 32% vs 2%; stable angina pectoris – 77% vs 32% pts Group 1 and 2 ($p=0,03$). Carotid artery atherosclerotic plaques were detected in 19% and 17%, carotid intima-media thickening (IMT) – in 53% and 57% pts from Group 1 and 2, $p>0,05$. The prevalence of TRFs was similar in both groups: hypertension – 77% and 88%, dyslipidemia – 26% and 33%, diabetes mellitus – 5% and 17%, smoking – 45% and 17%, physical inactivity – 58% and 42%, obesity – 45% and 32% pts in Group 1 and 2. Serum HDL cholesterol concentrations in Group 1 (1,2 [1,0; 1,6]mmol/l) was lower, than in Group 2 (1,6 [1,2; 2,0]mmol/l, $p=0,03$). Other lipids did not change in groups. There were no differences in therapeutic and dosing regiments DMARDs, GEBAs and oral glucocorticoids (GCs), with the only exclusion: the duration of GCs therapy was higher in Group 1 pts (5,4[4;12]) vs 3,2[1,5;8]years, $p<0,05$) Group 2. Left maximum IMT was positively correlated with DAS 28 ($R=0,85$, $p<0,05$) in women of Group 1. Correlations in Group 2 were found between left maximum IMT and total cholesterol ($R=0,38$), LDL cholesterol ($R=0,45$), triglycerides ($R=0,43$, $p<0,05$ in all cases) in women; right maximum IMT and levels of interleukin 6 ($R=0,85$, $p<0,05$) in men. The multiple regression analysis did not establish any direct relationship between CA stenosis and gender, age, RA activity, cholesterol and LDL cholesterol concentrations, use of DMARDs and oral GCs. Age was the strongest, but not statistically significant variable predicting stenosis (odds ratio (OR) 0,85; 95% CI [0,72-1,0], $p = 0,05$), with the following HDL-C <1,2mmol/L for women and <1,0 mmol/L for men (OR 0,82; 95% CI [0,64-0,90], $p = 0,09$).

Conclusion: Male gender, low HDL cholesterol and long-term GC therapy seem to increase the risk of CA stenosis in RA pts.

Keywords: coronary artery stenosis, rheumatoid arthritis, coronary angiography, traditional risk factors

Relationship between traditional factors of cardiovascular risk and subclinical carotid atherosclerosis

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Aim. Evaluation of relationship between the traditional cardiovascular risk factors (TFR) and prevalence of atherosclerotic plaque (AP) of the carotid arteries as a marker of subclinical atherosclerosis (SA).

Materials. We studied 515 inpatients (including 306 women) of Pokrovskaya City Hospital, aged $55,3 \pm 8,87$ (30 – 70 years), who admitted from 2009 to 2014 and did not have a verified coronary heart disease or its equivalents in terms of the level of cardiovascular risk. Ultrasound examination of the carotid arteries was performed on Sonoline g60s scanner (SIEMENS). Presence of nonstenotic AP was used as a criterion for SA. We analyzed the prevalence of SA in subjects with different TFR.

Results. In patients with hypertension prevalence of carotid AP was 63.0 % (95 % CI 54.6 – 70.8), and in normotensive subjects it was 37.13 % (95 % CI 32.2 – 42.3). In patients with dyslipidemia AP occurred more than two times more frequently than among people with normal serum lipids, 56.25 % (95 % CI 50.6 – 61.8) vs 25.13 % (CI 19.2 % – 31.8) respectively. Gender had practically no effect on the prevalence of SA: AP occurs in 42.11 % (95 % CI 35.3 – 49.1) in males vs 46.8 % (95 % CI 40.4 – 51,8) in females. The detection rate of AP among smokers was 48.8 % (95 % CI 39.8 – 57.9) vs 43.8 % (95 % CI 38.1 – 48.2) in nonsmokers. Among patients with diabetes mellitus AP was found in 57.39 % (95 % CI 45.9 – 73.1) vs 42.61 % (95 % CI 38.1 – 47.3) in non-diabetics. The prevalence of AP significantly increased with age: in the younger age group (30 – 39 y.o.) the prevalence of AP was 7.5 % (95 % CI 1.6 – 20.4) vs 58.7 % (95 % CI 51.2 – 65.9) in the older age group (60 – 70 y.o.).

To evaluate the relationship between the detection of AP and TFR χ^2 test was performed. Its values were 48.04 and 47.57 for age and dyslipidemia, that significantly exceeds the critical values for $\alpha = 0,05$ (7.8 and 3.8, respectively). This confirms a strong relationship between the SA and these risk factors. SA and diabetes mellitus were also significantly related, with the χ^2 value of 6.01 (the critical value is 3.8 for $\alpha = 0,05$). As for smoking and gender, the relationship was insignificant, χ^2 test values were 1.28 and 0.82, respectively (the critical value is 3.8 for $\alpha = 0,05$).

Conclusions. Age and total cholesterol significantly affect the prevalence of carotid SA. Considering the higher sensitivity of the χ^2 test, presence of diabetes also affects the prevalence of SA significantly. Relationship of smoking and gender and carotid SA prevalence has not been confirmed: additional analysis on a larger sample size is required.

Keywords: atherosclerotic plaque, ultrasound of the carotid arteries, risk factors

How well does the contemporary primary prevention strategy identify patients at risk: comparison with the results of carotid atherosclerosis imaging

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Purpose: The traditional risk factors included in common scoring systems are well-known makers of cardiovascular disease, but are sometimes claimed poor predictors of it. The aim of this study was to compare the ESC (European society of cardiology)/EAS (European atherosclerosis society) primary prevention guidelines based on the global cardiovascular risk assessment by SCORE (Systemic coronary risk evaluation) with the idea of actual cardiovascular risk based on the results of carotid ultrasound imaging.

Methods: This cross-sectional study included 165 patients (mean age 53±8 years, 48% females) without a history of coronary artery disease and with at least one traditional cardiovascular risk factor. For each participant primary prevention strategy was identified based on global cardiovascular risk calculation by SCORE and the level of low-density lipoprotein-cholesterol (LDL-C), as per the current cardiovascular disease prevention Guidelines. Thereafter, the identified strategy was compared to the findings of carotid ultrasound imaging. The presence of plaque was defined as a marker of subclinical atherosclerosis and was regarded as a surrogate of high cardiovascular risk. Carotid intima-media thickness values above 75th percentile for age and gender were not used as high-risk markers because of the lack of their reference values for Russian population.

Results: Mean LDL-C was 3,7±1 mmol/l, and the median calculated cardiovascular risk by SCORE was 2 [2]. 24 (14%) patients were referred to a low total risk, 117 (71%) had an intermediate risk, 23 (14%) had high risk and 1 (1%) had very high risk. According to the ESC/EAS guidelines, immediate drug intervention was required in 23 patients. Herewith in 18 of them the appropriateness of lipid-lowering therapy was confirmed by the presence of carotid plaque. Considering medical therapy after lifestyle modification should have been necessary in 106 participants and 34 of them had carotid plaque. On the other hand, among 36 patients who didn't require the drug therapy even after lifestyle modification, 6 (17%) had carotid plaque – a marker of actual high cardiovascular risk.

Thus, the calculated risk requiring hypolipidemic therapy for primary prevention had a sensitivity of 90% in prediction of carotid plaque presence. On the other hand, calculated risk not high enough to justify the drug intervention, predicted the absence of plaque with a specificity of 28%.

Conclusions: The criteria for primary prevention according to the ESC/EAS guidelines based on the use of SCORE and LDL-C level are highly sensitive in detecting patients who have actually high risk identified by carotid imaging. On the other hand, the specificity of these guidelines may be lower, which results in identifying 72% of patients not having a carotid plaque as candidates for drug therapy for primary prevention.

Keywords: cardiovascular risk, carotid plaque, SCORE, atherosclerosis

The influence of atorvastatin on endothelium dysfunction and combined course of ischemic heart disease, essential hypertension and chronic obstructive pulmonary disease

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Aim: To investigate the atorvastatin influence on severity of stable angina pectoris, blood pressure monitoring (BPM) and respiratory function indexes (RFE).

Materials and methods: 30 patients with ischemic heart disease in combination with essential hypertension (EH) and chronic obstructive pulmonary disease (COPD) with plasma concentration of the total cholesterol (TCH) more than 5.0 mmol/l and the cholesterol low density lipoproteins (LDL) more than 3.5 mmol/l before atorvastatin 20 mg per day treatment and three month after were surveyed. Blood pressure by BPM, tolerance to physical load by veloergometry, RF by computer spirograph, endothelium dysfunction by measuring a degree of the endothelium-dependent relaxation of a humeral artery with Doppler through a humeral artery diameter change at reactive hyperemia, C-reactive protein (CRP), interleukin-6 (IL-6), a tumor necrosis factor alpha (TNF- α) concentration, patients' quality of life were estimated. At realization of spirography we estimated the forced vital capacity (FVC), the forced expiratory volume in 1 s (FEV₁), Tiffno index (FEV₁/FVC).

Results: After three month atorvastatin treatment the average TCH level has decreased from 5.89 \pm 0.13 mmol/l to 4.08 \pm 0.09 mmol/l, the cholesterol LDL level has decreased from 3.77 \pm 0.07 mmol/l to 2.10 \pm 0.09 mmol/l, the physical loading tolerance has increased at 24 patients (80%), on average, by 20.4 \pm 11.8 w. The interrogation has revealed reduction of angina pectoris' attacks numbers by 46.1%, and quantity of accepted nitroglycerine tablets for day by 3.7, on average. The average daily systolic BP (SBP) level has decreased by 9.1 mm Hg (p<0.05), diastolic BP (DBP) level has decreased by 7.3 mm Hg (p<0.05), SBP night decrease index has increased by 4.5 mm Hg (p<0.05). Morning DBP raising index has decreased by 5.7 mm Hg (p<0.05). After atorvastatin treatment the bronchial resistance has authentically decreased. No one surveyed patients has FVC level changed. It is demonstrated that obstructive syndrome in the examined patients caused by increased resistance both small and large airways. The obstruction of large airway correlates with degree of endothelial dysfunction. After atorvastatin treatment forced expiratory volume in 1 second (FEV₁) has increased by 0.51 p/a (p<0.05) and occurred due to large bronchial tubes dilatation – by 11.2% (p<0.05). Tiffno index has increased by 6,4 \pm 1,1% (p<0,05), on average. Endothelial dysfunction in all examined patients decreased (a humeral artery diameter relaxation at reactive hyperemia has increased from 0.38 \pm 0.03 mm (8.2%) to 0.56 \pm 0.05 mm (13.3%) (p<0,05). Patients' quality of life is improved. The CRP level decreased by 0.79 pg/ml (p<0.05). IL-6 – by 1.7 pg/ml (p<0.05), TNF- α – by 17.6 % (p<0.05).

Conclusion: Atorvastatin inclusion in treatment of IHD in combination with EH and COPD promoted lipid exchange, systemic inflammation activity decrease and stimulation of synthesis of vaso- and bronchorelaxed nitric oxide. At this background the endothelial function is normalized, tolerance to physical load is increased, angina pectoris course, BP daily rhythm, RFE indexes and patients' quality of life is improved.

Keywords: atorvastatin, endothelial dysfunction, chronic obstructive pulmonary disease

The level of cardiovascular risk factors correction in patient undergoing myocardial revascularization

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Effective correction of cardiovascular risk factors is a key component of cardiac rehabilitation and secondary prevention programs, which has proven impact on both the prognosis of patients with coronary artery disease, including patients undergoing myocardial revascularization, and on the cost-effectiveness of high-tech and costly treatment. We evaluated risk factor correction and treatment compliance in patients with coronary artery disease 1 year after coronary artery bypass surgery (CABG). The study included 100 patients with coronary artery disease (70% – men) aged 36–69 years (mean – $57,7 \pm 7,8$ years) after CABG, performed in Federal Almazov North-West Medical Research Centre. All patients during the inpatient rehabilitation received information on issues related to the disease and its treatment, at discharge – verbal and written recommendations for drug therapy, lifestyle changes and risk factors correction. In accordance with the results of a survey conducted on the day of discharge 98% of patients were willing to follow the recommendations for drug therapy and 56% – for non-pharmacological risk factor correction and lifestyle changes.

At 1 year after CABG 74% of patients accurately used all recommended drugs. 82% of included in the study regularly monitored their blood pressure and heart rate. Target values of blood pressure have been reached in 71% of patients. Smoking cessation was 61% of smokers. Kept the recommended diet 64% of patients, 38% – fulfilled the recommendations on physical activity and physical training. 43% of patients lost their weight. According to the results of laboratory studies, the target values of blood lipid level reached only 30% patients: the level of total cholesterol was below 4.5 mmol/L in 49% of patients, LDL 1.0 mmol/l (men) and 1.2 mmol/l (women) – 61%, TG

Conclusions: Unsatisfactory level of cardiovascular risk factors correction may be the result of patient unwillingness to therapeutic lifestyle changes, failure to comply with the recommendations on nutrition and physical activity. Despite on adherence the majority of patients (74%) to physician recommendations for drug therapy, the target values of blood pressure were achieved in 71% of cases, LDL – in a third of cases only, that requires an analysis of the adequacy of drug treatment during outpatient rehabilitation of patients with coronary heart disease after myocardial revascularization.

Keywords: cardiac rehabilitation, patients adherence to treatment, risk-factors correction, lifestyle changes, myocardial revascularisation

Statins for the prevention of early postoperative cognitive dysfunction in patients undergoing coronary artery bypass grafting

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Purpose: To evaluate the effect of perioperative statin therapy on the incidence of early postoperative cognitive dysfunction (POCD) in patients undergoing coronary artery bypass grafting (CABG).

Methods: Cognitive performance was analyzed in 110 male patients (the mean age 56.3 ± 5.5 years) who underwent CABG between 2009 and 2011. All patients were randomized to two groups: the study group ($n=70$) received rosuvastatin, 20 mg daily, and the control group ($n=40$) didn't receive any statins. Both groups were comparable by all clinical and demographic data. All patients underwent on-pump CABG. The duration of cardiopulmonary bypass was 95.5 ± 18.2 minutes. Attention was assessed in all patients with the Bourdon's test. Visual short-term memory was assessed with 10 words memorizing test, and 10 numbers memorizing test. Moreover, all patients underwent neuropsychological testing using the automated complex software (Status PF). Complex visual-motor reaction (CVMR), level of functional mobility of nervous processes (FMNP) and nervous processing capability (NPC) were measured. Cognitive functioning was assessed prior to randomization, then at day 2 prior to CABG, and at days 7-10 after CABG. The statistical analysis was conducted using "Statistica 8.0". The presence of POCD was estimated on the basis of criteria defined as a 20% decline on 20% of the tests.

Results: Neurodynamic parameters before randomization did not differ between the groups. Rosuvastatin-treated patients at days 7-10 after CABG demonstrated an increase of reaction time for CVMR tests ($p = 0.005$), missed fewer signals for FMNP tests ($p = 0.03$), processed more symbols over 4 minutes of the Bourdon's test ($p=0.005$) and recalled more words ($p=0.008$) compared to patients without rosuvastatin treatment. The individual analysis of neurodynamic parameters reported the development of POCD in 81% of patients in the control group, and in 55% in the study group.

Conclusion: Preoperative rosuvastatin treatment (20 mg daily) reduces the incidence of early POCD in patients undergoing on-pump CABG, suggesting its positive neuroprotective effect.

The causes of termination of therapy: survey of patients of cardiological hospitals of Saratov and the small city of Saratov region

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Objective: based on the survey of patients of the cardiology hospital of Saratov and Central regional hospital of Saratov region to identify the main causes of termination of therapy.

Materials and methods: in 2013 year anonymous questioning of patients with cardiac profile of Saratov and Central regional hospital remote administrative center of Saratov region. The subject of the therapy and possible reasons for discontinuation of treatment.

Results: 70 patients attended the hospital of Saratov (40(57,1%) male, median age 67 years) and 108 patients CRH remote administrative center of Saratov oblast (62(57%) women, median age 60 years). History 106(89,8%) patients have arterial hypertension, 148(83,1%) – coronary heart disease, 42(23,6%) – myocardial infarction, 112(62,9%) in – chronic heart failure 32(17,9%) – diabetes, 120(67,4%) were obese. A large number of respondents claimed that when their disease requires constant medication – 46(65,7%) patients in the hospital of Saratov and 78(72%) of Central regional hospital, others felt that it could be treated rates (8(11,4%) and 6(6%)) and demand (6(8,6%) and 24(22%)). In this case, in fact, complied with the advice of a doctor 42(60%) patients of the city hospital and 66(61%) of Central regional hospital. Stopped previously prescribed treatment 40(57,1%) patients of the Saratov and 42(38,8%) of Saratov region. Calling the reasons for discontinuation of therapy at the time of admission, respondents indicated the following options: “feel good without drugs” – 10 (14,3%) patients of the cardiology hospital of Saratov and 38(35%) of Central regional hospital patients, “the drugs had side effects” – 8 (11,4%) and 12(11%), “inadequate financial situation and the cost of drugs” – 2 (2,9%) and 12(11%), “more serious problems than the disease” – 2(2,9%) and 2(2,2%), “drugs do not improve well-being” – 8 (11,4%) and 6(6%), “drugs worsened the health” – 8 (11,4%) and 10(9%) patients, respectively. Patients of the cardiology hospital of Saratov also noted why: “a complex and inconvenient regimen” – 2(2,9%), “fear of adverse effects of treatment” – 2 (2,9%), “it is not convenient to visit the doctor” – 2 (2,9%). Such an option as “not a relationship with your doctor” were not chosen by any patient.

Conclusions: the vast majority of patients of the hospital, as the Saratov and the Saratov region for one reason or another independently thrown medication. The main reasons for discontinuation of therapy, both in the city and region are in good health and no treatment, therapy side effects, lack of improvement of health or worsening of health during therapy. Reason for discontinuation of therapy for patients of Central regional hospital the Saratov region is the inconsistency between their financial situation and the cost of drugs.

Keywords: cardiovascular disease, termination of therapy

The features of atrial fibrillation in patients with myocardial infarction

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Objective: To evaluate the clinical and functional parameters in patients with myocardial infarction according to atrial fibrillation (AF).

Materials and Methods: The study involved 55 patients (25 men, 30 women) who were hospitalized in the cardiology department on the myocardial infarction with atrial fibrillation. Depending on the form of atrial fibrillation patients were divided into 2 groups: 1st totaled 35 (63.6%) patients with paroxysmal form of atrial fibrillation, 2nd – 20 (36.3%) patients with persistent form of atrial fibrillation.

Performed: physical examination, determination of the localization of myocardial infarction, form of myocardial infarction (primary, repeated), complications of a heart attack (acute left ventricular failure of Killip, 1967) and lipid profile (total cholesterol, LDL, triglycerides); interpretation of the results of echocardiography (EF%, EDSL (end diastolic size of left ventricle) mm, TRWL (thickness of rear wall of the left ventricle) mm, IVST (interventricular septum thickness) mm, size of LA, RA and RV mm).

Results: Among the patients in Group 1 – 18 patients had anterior myocardial infarction (51.4%), 17 patients had lower myocardial infarction (48.5%); 24 patients had primary (68.5%) myocardial infarction, 11 patients had repeated myocardial infarction (31.4%). Myocardial infarction combined with hypertension in 35 (100%) patients. 20 (57.1%) patients had the 1st grade of acute left ventricular failure (Killip classification), 12 (34.2%) patients – IIrd grade, 3 (8.5%) patients – IIIrd grade, IVth grade was not detected. Echocardiography indicators were: in primary paroxysm form of AF the EF was $49,9 \pm 0,7\%$; EDSL – $48,5 \pm 0,4$ mm; TRWL – $15,3 \pm 0,8$ mm, IVST – $14,64 \pm 0,2$ mm; during the reoccurring paroxysm of AF the EF was $44,4 \pm 0,4\%$; EDSL – $50,1 \pm 0,1$ mm; TRWL – $14,4 \pm 0,4$ mm, IVST – $15,7 \pm 0,2$ mm. The level of total cholesterol was $4,5 \pm 1,65$ mmol / l, LDL – $2,6 \pm 0,25$ mmol / l, TG – $1,44 \pm 0,14$ mmol / L.

Among patients of the 2nd group anterior myocardial infarction occurs in 12 (60%) patients, a lower myocardial infarction – in 8 (40%) patients; primary – in 14 (70%) patients, repeated – in 6 (30%) patients. Myocardial infarction combined with hypertension in 20 (100%) patients. 1st grade of acute left ventricular failure was detected in 11 (55%) patients, IIrd grade – in 5 (25%) patients; IIIrd grade – 4 (20%) patients, IVth grade was not detected. Echocardiography indicators were: EF – $37,2 \pm 0,4\%$; EDSL – $54,1 \pm 0,2$ mm; TRWL – $16,3 \pm 0,4$ mm, IVST – $16,2 \pm 0,4$ mm. The level of total cholesterol was $4,5 \pm 1,7$ mmol / l, LDL – $2,9 \pm 0,11$ mmol / l, TG – $1,14 \pm 0,4$ mmol / l.

Conclusions: Repeated myocardial infarction mostly of lower localization often combines with paroxysmal atrial fibrillation, as for myocardial infarction with persistent atrial fibrillation it accompanies with more severe structural and functional changes of the left ventricle.

Keywords: atrial fibrillation, myocardial infarction

Association of Pro12Ala polymorphism of PPAR-gamma2 gene with insulin resistance and coronary artery disease in Russia

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Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) is a nuclear hormone receptor that functions as mediator of whole body insulin sensitivity. Insulin resistance, hyperinsulinemia and high HOMA-IR levels are the risk factors of CAD.

Purpose: The purpose of our study was first to compare the frequency of Pro12Pro, Pro12Ala, Ala12Ala PPAR-gamma2 gene genotypes in a sample of men with coronary artery disease and their association with fasting plasma insulin concentration and HOMA-IR.

Methods: The Pro12Pro, Pro12Ala, Ala12Ala PPAR-gamma2 gene genotypes were determined in a sample of 278 Russian men 38-72 years old (middle age – 61.6±0.48) with CAD and 220 subjects of the same age without CAD (middle age – 60.09±0.72) by a polymerase chain reaction-restriction length polymorphism (PCR-RFLP)-based method. Fasting plasma insulin concentrations were investigated by ELISA (DRG). HOMA-IR was calculated.

Results: Pro12Pro genotype was revealed in 204 CAD patients (74%) and 187 subjects without CAD (85%); pro12Ala genotype – in 64 CAD patients (23%) and 31 subjects without CAD (14%); carriers of Ala12Ala genotype were 9 CAD patients (3%) and 2 subjects without CAD (1%), $p=0.004$. The frequency of ALA allele was 0.15 in patients with CAD and 0.08 in non CAD subjects ($p<0.0003$). The Ala allele was positively associated with CAD, giving an odds ratio 2.0 (CI:1,32÷3,04, $p=0,0006$). When stratified by CAD status, the Pro12Pro genotype was positively associated with type 2 diabetes, giving an odds ratio 2,12; CI:1,07÷ 4,19. In CAD patients Ala allele was positively associated with III functional class of chronic heart failure, giving an odds ratio 1,74; CI:0,98÷3,1. Fasting plasma insulin concentration was highest in patients- Pro12Pro genotype carriers, than in patients – Pro12Ala and Ala12Ala carriers (21,02±1,97 mU/ml and 11,06±1,12 mU/ml respectively, $p=0,008$). HOMA-IR of patients with Pro12Pro genotype was 5,98±0,55; HOMA-IR of patients -carriers Pro12Ala and Ala12Ala genotypes was 2,82±0,36, $p=0,007$. In non-CAD subjects fasting plasma insulin concentration and HOMA-IR were not significantly different according to the genotype.

Conclusion: The data suggest the contribution of Pro12Ala polymorphism of PPARgamma2 to genetic susceptibility to CAD type2 diabetes and insulin sensitivity in CAD patients.

Keywords: coronary artery disease, PPARgamma2, insulin resistance, Pro12Ala polymorphism, HOMA-IR

Renal denervation and its role in resistant hypertension

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Catheter based renal denervation (RDN) has been considered as a new promising method for patients with resistant hypertension (RH). The first two studies published by the same group of experts triggered widespread enthusiasm and the new method spread out quickly. However, this was slowed down in 2014 by publication of SIMPLICITY 3 trial, which showed comparable effect of RDN and pharmacological therapy.

We performed randomized, multicenter PRAGUE 15 study, which compared the relative efficacy of renal denervation versus pharmacotherapy alone in patients with true resistant hypertension and assessed the effect of pharmacotherapy with spironolactone addition. A total of 106 patients with true-resistant hypertension were enrolled: 52 patients were randomized to RD and 54 patients to pharmacotherapy with the spironolactone addition (PH). The intention-to-treat analysis found after one year comparable mean 24-hour SBP decline of 6.4 mmHg in RD versus 8.2 mmHg in PH. Per-protocol analysis revealed significant difference of 24-hour SBP decline between RDN (6.3 mmHg) and PH (15 mmHg) ($p \leq 0,01$). Recent metaanalysis of randomized controlled trials on RD in resistant hypertension published in Blood pressure 2015 also did not find convincing benefit of RDN in RH.

It thus seems that renal denervation with traditional technique used (Simplicity flex cathether) is safe, but not superior to intensified pharmacological therapy in patients with resistant hypertension. Future studies with more sophisticated renal denervation (RD) techniques needs to be performed before final evaluation of the RD role in hypertension can be assesed.

Keywords: resistant hypertension, treatment, renal denervation

Case Report

Elevated lipoprotein (a) (Lp (a)) levels and aggressive coronary heart disease (CHD); a casuistic approach

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Aim: Patients with hyperlipidaemia have an elevated risk of developing CHD. A high level of Lp (a) further increases the risk of CHD and premature death. The aim of this case study is to highlight that disease progression may occur despite potent cholesterol lowering medications and that other treatment modalities are available.

Background: The non-smoking male patient born in 1958 developed angina in 2007. He was treated with PCI for the first time in 2008, and after a series of angina and NSTEMI events the patient had a total of 11 coronary stents by the year of 2014. Lipid status in 2014 was total cholesterol 4,9 mmol/l, serum LDL 2,7 mmol/l and Lp (a) 237 nmol/l (the 95th percentile is at 210 nmol/l). He was at this time treated with Crestor 40 mg x1. Other cholesterol lowering medications gave intolerable side effects. In addition to polygenic hyperlipidaemia the patient is diagnosed with seronegative rheumatoid arthritis (RA) and obstructive sleep apnoea syndrome.

Results: The patient was referred to lipoprotein apheresis (LA) to lower the Lp (a) level. The weekly LA treatment from September 2014 lowered the Lp (a) level in average by 66%, correspondingly LDL was reduced 67% immediately after treatment. After initiation of LA treatment no more cardiac interventions were necessary, and the patient reported improvement in both angina and rheumatic pain.

Discussion: The patient has an unusually aggressive CHD despite having an on-treatment LDL level that is only moderately elevated. This may partly be due to the elevated Lp (a) level. LA is currently the most effective therapy to lower Lp (a) levels. LA treatment also has beneficial effects on the level of other plasma factors such as inflammatory proteins and oxidized phospholipids. LA has been proven to have immediate effects on unstable angina and to prevent major adverse cardiac events (MACE) in patients with coronary disease. Leebman et al. (2013) investigated the effect of LA in 170 patients with coronary disease and elevated Lp (a) levels, and demonstrated that the mean annual rates of MACE decreased from 0,41 for 2 years before LA to 0,09 for 2 years during LA. Safarova et al. (2013) demonstrated, in a randomized designed coronary angiography study, that Lp (a) specific apheresis treatment lead to atherosclerosis regression in patients with stable CHD with high Lp (a) levels. This implies that Lp (a) may have a causative role in the atherosclerotic process. High Lp (a) levels are also strongly associated with autoimmune diseases, in particular RA. It is therefore plausible that LA in addition to prevent recurrent MACE also alleviate symptoms of RA in our patient.

In conclusion, this patient case study illustrates that progression of CHD may occur despite a low LDL level on potent statin treatment. Lp (a) might be a key pathophysiological factor in this case, and RA is possibly an important cofactor. To our knowledge, this is the first patient in Norway where elevated Lp (a) was the indication for LA treatment.

Keywords: Hyperlipidaemia, Lp (a), Coronary Heart Disease

Patient-centered care for cardiovascular disease primary prevention in elderly patient

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Although atherosclerotic cardiovascular disease risk increases with age, risk prediction models are not well validated in older people since they are based on a patient cohort with upper age of 74. There is some evidence of the benefits of blood pressure and cholesterol lowering medication in older adults without clinical atherosclerotic cardiovascular disease (ASCVD), however, there are no specific recommendations regarding the use of potentially effective primary prevention therapy in patients over 75 years of age. Meanwhile otherwise healthy older people should not be denied primary prevention treatment on their age alone. Shared decision-making with healthy older adults in an area of ASCVD risk assessment and management (where the evidence is not entirely clear) likewise the use of additional tests is suggested.

Case: A 83-year-old non-smoking man with a history of hypertension and dyslipidemia wished on his office visit to receive information on his statin treatment health benefits. Other than blood pressure (BP) of 170/85 mm Hg and overweight, the exam was normal. Labs showed well-controlled lipids on atorvastatin. Potential risks of statin therapy (altered metabolism, cognitive limitations, side effects, etc.) were monitored. Additionally, pulse wave velocity (PWV) measurements for peripheral vascular health assessment were obtained in this patient at rest - 4.8 m/sec, and after physiologic challenge (cuff-induced ischemia in brachial artery) -14.3-11.4 m/sec. Blood pressure treatment was reassessed to meet BP target below 150/85 mm Hg. Healthy lifestyle was reinforced.

In the next visit his blood pressure was 135/75 mm Hg. PWV measurements at rest and after hemodynamic challenge were 3.0 m/sec and 5.7 m/sec, respectively.

Conclusion: For primary prevention, use of additional tests (e.g. pulse wave velocity) is helpful in cardiovascular risk assessment and management in the context of shared decision-making with older adults. Moderate-intensity statin therapy in our patient might confer short-term benefits (e.g. reversal of endothelial dysfunction) which was not stable without proper blood pressure control.

Absence of the posterior mitral valve leaflet detected in late adulthood

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A 62-year-old woman suffering from dyspnea and palpitation was referred to our hospital. Electrocardiography (ECG) revealed left bundle branch block and atrial fibrillation. She was hospitalized for decompensated heart failure due to atrial fibrillation with rapid ventricular response. Transthoracic echocardiography revealed the absence of the PMVL and mild mitral regurgitation (Figs. 1A and 1B). Posterior myocardial wall replacing of the posterior leaflet had proceeded to coaptation line of the mitral valve (Fig. 1C). Chordae tendineae and papillary muscles were attached to tip of posterior myocardial wall. Parasternal short axis view showed that coaptation line of the mitral valve was normal (Fig. 1D). We suspected persistent left vena cava superior due to dilated coronary sinus. But during an agitated saline injection into the patient's right and left upper extremity intravenous line was no detected any anomaly. Systolic function was mild depressed ejection fraction was measured 40% by method of Simpson. Subsequent transesophageal echocardiography (TEE) confirmed transthoracic echocardiography findings (Fig. 1E, all mid-oesophageal views, 87°). Color Doppler examination revealed mild mitral regurgitation in transesophageal echocardiography examination (Fig. 1F). Coronary angiography was performed because of reduced systolic function. As a result coronary angiogram was found to be normal. Congenital malformations of the posterior mitral leaflet are extremely rare and present with a wide spectrum of morphologic abnormalities. Hypoplasia of the posterior mitral valve leaflet was reported previously. Absent PMVL have been described in a few cases accompanied by atrial septal defect or atrioventricular septal canal defects. But in these cases in the presence of myocardial segment instead of PMVL had only one case previously reported. (Heper G, Yetkin E, Senen K. Absence of posterior mitral leaflet with secundum atrial septal defect. *Ann Thorac Surg.* 2010;90:2055-7) The absence of the PMVL is usually symptomatic due to severe mitral regurgitation and accompanied by such as intracardiac shunt. Our case remained asymptomatic until adulthood and no other cardiac anomaly. Absent PMVLs may be more prevalent in asymptomatic adults than known.

Keywords: mitral valve, mitral regurgitation, posterior mitral valve leaflet, absence mitral valve

Effectiveness of Mipomersen compared to Alirocumab for Heterozygous Familial Hypercholesterolemia

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Background: Mipomersen is an antisense oligonucleotide inhibitor of Apolipoprotein B-100 (Apo B) synthesis, an essential component of lipoproteins such as very-low-density lipoprotein (VLDL) and Low Density Lipoprotein (LDL). It utilizes short, single-stranded synthetic DNA molecules to target and complement a specific messenger RNA (mRNA) sequence that subsequently results in inhibition of protein translation. Ultimately, the production of atherogenic lipoproteins is decreased. Proprotein convertase subtilisin/kexin type 9 (PCSK9) serves as an important regulator of hepatocyte LDL receptor (LDL-R) expression and degradation. Gain-of-function mutations in PCSK9 are associated with familial hypercholesterolemia (FH), whereas loss-of-function mutations are protective against cardiovascular disease (CVD). Monoclonal antibodies to PCSK9 have been shown to reduce LDL levels in patients who cannot achieve adequate lipid control on pharmacotherapy or are intolerant to medication. The PCSK9 antibody binds free PCSK9 in the plasma resulting in reduction of LDL-C. In phase 2 studies lasting 8 to 12 weeks, PCSK9 inhibitors lowered LDL cholesterol levels by 40 to 70% when added to background statin therapy. In true null Homozygous FH (HoFH) patients, PCSK9 therapy is largely ineffective since there are no functional LDLR to be upregulated. However, if there is residual LDLR activity in at least one LDLR allele, PCSK9 inhibition is an effective means of LDL-C reduction, although to a lesser extent than that in Heterozygous FH (HeFH) patients.

Case Presentation: A 74 year old female with a history of severe HeFH and statin intolerance was referred to our clinic for lipid management. Past medical history includes CVD and CABG. Family history includes multiple first degree relatives who have suffered from severe hypercholesterolemia with CVD.

As part of a 6 week clinical trial, she was given Mipomersen 70mg three times a week. She responded extremely well to treatment showing an overall LDL-C decrease of 74%. After finishing the Mipomersen trial, the patient entered a Compassionate Use Trial with biweekly PCSK9 inhibitor (Alirocumab 150mg). Treatment resulted in an overall LDL-C decrease of 44% after 24 weeks of therapy. The patient reports feeling well overall with no significant complaints.

Results:

	Mipomersen (Start)	Mipomersen (End)	Alirocumab (Start)	Alirocumab (End)
Lab Parameters	6/25/14	8/18/14	7/24/15	1/22/16
Total Cholesterol (mg/dl)	379	145	419	266
Triglycerides (mg/dl)	139	57	138	259
LDL-C (mg/dl)	292	76	298	168
HDL-C (mg/dl)	59	58	47	40

Conclusion: Mipomersen decreased LDL-C by over 70% compared to PCSK9 inhibitor which reduced LDL-C by 40 % even after 6 months. Although Mipomersen has been approved for use in HoFH, it could be an effective alternative to PCSK9 inhibitors in some patients with HeFH.

Keywords: Mipomersen, PCSK9 Inhibitors, Familial Hypercholesterolemia

Epidemiology

Analysis of the prevalence of hypercholesterolemia in the outpatient practice (according to the ARGO study)

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Aim: To study the level of total cholesterol in patients at high and very high cardiovascular risk in clinical practice, and that their conduct current recommendations for the treatment of dyslipidemia ESC/EAS (2011) and RSC/SSA (2012).

Material and methods: Patients aged 30 years and older who see by physician or a cardiologist in the outpatient clinic in the period from October 2013 to July 2014 were included in the study. Each patient filled out a questionnaire. The total cholesterol test was performed without special training of the patient by portable blood photometric analyzer allowing for 3 minutes to evaluate the total cholesterol.

Results: 18.273 patients (58.9% women) included in the final analysis. Hypercholesterolemia was found in 81.3% women and 78.9% males. Total cholesterol level was significantly above the target in all federal districts (from 5.82 to 6.10 mmol/L). Statins had not been prescribed to almost half of the patients. Total cholesterol >5 mmol/L was found in 84.7% of patients treated by simvastatin, in 75.2% of patients treated by atorvastatin, in 59% of patients treated by rosuvastatin.

The maximum dose of atorvastatin (80 mg/days) was appointed only 12 of 3348 patients (0.36%), rosuvastatin (40 mg/days) – only 8 of 1095 patients (0.73%). Maximum dose of simvastatin (40 mg/days) 121 of 1468 patients (8.2%) was appointed. Practically didn't appoint the maximum doses of preparations. The maximum dose of atorvastatin (80 mg/days) was appointed only 12 of 3348 patients (0.36%), rosuvastatin (40 mg/days) – only 8 of 1095 patients (0.73%). Maximum dose of simvastatin (40 mg/days) 121 of 1468 patients (8.2%) was appointed. It is noteworthy that the most frequent doses of 10 and 20 mg/day regardless of the drug taken. The very high cardiovascular risk patient achieved target levels of total cholesterol (<4 mmol/L) in 2.04-7.38% of cases.

Conclusion: The situation with the diagnosis and treatment of dyslipidemias in clinical practice is far from ideal in spite of the availability of information for doctors and patients. This requires a study of the causes of this problem. Also there is a wish to note that many patients who weren't receiving statin specified lack of the corresponding medical appointments as the reasons of their not reception (30% of patients with Coronary Heart Disease, 70% – with Arterial Hypertension).

Keywords: dyslipidemia, total cholesterol, the real practice, statins

Long-term risk of arterial hypertension and stroke in women aged 25-64 years with sleep disturbances in Russia/Siberia: based on WHO epidemiological program MONICA-psychosocial

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Aim: To study the effect of sleep disturbances (SD) on relative risk of arterial hypertension (AH) and stroke in female population of 25-64 years in Russia over 16 years of follow-up.

Methods: Under the third screening of the WHO “MONICA-psychosocial” program random representative sample of women aged 25-64 years (n=870) were surveyed in Novosibirsk in 1994. Questionnaire “Awareness and attitude towards the health” was used to estimate quality of sleep. From 1995 to 2010 women were followed for incidence of AH, stroke. Cox regression model was used for relative risk assessment (HR) of stroke, AH.

Results: The prevalence of SD in women aged 25-64 years was 64.9%. AH was developed in 33.4% women, stroke – in 5.1% women.

HR of AH in women with SD was 4.35-fold higher (95.0%CI:1.29-14.59; $p<0.05$) and it was 2.69-fold higher (95.0%CI:1.01-7.15; $p<0.05$) compared to those with good sleep for the first 5 and 10 years of follow-up, respectively. HR of stroke in women with SD was 1.95-fold higher (95.0%CI:1.01-3.79; $p<0.05$) than in those without SD over 16-years of study. Rates of AH incidence were significantly higher in middle and first-line managers and physical labor workers with SD ($p<0.05$). There were tendencies of growth stroke rates in married women with SD having college degree.

Conclusions: The prevalence of SD in women aged 25-64 years is more than 60%. Women with SD had significantly higher relative risk of AH and stroke. Rates of AH development were more likely in managers and physical laborers.

Keywords: sleep disorders, women, risk, hypertension, stroke

Analysis of detection rate of carotid atherosclerosis in the Russian population

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Objective: To evaluate detection of carotid atherosclerosis and the degree of atherosclerotic carotid arteries in the cohort of patients FSI Joint Hospital and Outpatient department of the Executive Office of the President (Presidential Administration) of Russian Federation.

Materials and Methods: Formation of the cohort study was carried out on the rules of formation of the registry. In the present study we included all patients who received outpatient and inpatient examination and treatment on the basis of FSI Joint Hospital and Outpatient department of the Executive Office of the President (Presidential Administration) of Russian Federation in 2013.

Duplex scanning of the carotid artery was the reference method, will serve as a criterion for inclusion in the study, as part of the survey. Thus, 2423 patients were included consecutively in the study, which compiled a database registry of duplex scanning of carotid arteries FSI Joint Hospital and Outpatient department of the Executive Office of the President (Presidential Administration) of Russian Federation (Duplex registry 2013).

Results:

Depending on the absence or extent of atherosclerotic lesions of the carotid arteries, all patients were divided into 5 main groups:

- 1) without the pathology – 199 patients (8.2%);
- 2) stenosing lesion (less than 20%) – 974 patients (40.2%);
- 3) 20-50% stenosis – 1122 patients (46.3%);
- 4) 50-70% stenosis – 100 patients (4.1%);
- 5) more than 70% stenosis, occlusion – 28 patients (1.1%).

It is worth noting also the presence in these patients, additional imaging characteristics, allowed to divide them into additional groups, namely anomalies of structure and especially the location of blood vessels – 67 patients, misalignment of vertebral arteries – 609 patients, post-operative treatment – 19 patients.

Conclusions:

We have noted more than the official data, the incidence of carotid atherosclerosis in the national population register on the example of the patients of our hospital.

Stenotic lesions and significant stenosis were registered, respectively, 51.6% and 5.3% of patients according to their own research.

All this points to the possibility of the method of routine use of duplex scanning of carotid arteries for the early detection of pre-clinical atherosclerosis, its effectiveness as a screening method for coating the pathogenesis induced by lipid-lowering therapy to a wider audience of patients

Keywords: carotid atherosclerosis, duplex scanning, early detection, pre-clinical atherosclerosis

Cardiovascular morbidity and mortality in ankylosing spondylitis and psoriatic arthritis, results of 10-year prospective controlled single-center study

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Current data about cardiovascular (CV) morbidity and mortality in ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are contradictory. The aim of the study was to evaluate CV morbidity and mortality in patients with AS and PsA.

Methods: 676 patients with AS and PsA, without CV diseases at entry, were involved in 2004-2005 years. 160 randomly selected healthy individuals included like controls. In 10 years of follow-up a new CV events (cardiac death, angina, myocardial infarction (MI), stroke, arterial hypertension (AH), arrhythmias or conductive disturbances) were recorded. Statistical analysis was performed using SPSS17.

Results: 313 patients and 10 controls loss the follow-up during 10 years, 363 patients had 10-year results (278 patients with AS, 85 - PsA). Mean age \pm SD at the time of the entry was 40.0 ± 11.4 years in AS, 40.55 ± 10.6 in PsA, 39.0 ± 11.2 in controls, $p \geq 0.05$ for all. 76.3%, 48.2%, and 56% were male in AS, PsA patients, and controls, respectively ($p < 0.01$ for difference between PsA and AS, other groups were matched, $p \geq 0.05$). Smoking was frequently occurred in AS (68% vs. 42% in PsA and with 39% in controls).

Totally, during 10 years of follow-up angina recorded in 57 (15.7%) patients, MI - in 41 (11.3%), stroke - in 9 (2.47%), AH - in 200 (55%), arrhythmias - in 55 (15.2%), conduction disorders - in 48 (13.22%) patients, 9 (2.47%) patients and 0 controls died.

MI occurred in 28 patients with AS (RR 1.77; 95% confidential interval (CI) 1.5 - 2.1), in 14 patients with PsA (RR 4.3, 95% CI 2.5 - 14.5), in 3 controls (RR 1.24 95%, CI 0.96 - 1.59, compared with the population). The risk of MI in patients with PsA exceeded risk in controls OR 6.7, 95%CI 3.05 - 12.44, $p < 0.0001$, in AS - exceeded risk compared with controls OR 2.5, 95%CI 1.39 - 4.51, $p < 0.0001$.

AH recorded in 132 patients with AS (RR 2.23, 95%CI 1.6 - 3.1), in 56 patients with PsA (RR 3.09, 95% CI 2.19 - 4.35) and in 32 controls.

In AS died 2 patients, mortality comparable with that in the control group HR 4.6 (95% CI 0.4 - 10.6). 7 PsA patients died - HR 8.0 (95%CI 5.7-16.1) compared to controls and HR 9.9 (95%CI 6.0 - 18.1) compared to AS.

Conclusion: Cardiovascular mortality in AS is comparable to population level. Mortality in patients with PsA is higher, than in healthy controls and in AS. The incidence of angina, MI, AH in patients with AS and PsA exceed the incidence in healthy controls and in population.

Keywords: Cardiovascular morbidity, Cardiovascular mortality, Spondyloarthritis, Ankylosing spondylitis, Bechterev's disease

The association of nut consumption with cardiovascular mortality and coronary heart disease risk in women

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Background: Recent epidemiological studies suggest that frequent nut consumption may be protective against coronary heart disease, primarily due to beneficial effects on serum lipids.

Objectives: We sought to examine whether frequency of nut consumption is associated with cardiovascular (CVD) mortality in a large cohort of women. A secondary aim was to examine whether nut consumption is associated with incident coronary heart disease (CHD) in this population.

Methods: We studied 39,167 women from the Women's Health Study (WHS) who did not have cardiovascular disease at baseline. Nut consumption (peanut butter, peanuts and other nuts) was self-reported at baseline in the food frequency questionnaire. CVD deaths and incident CHD (fatal and nonfatal myocardial infarction, coronary artery bypass grafting, and percutaneous transluminal coronary angioplasty) were ascertained via follow-up questionnaires, medical records, and adjudicated by the WHS endpoint committee.

Results: Participants had a mean age of 54.6 years, range (38.7-89.9). During a mean follow-up of 18.9 years, 959 CVD deaths and 1,774 incident CHD events occurred. In a multivariable Cox regression model adjusting for age, smoking, alcohol use, physical activity, postmenopausal status and family history of premature myocardial infarction in a parent, the hazard ratio for CVD mortality was 0.96 (95% CI: 0.81-1.13) for the nut consumption of 1-3 times/month, 0.94 (95% CI: 0.78-1.20) for nut intake of 1 time/week, and 0.90 (95% CI: 0.74-1.10) for nut consumption of ≥ 2 times/week when compared to women who did not consume nuts (p linear trend = 0.25). In a secondary analysis, nut consumption was inversely associated with incidence of CHD: multivariable adjusted HRs (95% CI) for CHD were 1.0 (ref), 0.96 (95% CI: 0.85-1.09), 0.93 (95% CI: 0.81-1.06) and 0.86 (95% CI: 0.74-0.99) for nut consumption of 0, 1-3 times/month, 1 time/week, and ≥ 2 times/week, respectively (p trend = 0.037). Further adjustment for dietary variables such as fiber, fruits, and vegetables did not significantly alter the effect estimates.

Conclusion: This study suggests that nut consumption is not associated with cardiovascular mortality in apparently healthy women. However, our secondary analysis is consistent with a lower risk of CHD with nut consumption in women.

Keywords: nut consumption, cardiovascular mortality, coronary heart disease risk

The 4-year follow-up of medications compliance in patients after elective percutaneous coronary intervention with drug-eluting stent (data from OPTIMA II study)

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Background/Introduction: OPTIMA II is an observational study that was planned as a follow-up of the OPTIMA study of patients who took statins at baseline and underwent elective percutaneous coronary intervention (PCI) with a drug-eluting stent (DES).

Purpose: The main objective of OPTIMA II was to estimate the rate of major adverse cardiovascular and cerebrovascular events (MACCE) in patients 4 years after PCI who were taking statins at baseline. One of the secondary objectives of the OPTIMA trial was to evaluate the proportion of patients who discontinued statin therapy, beta-blockers and angiotensin-converting-enzyme (ACE) inhibitors therapy and identify their characteristics in patients were taking 4 years after PCI.

Methods: OPTIMA II (NCT02099565) – follow-up of Russian observational study OPTIMA that included 543 patients, i.e. 90.2% of patients participated in the OPTIMA study (n=602).

Results: The OPTIMA II population comprised Russian patients with stable coronary artery disease (CAD) who underwent PCI (80.5% men; mean age, 64.75±9.33 years). At the time of enrolment in OPTIMA II study (4.42±0.58 years after PCI and an inclusion in OPTIMA study), 75.5% of patients were being treated with a statin during follow-up; 24.3% of patients had discontinued statin intake during 4 years after PCI. Only 7.7% of patients achieved target LDL-C level <1.8 mmol/L (mean LDL-C level was 2.8 mmol/L). The most frequently taken statins were atorvastatin (283 [52.1%] patients; mean daily dose [MDD], 18.3 mg), rosuvastatin (89 [16.4%] patients; MDD, 13.5 mg), and simvastatin (31 [5.7%] patients; MDD, 18.4 mg). Five patients were taking pravastatin, and 1 patient was taking fluvastatin. The most common classes of concomitant medications were the following: antiplatelets (394 [72.56%] patients [most frequently administered was aspirin, 377 (69.43%) patients]), selective beta-blocking agents (318 [58.56%] patients [most frequent was bisoprolol, 258 (47.51%) patients]), angiotensin-converting-enzyme inhibitors (213 [39.23%] patients [most frequent were perindopril, 90 (16.57%) patients, and enalapril, 69 (12.71%) patients]), dihydropyridine calcium blockers (121 [22.28%] patients [most frequent was amlodipine, 105 (19.34%) patients]). Angiotensin II receptor antagonists were being taken by 65 (11.97%) patients.

Conclusions: The majority of patients received the standard therapy for stable CAD post PCI. However, guidelines are not being followed appropriately in these high risk patients. About 1/4 patients had discontinued statins by 4 years after PCI. Most patients took low doses of statins, and LDL-C target level <1.8 mmol/L was achieved in only 7.7% patients. Compliance with antiplatelet therapy was unsatisfactory.

Keywords: coronary artery disease, percutaneous coronary intervention, statins, concomitant medications

Hemodynamic parallels between erectile dysfunction and diastolic dysfunction of left ventricle

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Introduction: Recent studies show the link between erectile dysfunction (ED) and cardiovascular diseases, particularly coronary heart disease.

Materials and methods: For clarifying this we examined 126 men complaining ED (mean age 42.6 ± 6.8 years) who underwent a standardized diagnostic management for ED (EAU guidelines, 2015). We also performed cardiological investigation including Echocardiography with Doppler exercise tolerance test, Holter monitoring.

Results: It was found moderate correlation between peak systolic blood flow velocity in the cavernous bodies of the penis (V_{max}) and maximal velocities of early and late left ventricular filling (E/A). The correlation coefficient = 0,568 (95% CI: 0,417 – 0,688). The level of significance of $P < 0.0001$. We also Identified a weak correlation between the resistance index of the cavernous artery (RI) and maximal velocity of early and late left ventricular filling (E/A). The correlation coefficient = 0,2327 (95% CI: 0,037 – 0,4112). The level of significance $P = 0,0204$.

We Identified a weak correlation between the resistance index (RI) in the cavernous arteries of the penis and the deceleration time of early diastolic filling (DT). The correlation coefficient = 0,2341 (95% CI: 0,03848 – 0,4125). The level of significance $P = 0,0197$.

Conclusion: Our results show that vasculogenic erectile dysfunction, confirmed by Doppler study of the corpora cavernosa was significantly correlated with the presence of diastolic dysfunction of the left ventricle.

Keywords: erectile dysfunction, coronary heart disease, atherosclerosis

How important is health for young people? – The health care scales' results among young participants of Woodstock Festival Poland

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It is well known that aging increases the risk of diseases of civilization. Therefore, the percentage of young people who suffer from these problems is small compared to elderly people. Young people often think if they are not suffering from chronic diseases they do not have to worry about their health. However, many studies confirm that the initiation of healthy lifestyle (including physical activity and a well balanced diet) may delay the consequences of chronic diseases, such as: diabetes, cardiovascular disease, hypertension. There is a great need to find an effective way of educating young people in this field. We need to ask the question: how important is health for young people? This study helps to provide an answer. The aim of our study was to investigate the level of health concern among young Polish people.

The patients involved in the project were the participants of the Woodstock Festival Poland (30 July – 1 August 2015, Kostrzyn, Poland). A sample of 1316 Polish people aged 18-35 (750 men and 566 women) participated in this study. In order to evaluate the level of health concern, the Health Concern Scale (HCS), which was developed by Kähkönen and Tuorila, was used. The questionnaire allows to assess how much young people are afraid of chronic diseases (diabetes, cardiovascular disease) and how much they are afraid of negative effects of their diet.

The results revealed a significant positive correlation between health concern and body mass index (BMI) ($p < 0,01$). We also found a significant correlation between sex and health concerns. Women were more afraid of their health than men ($p < 0,05$). Furthermore, we can see the positive correlation between health concerns and age ($p < 0,05$). We observed that men were less worried about their health if they lived in a smaller city ($p < 0,06$). The opposite trend was observed in women. We noticed a positive correlation between the level of education and health concerns among both women and men ($p < 0,06$). It was observed that the bigger the waist circumference the greater the health concerns.

Women pay more attention to their health than men and they show this tendency lifelong. Their fear increases when they with the increase of waist circumference and body mass index. Men begin to worry more about health only when they are older or when they have problems with overweight and obesity. It seems that it would be worthwhile to start health education directed especially at young men.

Keywords: health care, young people, population, education, epidemiology

Carotid plaques, intima-media thickening and 10-year risk of cardiovascular outcomes and mortality in a Russian population sample

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Purpose. Carotid intima-media thickness (CIMT) is a sensitive marker of early atherosclerotic lesion and carotid plaques present established predictor of cardiovascular (CVD) risk. The differential in prognostic significance of carotid plaques and intima-media thickening for CVD risk is discussed. We aimed to study the predictive significance of carotid intima-media thickening and plaques in relation to cardiovascular outcomes and all-cause mortality in Russian population cohort.

Methods: The random population sample (491 men, aged 18-64 years, predominantly of Caucasian ethnicity) from Novosibirsk (Russia) was examined by high-resolution carotid ultrasonography and standard epidemiological methods. We performed PC-assisted automatic measurement of carotid intima-media thickness (CIMT) at the far wall of distal common carotid arteries and identified the presence of carotid plaques elsewhere. Population-based cohort of 372 men aged 35-54 at baseline were followed-up on the average for 10 years, participants with CVD at baseline were excluded from further analysis. Incident cases of myocardial infarction (MI) and stroke (STR), deaths from CVD and all-cause death were registered as end points. Cox-regression was applied for analysis in age- and multivariable-adjusted models (controlled for age, blood pressure, smoking, body mass index, total and HDL cholesterol, triglycerides, physical activity, alcohol consumption).

Results: The average CIMT in population male sample was of 0.64 mm (SE0.01), the prevalence of carotid plaques was of 28.6 %, both indicators consequently increased with age. Combined phenotype "carotid artery atherosclerotic disease" (CAAD) was defined by presence of multiple plaques and/or by intima-media thickening (CIMT \geq 0.9 mm); the prevalence of CAAD comprised 21.4%. Over the follow-up period the CAAD increased the age-adjusted risk of incident myocardial infarction by more than three times (RR=3.4; 95%CI: 1.0-11.79; p=0.039) and the risk of death from all causes by six times (RR=6.3; 95%CI: 2.86-14.0; p<0.001). The presence of plaques, as separate phenotype, was associated with increased risk of incident MI (RR=3.5; 95%CI: 1.0-12.56, p=0.036), death from incident CVD (RR=6.0; 95%CI: 1.43-24.96, p=0.005) and all-causes death (RR=7.5; 95%CI: 3.62-15.65, p<0.001) in age-adjusted model. After controlling for conventional risk factors, the RR coefficients comprised 1.7 (95%CI: 0.31-9.22) for MI and 2.0 (0.81-4.75) for all-cause death, however the estimates were reduced to statistically insignificant. We did not reveal association between CIMT, as a separate phenotype, and CVD outcomes.

Conclusion: In Novosibirsk cohort carotid plaques combined with thickening of intima-media strongly associated with the risk of cardiovascular outcomes and mortality. Carotid plaques appeared to be more powerful predictor of cardiovascular events and mortality compared to CIMT thickening, that is consistent with the recent data from other populations. In studied sample, the excess risks might be substantially explained by the effect of conventional risk factors clustered in subjects with atherosclerotic lesion.

Keywords: Carotid intima-media, Atherosclerotic plaques, Cohort, Cardiovascular risk

Physical activity monitoring in population-based sample of Saint Petersburg inhabitants

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Introduction: Physical inactivity is leading risk factors for global mortality. Current research shows that only objective measurement of physical activity may provide accurate information on this parameter. The aim of our study was to assess the 7-day physical activity monitoring using triaxial accelerometers in a random sample of Saint-Petersburg inhabitants.

Design and methods: As a part of all-Russian epidemiology survey ESSE-RF a random sampling of 1600 Saint-Petersburg inhabitants (25-65 years) stratified by sex and age was involved. After that, a random sub-population of 100 subjects was selected. Questionnaire regarding education, occupation status, physical activity level and nutrition habits was filled in; anthropometry, blood pressure measurement, biochemistry were performed. Actigraph GT3X+ (Actigraph LLC, USA) accelerometer and physical activity (PA) diary were used in order to evaluate physical activity for 7 days. Adequate levels of physical activity were defined as more than 10 000 steps/day and at least 150 minutes/week of moderate and vigorous physical activity (MVPA) in bouts of 10-minutes or more.

Results: About 30% of subjects were physically active according to MVPA time criteria and a half – to steps count criteria. According to PA diaries, in most of cases physical inactivity was related to the usage of private or public transport. Almost 50% of physically active subjects had balanced workweek-weekend PA profile, and the same criterion is true only for 13% of subjects in inactive group, without body composition, gender or occupation differences. In both groups the same peaks of MVPA were revealed – at 8.00-9.00 and 18.00-19.00, which are typical transportation time, but in active group these peaks were significantly higher.

Conclusion: The type of occupation, sex or age did not determine the physical inactivity. Objective measurement have shown, that 40%-60% of subjects were physically inactive, and it was mainly caused by usage of cars in the morning and evening transportation time, rather than walking. So, 150-min MVPA goal can easily be achieved by only increasing walking time during transportation peaks.

Keywords: Physical activity level, triaxial accelerometer, objective measurement, hypodynamia

Prevalence and clinical features of diabetes and prediabetes in patients with hypertension in Korea: a nationwide community study

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Background: Although prediabetes and hypertension are major components of metabolic syndrome, there is no reported data on the prevalence of prediabetes (FBS 100-125mg/dL or HbA1c 5.7-6.4%) in hypertensive patients. We evaluated the prevalence and characteristics of prediabetes among hypertensive patients treated at primary clinics in Korea.

Methods: Anthropometric, hemodynamic and laboratory tests were done for 3109 patients who participated in the Wonder study which is a nation-wide, multi-centered, cross-sectional study. Risk factors and comorbidities according to diabetes status tertiles (normal, prediabetes and diabetes) were identified using multilevel logistic regression models.

Results: The overall prevalence of normal, prediabetes and diabetes in patients with hypertension was 21.8%, 48.7 and 29.5%, respectively. Smoking is significantly less in prediabetes and diabetic patients compared to normal glucose hypertensive subject. However, Risk factors (high waist circumference and serum triglycerides, and low serum high-density lipoprotein), and subclinical organ damages such as LVH and microalbuminuria, and coronary artery disease, CKD and peripheral arterial disease were significantly increased as increasing diabetes status tertiles.

Conclusion: Epidemiological factors of the prediabetes in hypertension patients showed higher CV risk factors and CV comorbidities. Almost half adults in Korean hypertensive patients was found to have prediabetes. We should have action to prevent prediabetes to be diabetes through better detection, awareness, prevention and treatment.

Keywords: prediabetes, hypertension, prevalence, risk factor, comorbidity

Comparison of lipid profile of 617 professional ice hockey players with non-athletes

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Background: The benefits of regular exercise, physical fitness and sports participation on cardiovascular and metabolic health are undeniable. Physical activity produces beneficial effects on cholesterol levels. But a comprehensive comparative analysis of the lipid spectrum of elite ice hockey players and general population has not been conducted.

Purpose: To compare lipid profiles of Russian male professional ice hockey players and populational data from WHO MONICA and Russian LRC Study (two large Russian epidemiological projects).

Methods: 617 healthy male elite ice hockey players from Continental hockey league (the biggest sports league in Eurasia) aged 20-40 years (mean – 22 y.o.) were included, and divided into 4 age groups: Ist group (21-25 y.o., N=253), IInd group (26-30 y.o., N=208), IIId group (31-35 y.o., N=121) and IVth group (36-40 y.o., N=35). Height, weight, BMI, serum levels of total cholesterol, triglycerides, HDL- and LDL-cholesterol during clinical preseasonal baseline testing were measured. The same data for the same age groups from the WHO MONICA project and Russian LRC database (Moscow and St-Petersburg) were obtained (n=4275 males): Ist group (N=651), IInd group (N=1232), IIId group (N=1105) and IVth group (N=1287).

Results: Professional hockey players from all age groups had higher height ($p < 0.0001$), weight ($p < 0.0001$) and BMI ($p < 0.0001$), serum levels of HDL (mmol/l) (Ist group 1.47 ± 0.03 vs 1.32 ± 0.01 , $p = 0.0001$; IInd group 1.51 ± 0.04 vs 1.35 ± 0.01 , $p = 0.0002$; IIId group 1.55 ± 0.05 vs 1.37 ± 0.01 , $p = 0.0004$, IVth group 1.63 ± 0.08 vs 1.36 ± 0.01 , $p = 0.0015$) and lower serum levels of total cholesterol (mmol/l) (Ist group 4.42 ± 0.06 vs 4.67 ± 0.03 , $p = 0.0011$; IInd group 4.82 ± 0.07 vs 5.00 ± 0.03 , $p = 0.0216$, IIId group 5.13 ± 0.09 vs 5.39 ± 0.03 , $p = 0.0083$, IVth group 5.14 ± 0.15 vs 5.59 ± 0.02 , $p = 0.0047$) and LDL (mmol/l) (Ist group 2.31 ± 0.08 vs 2.94 ± 0.04 , $p < 0.0001$; IInd group 2.78 ± 0.09 vs 3.17 ± 0.03 , $p < 0.0001$, IIId group 3.24 ± 0.12 vs 3.49 ± 0.03 , $p = 0.0444$, IVth group 2.96 ± 0.21 vs 3.67 ± 0.03 , $p = 0.0010$). There were no differences in serum triglycerides levels (mmol/l) (Ist group 0.95 ± 0.04 vs 0.91 ± 0.03 , $p = 0.507$; IInd group 1.07 ± 0.05 vs 1.04 ± 0.02 , $p = 0.592$, IIId group 1.05 ± 0.02 vs 1.16 ± 0.07 , $p = 0.1641$, IVth group 1.01 ± 0.12 vs 1.24 ± 0.01 , $p = 0.0526$).

Conclusion: As expected professional ice hockey players from all age groups had higher body size including BMI and more favorable lipid profile as compared with general population. Surprisingly lifestyle with regular strenuous aerobic physical training did not significantly affect blood level of triglycerides.

Keywords: lipid profile, competitive sport, population study, preseason testing, triglycerides

Current cardiovascular risk factors estimate in a representative population of Casablanca (Morocco)

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Background: Worldwide, Cardiovascular diseases (CVD) have been the leading cause for mortality in the last decades. Controlling the modifiable CVD risk factors has reduced mortality, but risk factors levels can change and need continuous monitoring. This study aims to provide current estimates of prevalence of these cardiovascular risk factors in a representative population of Casablanca.

Methods: Our study concerned 364 subjects, 225 women and 139 men that were aged from 18 to 70 years old. The analyses were based on data from a health and lifestyle questionnaire with sociodemographics characteristics, medication intake, medical history and lifestyle. Our population was subdivided into three groups: Obese, overweight and a control group. Then an anthropometric measurements (waist circumference, waist to-hip ratio, blood pressure, BMI) and a lipid profile (TC, HDL, LDL, and TG) were assessed.

Results: The mean-age was 54.31 ± 10.61 years old and 58.8% were female; waist to-hip ratio and waist circumference showed increasing numbers in obese and overweight in comparison to normal subjects, the prevalence of diabetes was higher in obese 17.52% and overweight 16.95%. On the other hand, the prevalence of high atherogenic index of plasma was present especially in obese and overweight patients that was respectively 30.74% and 28.73%. The prevalence of hypercholesterolemia was 9.77% in obese, 11.20% in overweight and 2.87% in normal BMI subjects. Physical activity practicing was higher (43.5%) in overweight group in comparison to the obese and control groups (40.9% and 15.4%), we noted too that the patients with physical activity showed a decreasing level of TC and diastolic blood pressure. The prevalence of diabetes in the three groups was respectively 1.6, 15.1, and 9.9%. The prevalence of HTA 12.1, 6.6, and 16.8%, respectively. The prevalence of diabetes associated to HTA was 10.4, 7.4 and 6.3% respectively. Last but not least, we observed that 26%, 13.8% and 6% had respectively three, four and six cardiovascular risk factors whereas 1.4% had none. We noticed too that women had more cardiovascular risk factors (61.49%) than men (38.51%).

Conclusion: There is a high prevalence of cardiovascular risk factors in this population of Casablanca, which is due to unhealthy habits like sedentary life style, diabetes and/or hypertension. These results lead us to initiate the alarm signal to be more perspicacious, and to manage national programs in order to investigate for planning, execution, and assessment of cardiovascular disease.

Keywords: Cardiovascular diseases, risk factors, lipid profile, BMI

Lipoprotein (a) and apolipoprotein (a) phenotypes in healthy Macedonian children

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Background: High lipoprotein(a) [Lp(a)] level predicts risk of early atherosclerosis independently of other cardiac risk factors. Plasma levels of Lp(a) are determined largely by genetic variation in the gene encoding apolipoprotein(a) [apo(a)], the unique protein component of Lp(a). High plasma levels of Lp(a) increase the risk of premature atherosclerosis. However, the association of apo(a) phenotypes with the development of these diseases remains largely unexplored.

Material and Methods: One hundred healthy children (51 boys, 49 girls), aged 9-18 were included in the study. Lp(a) and apo(a) isoforms were determined in apparently healthy children selected from families with: premature cardiovascular disease, familial hypercholesterolaemia, family history of premature cardiovascular disease and family history of elevated lipoprotein (a).

We used 3-15 % gradient SDS-PAGE for separation of apo(a) isoforms. According to the different apo (a) electrophoresis motilities, Apo (a) was classified into five single and respective double-band phenotypes. Nephelometry technique was used for determination of Lp(a) concentration.

Results: Each individual expressed a single (homozygotic), double-band (heterozygotic) or no band (null phenotype). The apo(a) phenotype frequencies revealed that the frequency of single-band phenotype expression (64 %) was higher than that of double bands (32 %) and that the frequency of phenotypes representative of low molecular weight was very low (4%). The most frequent phenotype was S4 (42.65%). The distribution of plasma Lp(a) levels was skewed, with the highest frequencies at low levels. The mean Lp(a) concentration was 11.95 (SD of 5.98 and median of 9.62 mg/dL). We did not find differences in the mean and median plasma Lp(a) levels between boys and girls ($p > 0.05$). A strong inverse relationship was found between the apparent molecular weight of apo(a) phenotypes and plasma Lp(a) concentration ($r = -0.4257$).

Conclusion: Recommendation is that all children should be screened for cholesterol between the ages of 9 and 11. Lipoprotein(a) levels should be considered in particular in children with a family history of early heart disease or high blood cholesterol levels. Unfortunately, there have not been enough studies to determine which therapies might be beneficial. Determination of Lp(a) levels and apo(a) phenotypes in children, may help in preventing and reducing the risk of atherosclerotic development.

Keywords: Lp(a), apo(a), cardiovascular risk

Diabetes Awareness Among Coronary Artery Disease Patients Differs Significantly Between Men and Women

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We aimed at investigating diabetes awareness among men and women with established coronary artery disease (CAD).

We enrolled a total of 814 consecutive patients with angiographically proven CAD, 587 men and 227 women. Fasting glucose and HbA1c were measured and oral glucose tests were performed in all patients who did not report a history of diabetes.

Overall, 74 men and 28 women (12.6 and 12.3%, respectively) reported a history of diabetes. Based on glucose criteria only (fasting plasma glucose ≥ 126 mg/dl or glucose ≥ 200 mg/dl two hours after a 75g oral glucose challenge), diabetes was newly diagnosed in 33 men and 3 women (5.6 and 1.3%, respectively); when also HbA1c values $\geq 6.5\%$ were considered for diabetes diagnosis, diabetes was newly diagnosed in 67 men and 13 women (11.4 and 5.7%, respectively). Thus, among those with diabetes, the proportion of newly diagnosed diabetes was higher in men than in women both when only glucose criteria and also when additionally the HbA1c criterion was applied for the diagnosis of diabetes (30.8 vs. 9.7%; $p=0.007$ and 47.5 vs. 31.7%; $p=0.014$; respectively).

We conclude that among CAD patients with diabetes significantly more women than men are aware of their condition.

Keywords: diagnosis, type 2 diabetes mellitus, epidemiology, coronary artery disease, gender

Familial hypercholesterolemia

The prevalence of heterozygous familial hypercholesterolemia in the West Siberian region of the Russian Federation

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Background: The prevalence of familial hypercholesterolemia (FH) in Russia has not previously been evaluated. The aim of our study is to investigate the prevalence of FH in the population of the West Siberian region of Russia, and then estimate the frequency of coronary artery disease (CAD) and treatment with cholesterol-lowering medication in FH patients.

Methods and materials: The sample of our study consisted of participants from The Epidemiology of Cardiovascular Risk Factors and Diseases in Regions of the Russian Federation Study (ESSE-RF), led in the Tyumen and Kemerovo regions. The samples from Tyumen and Kemerovo regions included 1,630 and 1,622 people, respectively, aged 25-64. Data including information about CAD and myocardial infarction (MI) was obtained from questionnaires. All participants who had LDL-cholesterol higher than 4.9 mmol/l (142 and 138 persons from Tyumen and Kemerovo regions, respectively) and who had LDL-cholesterol lower than 4.9 mmol/l but had statin therapy (10 and 71 persons from Tyumen and Kemerovo regions, respectively) were examined and interviewed by experts in FH additionally. The diagnosis of FH was determined using the Dutch Lipid Clinical Network Criteria.

Results: In the West Siberian region, the prevalence of patients with definite FH was 0.24% (one in 407), probable FH was 0.68% (one in 148), definite or probable FH combined was 0.92% (one in 108), and possible FH was 7.07% (one in 14).

40% of patients with definite or probable FH combined in the Tyumen and Kemerovo regions had CAD. Most of these patients had early onset of CAD. Hence, only 23% of patients with definite or probable FH were on statins.

The adjusted for age, gender, and region odds ratio for CAD was 4.31 (95% CI: 1.99, 9.33) ($p < 0.0001$) for individuals with definite or probable FH relative to those with unlikely FH. The adjusted odds ratio for MI was 7.49 (95% CI: 1.61, 34.88) for persons with definite or probable FH relative to those with unlikely FH. The adjusted odds ratio for CAD and MI for patients with possible FH was not significant.

Conclusions: The prevalence of heterozygous FH in the West Siberian region is one in 108. The prevalence of FH in Russia may be significantly higher than previously estimated. There is underdiagnosis and undertreatment of FH in Russia.

Keywords: familial hypercholesterolemia, prevalence, coronary artery disease, statin

Myocardial infarction regional register use for targeted screening of familial hypercholesterolemia

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The research aim has been to determine the possibilities of using the regional register of the patients who underwent myocardial infarction (MI) for targeted screening of their familial hypercholesterolemia (FH).

Materials and methods. The regional register is a specially developed web-application, where the major clinical data about all patients who were admission in the hospitals with acute MI (ICD-10: I21, I22) is included and fixed. In 2014 year, the regional register contained data on 3603 patients, and among them, there were selected data on 3426 (95.1%) patients with first MI in current year. To find the index patients the selected criterion was MI development before the age of 50 years. Comparison of quantitative variables was performed by using the Mann-Whitney test, while quality ones by χ^2 test. Confidence intervals (CI) for the rates were calculated using the modified Wald method.

Results. There has been found that 315 (9.2%) patients before the age of 50 years suffered from developed MI. The average age of patients with MI arose before 50 and after 50 years was respectively 44.1 ± 6.5 years old and 68.9 ± 10.2 years ($p < 0.0001$). The analysis has showed that among patients with early onset MI there were significantly more men (286 (91%) vs 1813 (58%); $p < 0.0001$).

Patients with early MI were significantly less frequently suffering from hypertension (191 (61%) vs 2288 (74%); $p < 0.0001$), diabetes (17 (5.4%) vs 408 (13.1%); $p < 0.0001$), arterial fibrillation (4 (1.3%) vs 254 (8.2%); $p < 0.0001$), heart failure (117 (37%) vs 1381 (44.4%); $p = 0.0131$), and they less frequently had a history of previous MI (17 (5.4%) vs 305 (9.8%); $p = 0.0106$) or stroke (2 (0.6%) vs 148 (4.8%); $p = 0.0011$).

Patients younger than 50 years less frequently anterior MI (166 (53%) vs 1873 (60%); $p < 0.0001$). More than that, this category of patients has been found to be more often admission to the hospital on the first day of the MI development (234 (74%) vs 1980 (64%); $p = 0.0002$), they have often been performed by fibrinolysis (511 (16.2%) vs 355 (11.4%); $p = 0.0126$) and coronary interventions (67 (21.3%) vs 216 (6.9%); $p < 0.0001$). Older than 50 years patients have had significantly higher ratio MI class III-IV severity according to Killip (856 (27.5%) vs 67 (21.3%); $p = 0.0170$), hospital mortality (445 (14.3%) vs 18 (5.7%); $p < 0.0001$) and hospitalization duration (13 (10-15) vs 12 (9-14) days; $p = 0.0442$).

Generally, regional target screening could have observed the rate of patients with early MI as 297 (10.0%, 95% CI 9.0-11.2%) people without taking into account the dead. A 271 overwhelming number of men (91%, 95% CI 87.4-94%) has been presented among this category. As for the other risk factors 181 (61%, 95% CI 55.3-66.3%) cases have marked hypertension, 16 (5.4%, 95% CI 3.3-8.6%) – diabetes, 1 (0.34%, 95% CI 0-2.1%) case – has fixed a previous stroke, and 16 (5.4%, 95% CI 3.3-8.6%) cases – have marked a previous MI.

Conclusion. MI unified regional register use, which contains all the necessary personal data, provides an easy, reliable and permanent on-line search of index patients for the targeted screening FH.

Keywords: familial hypercholesterolemia, myocardial infarction, targeted screening, web-register

Familial Hypercholesterolemia (FH): Efficiency and Safety of the Treatment by LDL aphaeresis: “Lebanese Experience”

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Objectives: In Lebanon, Familial Hypercholesterolemia FH shows an incidence about 25 times higher than in Europe, Homozygous FH has estimated prevalence between 20 to 30 cases per one million inhabitants (Lebanese population: 4,7 million). This high prevalence is due to intermarriage between family members (e.g. cousins) in isolated villages. There are currently 45 FH patients regularly treated to achieve better quality of life by reduction co-morbidity and mortality from cardiovascular events.

Method: More than 9,500 sessions were performed until July 2011 for adults and children. 45 patients are regularly treated twice a month. 10 y.o. no patients, 16% are between 10-18 y.o. (7/45 pats.), 64% are between 19-35 y.o. (29/45 pats.), 18% are between 30-60 y.o. (8/45 pats.), 2% are older than 60 y.o. (1 pat.). The sex distribution is: 19/45 male and 26/45 female. 91% of the patients are homozygous (41/45 pats. with Low Density Lipoprotein LDL-cholesterol level >600mg/dl at date of arrival to the center) 9% of the patients are severe heterozygous (4/45 pats.). All the patients have severe hypercholesterolemia with LDL-C levels ranging from 420 mg to appx.900mg/dl despite conservative treatment (diet, resin, ezetimib, statins, MenaQ7 & Q 10 and omega 3).

All of them have multiple xanthomas and ~2/3 of the patients have a lipid corneal arch. 9 of the patients lost family members due to CAD.

In 1996 LDL apheresis was approved by the Food and Drug Administration FDA as a treatment for use in patients who despite diet and maximum tolerated drug therapy have: LDL-C higher than 300 mg/dl in the absence of Coronary Heart Disease CHD and higher than 200 mg/dl when CHD is present. The procedure is usually performed in regional centers.

Results: An average of 64-65 % of Acute LDL-C reductions was observed in all 7 infants and 15/29 adults patients for a total of ~1540/2532 sessions

- 1-No deaths during sessions
- 2-Overall physical improvement in the patients
- 3- Disappearance of the angina and dyspnea
- 4-Net regression of xanthomas and xanthelasmas
- 5-Reduction of coronary events
- 6-Better exercise tolerance
- 7-Better Quality of Life
- 8-All the patients approved and accepted the concept of a chronic apheresis treatment without any psychological problems and without fistula operations
- 9-No serious adverse effects were observed
- 10-LDL-C reduction averaged 64-65%(compared with 58 % LDL-reduction in 2008)
- 11- The long-term reduction of LDL-Cholesterol induced reduction of the cardio-vascular CV events and decrease the morbidity of the patients
- 12-Direct Adsorption of Lipoproteins system of safe well tolerated, effective and a simple way to reduce LDL-C in patients not responding adequately to drug therapy
- 13-LDL apheresis gives good long-term results both in adults, infants and in children.

Conclusion: LDL apheresis induced reduction of CV events in FH patients and may be an effective treatment for other vascular diseases including cholesterol embolic disease, focal segmental glomerular sclerosis, sudden hearing loss, and age-related macular degeneration.

The development of FH screening in Hungary

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Recent studies indicate that the incidence of FH is higher than we believed before. The estimated prevalence of FH is between 20,000-50,000 patients in Hungary. Unfortunately, the screening of these patients was ineffective previously. About ten years ago, we joined the MedPed program, but the program is not operating; therefore, we started to organize a new FH screening action for experts.

In the first step, a homepage was created to provide information about FH both for the lay population and the experts. The homepage includes also the Hungarian FH registry, which is based upon the Dutch criteria: GPs fill in the patients' data and the program automatically calculates the FH score and the suspected patient are sent to the regional center. The experts of the regional centers make the risk stratification and the final diagnosis of FH; and they also start the suitable lipid lowering therapy for the patients. The experts of the 10 regional lipid centers are responsible for the continuous education of the GPs and the lay people who belong to their centers.

FH screening is coordinated by 2 national coordinators and 5 members of the National Board. National coordinators are responsible for media appearance and regional center education. It is also worth to mention that a pilot study was initialized a month ago with a meeting for the regional centers to inform them about the practicals of FH screening. During this half-year study, we will evaluate the efficacy of FH screening and the experiences of the examiners. On the basis of these data, we may modify the implementation of the FH screening and finally we are planning to introduce this screening in the whole country.

Keywords: FH, FH registry, Dutch criteria

Do lipid peroxidation products contribute to atherosclerotic calcification?

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Background: Cardiovascular diseases, including atherosclerosis, are the leading cause of death in the United States. Atherosclerotic lesions are formed by deposition of lipids in the intima of arteries. Upon exposure to oxidative stresses, low-density lipoprotein (LDL) is converted to highly atherogenic oxidized LDL (ox-LDL) particles, which contribute to disease development and progression. Advanced disease stages may result in calcification of lesions. This calcification process is important, as it has been shown to be associated with stable plaques that are less prone to rupture. Calcification is present in lipid rich domains of lesions and correlates well with overall plaque burden. However, neither the composition of the mineralized calcium deposits nor its relationship to lipid peroxidation is known.

Methods: In this study, the potential of lipid peroxide-derived lipophilic dicarboxylic acid (DCA, e.g. azelaic acid) to promote calcification upon exposure to vascular smooth muscle cells was tested. Using 13-Hydroperoxyoctadecadienoic acid (13-hydroperoxylinoleic acid, 13-HPODE) and thin-layer and gas chromatography–mass spectrometry we characterized the conditions where HPODE is decomposed to aldehyde product 9-oxo-nonanoic acid and its corresponding DCA azelaic acid (AZA).

Results: HPODE treatment resulted in the cellular conversion to ONA and AZA as determined by GC-MS. Both free AZA and intracellular delivery of AZA via lyso phosphatidylcholine (lysoPtdCho) micelles induced calcification of aortic smooth muscle cells, as determined by Von Kossa and alizarin red staining.

Conclusion: These results demonstrate that DCAs may contribute to atherosclerotic calcification thus accounting for the latter's relationship to plaque burden and association with lipids. This study also challenges the dogma that arterial calcification represents the deposition of calcium phosphate. Our future work aims to delineate the association of calcium with lipid rich plaques and lipid oxidation with calcification in animal and human atherosclerosis.

Keywords: Atherosclerosis, Calcification, Lipid peroxidation, Azelaic acid

Familial Hypercholesterolemia: Cascade Screening Diagnostic Impact, a case report

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Introduction: Familial Hypercholesterolemia (FH) is an autosomal disorder inherited in a dominant manner characterized by very high LDL-cholesterol levels (>190mg/dl). It is responsible by 5-10% of all Coronary Arterial Disease below 55 years of age. Familial screening and early diagnosis impact its prognosis.

Goals and Methods: To describe a Cascade Screening performed by medical chart's review

Results: Index case: 28 yo female presenting with effort-related chest pain, dyslipedemia and grade I obesity, In use of 40 mg Simvastatin daily. Physical examination revealed corneal arch and tendom xanthomas. Family history reveals 9 brothers, 2 of which dead by Myocardial Infarction at ages 38 and 42 and 1 sister with known dyslipedemia (as well as the mother). Exams: Total cholesterol (TC) 646 mg/dl; LDL-c 575 mg/dl; HDL-c 50 mg/dl; Triglycerides (Tgy) 107 mg/dl. Functional tests: Ischemia-positive Ergometric test; 2,9% low anterior wall ischemia with ejection fraction of 54% at Myocardial scintigraphy; 40% lesion at medium right coronary artery on cardiac angiography.

Family cases:

71 yo Mother: TC 259 mg/dl; LDL-c 174 mg/dl; HDL-c 66 mg/dl; Tgy 95 mg/dl;

2 yo Daughter: TC 226 mg/dl; LDL-c 132 mg/dl; HDL-c 74 mg/dl; Tgy 95 mg/dl;

4 sisters at ages 47, 42, 53 and 40 years old: TC 231, 242, 167 and 517 mg/dl respectively; LDL-c 134, 182, 109 and 446 mg/dl respectively; HDL-c 74, 49, 40 and 59 mg/dl respectively; and Tgy 114, 53, 84 and 61 mg/dl, respectively (42 yo sister was already on a 80 mg daily Atorvastatin regimen because of TC levels > 400 previous to treatment).

Conclusions: 2 cases of FH (2 sisters), possibly homozygous, were identified from index case. Initial treatment for all cases was 80 mg Atorvastatin and 10 mg Ezetimibe PO daily. We yet await results of this treatment to start lomitapide treatment.

FH cases are estimated in 10.000.000 worldwide, 10% of which are diagnosed and 25% receive appropriate treatment. Effort directed at early case identification of family members with consequent early treatment is a key factor in early prevention of cardiac disease and reduction of death risk in this population.

Keywords: familial hypercholesterolemia, cascade screening, atherosclerosis, coronary artery disease

Analysis of lipid metabolism genes variability in patients with familial hypercholesterolemia in Russia using targeted high throughput resequencing

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Introduction: Familial Hypercholesterolemia (FH) is an inherited disease that is most frequently caused by mutations in the genes encoding the receptor for low density lipoproteins (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin/kexin type 9 (PCSK9) and gene of the low density lipoprotein receptor adaptor protein 1 (LDLRAP1).

Purpose: The study is aimed at analyze of variability of LDLR, APOB, PCSK9 and LDLRAP1 genes in patients with familial hypercholesterolemia in Russia using targeted high throughput resequencing.

Methods: 32 patients with hypercholesterolemia (total cholesterol level >7 mmol/l) were examined in clinical department in 2015 year. Examination included full clinical examination and biochemical analysis (including total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, very low-density lipoprotein cholesterol, APOB, APOA1, CRP, Lp(a)). FH according clinical criteria was identified in 12 patients. The plasma lipid levels were determined by standard enzymatic assays. The genes of APOB, LDLR, LDLRAP1, PCSK9 were analyzed by targeted next-generation sequencing, including all exons and introns of genes. Panel size was 118,50 kb, coverage – 92%.

Results: Mean TC level was 8 ± 1.8 mg/dl in patients with FH. 50% of patients used statins. 42% of patients with FH had xanthomas and 100% had thickened Achilles' tendons. We identified rs5930 (Cys352Tyr), rs121908038 (Leu401His), rs755757866 (Cys340Phe) and rs11669576 (Ala391Thr) SNPs in the coding region of the LDLR gene. All of non-synonymous SNP were presented in heterozygous state.

We found rs505151 (E670G) of the PCSK9 gene in patients with familial hypercholesterolemia in the heterozygous form. Also one FH patient has minor alleles of rs1801701, rs1801703 and rs1367117 of APOB gene and rs11591147 (R46L) SNP of the PCSK9 gene associated with low level of total cholesterol and low risk of myocardial infarction.

All patients had synonymous SNPs in LDLR, PCSK, LDLRA1 and APOB. All patients had many SNPs in introns of APOB, LDLR, LDLRAP1 and PCSK9 genes.

Conclusion: Heterozygous FH was confirmed by molecular-genetics method in all patients. All patients have SNPs associated with high level of lipids.

The reported study was partially supported by RHE, research project No. 14-06-00867.

Keywords: familial hypercholesterolemia, LDLR gene, PCSK9 gene, targeted high throughput resequencing

Genetics

Cytokine gene polymorphisms impact healthy life expectancy and coronary heart disease

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Cardiovascular diseases, and particularly coronary heart disease (CHD), significantly limit the lifespan and are the leading cause of death in the world. Most cases of CHD are caused by atherosclerosis of coronary arteries. Coronary atherosclerosis leads to malnutrition of the heart muscle, causing angina and myocardial infarction (MI). Chronic inflammation is one of the triggers initiating pathological processes in cardiovascular system. It is hypothesized that pro- and anti-inflammatory factors can significantly affect survival and mortality.

The goal of this study was to assess the contribution of polymorphic variants in pro- and anti-inflammatory cytokine genes to survival and mortality in healthy individuals and in patients with MI.

Study group consisted of 426 unrelated men of Tatar ethnic origin from the Republic of Bashkortostan. The group of patients was comprised of 115 patients with myocardial infarction (MI), and 41 cases of sudden cardiac death (SCD) confirmed by autopsy. The control group consisted of 260 individuals aged between 20-100 years without history of cardiovascular disease, including the subgroup of healthy long-livers (90 to 100 years old). DNA was isolated from venous blood lymphocytes by standard phenol-chloroform extraction. Polymorphic markers of *IL6* (-572G/C, rs1800796), *IL10* (-627C/A, rs1800792), *IL12* (-1159A/C) and *TNFA* (-308G/A, rs1800629) genes were analyzed by PCR-RFLP method. Statistical analysis was performed using SPSS V. 13.0. Pair-wise comparison of allele and genotype frequencies in the study groups was performed using Fisher's exact test.

No differences in either genotype or allele frequency distribution of *IL6*, *IL10*, *IL12* and *TNFA* gene polymorphisms were detected between healthy middle-aged men and long-livers. However, we found that the polymorphic markers of pro-inflammatory cytokine genes were associated with MI and SCD. *TNFA**G allele and *TNFA**G/G genotype frequencies were increased in the group of patients with MI compared to the control group ($P < 0.05$). In the SCD group, *IL6**C allele and *IL6**G/C genotype frequencies were increased, while *IL6**G allele and *IL6**G/G genotype frequencies were decreased compared to the control group, patients with MI and long-livers.

The results of our study suggest that *TNFA* (-308G/A, rs1800629) polymorphism is associated with MI, and *IL6* (-572G/C, rs1800796) polymorphism is associated with the risk of SCD in men of Tatar ethnicity, and may contribute to the development of cardiovascular disease, thus limiting life expectancy.

The study was supported by grants RFBR (14-04-01561_a and 14-04-97094_a).

Keywords: life expectancy, cytokine, coronary heart disease, sudden cardiac death, gene polymorphism

Presence of cardiovascular disease and telomere length in middle-aged and older Russians

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Introduction: Shortening of telomere length of replicating somatic cells is believed to be a marker of ageing. Epidemiological studies have suggested inverse associations between leukocyte telomere length and age-related chronic conditions, including cardiovascular disease (CVD), atherosclerosis, hypertension and diabetes, but the link is not firmly established.

Objective: We investigated cross-sectional associations between relative leukocyte telomere length and history of cardiovascular disease and selected risk factors in a subsample of middle-aged and older Russians from a well-characterised population-based urban cohort.

Methods: Leukocyte telomere length was measured by quantitative PCR-based method in 398 men and 365 women aged 45–69 years at baseline in 2002–2005 from the Novosibirsk branch of the HAPIEE (Health, Alcohol and Psychosocial factors In Eastern Europe) study. Self-reported history of physician diagnosed chronic conditions included myocardial infarction, angina/ischaemic heart disease, stroke, hypertension and diabetes (all binary). In addition, prevalent hypertension was defined as >140/90 mm Hg or antihypertensive medication, and prevalence of diabetes was defined as plasma glucose levels ≥ 7.0 mmol/L or treated diabetes. Associations between cardiovascular disease history and risk factors with telomere length as outcome were estimated using multiple linear regression.

Results: Mean relative telomere length was 1.24 ± 0.40 in men and 1.33 ± 0.36 in women (two-sample t-test $p=0.002$). Telomere length decreased substantially with age at the rate of -0.17 s.d. per year ($p=0.001$) in men and -0.15 s.d. per year ($p=0.005$) in women. In age-adjusted models, having raised blood glucose or being treated for diabetes was associated with shorter telomeres in women ($\beta=-0.12$; $p=0.027$). Self-reported hypertension was also inversely associated with telomere length ($\beta=-0.12$; $p=0.023$) only in women. These associations remained significant after additional adjustment for other potential confounders. Although most observed associations were largely in the expected direction, self-reported history of coronary conditions, stroke and diabetes or raised blood pressure were not significantly associated with telomere length in either gender.

Conclusions: In this population sample of middle-aged and older Russians, age was strongly predictive of telomere length which is consistent with the telomere-shortening hypothesis of ageing. Shorter telomeres were found in women with raised blood glucose or being treated for diabetes and in women with a history of hypertension. No significant associations were observed with other measures of cardiovascular disease history or raised blood pressure. Given the low statistical power due to small sample size, our results do not provide strong support for the hypothesis that age-related cardiovascular conditions are independently associated with shortening of telomeres.

Acknowledgments: The study was supported by the Russian Scientific Foundation (grant no. 14-45-00030).

Keywords: Telomere length, Cardiovascular disease, Russia, Ageing

Modern estimation of hypolipidemic efficiency of inhibitors of synthesis of cholesterol by means of pharmacogenetical markers for patients by ischemic heart disease and hyperlipidemias

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Aim: estimation of hypolipidemic efficiency of inhibitors of synthesis of cholesterol by means of pharmacogenetical markers for patients by ischemic heart disease (IHD) and hyperlipidemias (HLP).

Methods: laboratory-instrumental research was conducted to beginning of pharmacological interference, through 4, 8, 24 and 48 weeks of hypolipidemic therapy: anthropometry, determination of lipid spectrum of blood (of total cholesterol (TChol), cholesterol of lipoproteins of high-density (HDL), cholesterol of lipoproteins of low-density (LDL), triglycerides (TG), atherogenic index (AI), realization of daily monitoring of electrocardiography, ultrasonic scan-investigation of vessels, pharmacogenetical testing for determination of allelic variants of genes of Cholesteryl ester transfer protein (CETP), endothelial Nitric Oxide Synthase -3 (NOS-3).

In research 120 men were suffered with IHD (II functional class of stenocardia) and HLP. The pharmacological correction of HLP was presented by statins of IV generation – rosuvastatin.

Results: The polymorphic variants of the genes studied in adjusting of lipid exchange for determination of efficiency of rosuvastatin. The estimation was made on influence of polymorphism of gene of CETP on efficiency of treatment of patients by rosuvastatin. Among the tested genetic models of phenotypical effects of CETP Taq1B polymorphism on the level of indexes of lipid exchange a recession model showed the most meaningful genes-phenotypical intercommunications. Homozygotes +279AA had the less expressed violations of indexes of lipid exchange initially – TChol, cholesterol of LDL, TG, AI, and greater basale level of cholesterol of HDL. The dynamics of changes of index of cholesterol of HDL of therapy of rosuvastatin differed for patients with a genotype +279AA by comparison to other genotypes of CETP. At homozygote +279AA predominance of level of cholesterol of HDL found out already on 8 week and saved during all period of research (27,3% $P=0,004$), comparatively with the carriers of other genotypes (16,7% $P<0,001$) to 48 week. The polymorphic variants of NOS-3 did not have influence on the basale levels of lipoproteins for patients with IHD and HLP, except for maintenance of TG ($P=0,054$). Presence of genotype – 786CC resulted in resistanse of used of statin as hypolipidemic means, that showed up the less decline of atherogenic indexes of lipid-transport system. There were not distinctions in the basale level of TChol for patients with the different genotype of NOS-3, during the pharmacological correction of violations of lipid exchange at homozygote – 786CC this index remained high and went down insignificantly to 48 weeks (-11,55% $P=0,524$) on a background treatment of rosuvastatin for patients with IHD and atherogenic HLP by comparison to a genotype – 786tt/TC, at that the decline of TChol attained 39% ($p<0,001$).

Conclusion: Determination of genotypes on polimorfism CETP Taq1B and NOS-3 – 786TC to the marker it can be used for the individual going near setting of statins for patients by IHD and HLP.

Keywords: hyperlipidemias, pharmacogenetical markers, ischemic heart disease

A loss-of-function variant in OSBPL1A predisposes to low plasma HDL cholesterol levels and impaired cholesterol efflux capacity

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Oxysterol-binding protein-like (OSBPL) or -related (ORP) proteins constitute a large family of lipid-binding/transport proteins many of which act at close contacts between subcellular organelles, designated membrane contact sites (MCS). Such sites act as platforms for the inter-organelle transport of small molecules and signals. OSBPL1A, also called ORP1L, mediates endoplasmic reticulum-late endosome/lysosome (LE) contacts and regulates the motility, tethering and fusion of the LE.

In subjects with HDL-C <1st percentile in the general population, we identified a heterozygous variant OSBPL1A p.C39X encoding a truncated protein fragment, that co-segregated with low plasma HDL-C. We investigated the composition and function of HDL from the carriers and non-carriers and studied the properties of the mutant protein in cultured hepatocytes.

Plasma HDL-C and apoA-I were lower in carriers versus non-carriers, whereas the other analyzed plasma components or HDL parameters did not differ. Sera of the carriers displayed a reduced cholesterol acceptor capacity (P<0.01), whereas the acceptor capacity of their isolated HDL was normal. Fibroblasts from a p.C39X carrier showed reduced cholesterol efflux to HDL (P=0.038) and a similar tendency in efflux to apoA-I (P=0.130). GFP-OSBPL1A partially co-localized in endosomes with endocytosed fluorescent apoA-I, suggesting that OSBPL1A may regulate the cellular handling of apoA-I. The GFP-OSBPL1A-39X mutant protein remained cytosolic and failed to interact with Rab7 which recruits OSBPL1A on late endosomes/lysosomes, showing that the mutation represents a loss-of-function.

The present work represents the first report on a human OSBPL1A mutation; It suggests that a loss-of-function mutation in OSBPL1A affects the first step of the reverse cholesterol transport process associated with the low HDL-C phenotype, and brings up the possibility that rare mutations in OSBPL genes may contribute to dyslipidemias.

Keywords: cholesterol efflux, HDL, oxysterol-binding protein, OSBPL1A, rare variant

Single Nucleotide Polymorphisms at the Hydroxy-Methyl- Glutaryl-CoA Reductase Gene Locus Significantly Predict Cardiovascular Events in Coronary Patients with Type 2 Diabetes

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Hydroxy-methyl-glutaryl-CoA reductase (HMGCR) protein catalyzes the rate-limiting step in cholesterol biosynthesis and is the major target for cholesterol-lowering drug therapy. Recently, genetic variations at that locus have been linked with lipid levels and coronary heart disease risk. The association of HMGCR gene variants with cardiovascular events in patients with type 2 diabetes (T2DM) has not yet been evaluated and is addressed in the present study.

We prospectively investigated the impact of the HMGCR tagging single nucleotide polymorphisms (SNPs) rs3761739, rs10515198, rs3846662, rs7717396, rs3846663, and rs4703670 on the incidence of vascular events in a high-risk cohort of 262 consecutive patients with T2DM undergoing coronary angiography for the evaluation of established or suspected stable coronary artery disease. Furthermore, variants rs12654264 and rs12916 were included in the present study based on previously published associations.

All variants apart from tagging variant rs10515198 significantly predicted future cardiovascular events in patients with T2DM after multivariate adjustment including LDL cholesterol and statin therapy.

We conclude that in patients with T2DM common HMGCR variants significantly predict cardiovascular events.

Keywords: single nucleotide polymorphism, hydroxy-methyl-glutary-CoA reductase, risk prediction, cardiovascular disease, type 2 diabetes mellitus

Mitochondrial mutations and monocyte activation

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Atherogenesis is accompanied by chronic inflammation. We investigated the ability of monocytes isolated from atherosclerotic patients to be activated in proinflammatory way. The degree of activation was determined by the culture medium level of TNF α measured by ELISA and TNF α gene expression measured by RT-PCR. When comparing the values of activation of monocyte obtained from patients, we were faced with dramatic individual differences. We have recently reported that several mtDNA mutations of leukocytes are associated with asymptomatic carotid atherosclerosis. In this study, we investigated the relationship between these mutations and atherosclerotic features of cultured cells. There was a statistically significant positive correlation between proinflammatory response of cells to IFN-gamma stimulation and the level of heteroplasmy of two mitochondrial mutations, namely, A1555G and G14459A ($r=0,325$, $p=0,026$, and $r=0.320$, $p=0,028$, respectively). The first one occurs in MT-RNR1 gene encoding 12S ribosomal RNA, and the second one – in MT-ND6 gene encoding NADH dehydrogenase subunit 6. Besides, the prevalence of homoplasmic A1811G was 3-fold higher in activated monocytes. This mutation occurs in MT-CO3 gene encoding cytochrome C oxidase subunit III. THP-1 cells of monocytic origin were transduced with G14459A. As a result, increased cell proliferation and intracellular cholesterol accumulation caused by atherogenic modified low-density lipoprotein were observed. It is well known that both enhanced cell proliferation and cholesterol-laden cells are the major manifestations of atherosclerosis at the cellular level. Thus, at least several mitochondrial mutations are associated with cellular features of atherosclerosis. Supported by Russian Scientific Foundation (Grant # 14-15-00112).

Keywords: Activation, Atherosclerosis, Cytokine, Mitochondrial DNA Mutations, Monocyte

Dynamics of subclinical carotid atherosclerosis and telomere length in ageing population

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Objective: Leucocyte telomere length (LTL) is considered as ageing biomarker. Atherosclerotic diseases are also strongly associated with age but the evidence of the relationship between LTL and subclinical atherosclerosis is inconsistent. We investigated the relationship between dynamics of carotid intima-media thickness (CIMT) and plaques and LTL in serial measurements in a population sample of middle and older age in Russia.

Methods: A random population sample of Novosibirsk residents was examined at baseline in 2003/05 (men and women, age group 45-69 years, n=9360) and re-examined in 2006/08 (wave 2) and 2014/16 (wave 3, participants reached age 55-79). The ongoing wave3 is funded by Russian Scientific Foundation project. Carotid ultrasound study and LTL measurement were conducted in a subsample at baseline and in wave 3 (796 subjects at baseline, 406 have repeated measurements). We measured mean-mean CIMT on the far wall of both common carotid arteries and identified carotid plaques (CP) with high-resolution ultrasound. LTL was measured by real-time quantitative PCR-based method. Associations between LTL and carotid phenotypes were estimated in cross-sectional and prospective analysis using ANOVA, linear and logistic regression.

Results: The mean follow-up period of serial measurements was 7.1 years for carotid phenotypes and 11.9 years for LTL. The mean CIMT was 0.75 (SD 0.18) mm at baseline and 0.91 (0.18) at wave 3 ($p < 0.001$); the average thickening rate was 0.03 (95%CI 0.029-0.032) mm/year. The mean relative LTL was 1.28 (0.39) at baseline and 0.80 (SD 0.20) at wave 3 ($p < 0.001$), with average shortening rate of -0.045 (95%CI -0.050 ; -0.040) per year. In cross-sectional analysis, there was no association between CIMT and LTL in crude or adjusted modes. In prospective analyses, changes in CIMT were not associated with changes in LTL during follow-up. For further analyses, a “progression of CIMT” was defined as increment larger than the mean increment during follow-up and contrasted with “no progression”. In wave3, in unadjusted model the CIMT progression was seen in 52%, 80%, 63%, 64% across quartiles of LTL (ordered smallest LTL quartile to largest); the difference between the 2nd vs. 4th quartile was marginally significant ($p=0.049$) but it became insignificant in multivariable models. In addition, LTL in wave3 was shorter in men with CP than in those without CP ($p=0.019$ in crude analyses and 0.090 after adjusting for age).

Conclusion: In this population sample of middle and older aged subjects in Novosibirsk, the age-related changes in carotid atherosclerosis and LTL were both of expected direction. However, we did not detect cross-sectional associations between CIMT and LTL, and the changes in LTL were not associated with changes in CIMT. CP appeared to be associated with shorter telomeres. It is possible that the association between LTL shortening and subclinical atherosclerosis is confined to more advanced vascular lesion; detecting such an association in population based samples may require larger number of subjects.

Acknowledgments. The study was supported by the Russian Scientific Foundation (grant no. 14-45-00030).

Keywords: Intima-media, Carotid, Telomeres, Ageing, Population

Analysis of risk factors and characteristics of genetic predisposition and clinical- angiographic manifestations of atherosclerosis in patient with ischemic organ damage without stenotic vascular damage.

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Relevance: Heart and brain are interrelated target organs of vascular pathology, clinical variants which (ischemic heart disease, stroke) continue to lead in structure of death causes in developed countries. It is known that approximately 10-20% of patients undergoing diagnostic coronary angiography due to acute or chronic ischemic syndrome, arteries are intact.

Scientific novelty: We will summarize risk factors, clinical and angiographic, genetic testing in patients with myocardial infarction or ischemic stroke, but no signs of atherosclerotic vascular damage. Genetic testing involves identifying the examined genetic polymorphisms of the following genes: lipid metabolism; structure and tone of the vascular wall; platelet coagulation and hemostasis; inflammation, histone deacetylase, CRP, VEGFR (epidermal growth factor receptor).

Materials and methods: Pool for inclusion in the study was defined as all patients who have suffered myocardial infarction or stroke, under the supervision of the Hospital No. 40 at the age of 20-59 years. The control group consists of healthy or practically healthy people. Each patient in the study starts up map of the test, including the results of lipid profile with detailed indicators of coagulation, glycemic profile; ECG evaluation of possible focal changes, signs of coronary heart disease, echocardiography assessment of contractile ability of hypo-akinesia and ejection fraction, stress tests or Holter monitoring, ultrasound of cerebral arteries, the arteries of the lower limbs, measuring ankle-brachial index, coronary angiography and study of polymorphisms of genes predisposing to the development of coronary artery atherosclerosis and cerebral arteries.

Results: Mean age was studied contingent 55; 47 women (31%), 113 men (69%); 101 of which have a history of coronary artery disease (67%), and 17 (11%) revealed stroke, repeated history of myocardial infarction had 9 people. Operations on the coronary arteries in 52 (35%) patients. The total duration of CHD was on average 1.2 years. Risk factors: smoking 88 (59%) patients, 43 (29%) patients with obesity according to BMI calculation. Dyslipidemia is revealed in the evaluation lipid 46 (31%), 89% have a history of hypertension, 77 (51%) diabetes. In assessing lipid: average total cholesterol level was 5.2 mmol/l, LDL 3.15 mol /l, TG 1.81 mmol/l. Preliminary data suggest that there is a group of patients studied genotype and phenotype features in generalized atherosclerosis without evidence of stenosis, and identify a correlation between the severity of clinical manifestations and the degree of arterial injury with existing risk factors and structural features of DNA. The results will clarify the pathogenesis of fatal cardiovascular complications in patients regardless of the presence of atherosclerotic lesion.

Keywords: atherosclerosis, gene polymorphism, heart stroke

PCSK9 regulates lipid metabolism, autophagy, and atherosclerosis

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PCSK9 (Proprotein convertase subtilisin/kexin type 9) increases the LDL levels by binding to hepatocyte LDL receptors (LDLR) and subjects it to degradation. We show that PCSK9 regulates apolipoprotein B (apoB) production by inhibiting its degradation process via the autophagic pathway irrespective of the presence of LDLR. Autophagy is a lysosome-mediated, evolutionarily conserved catabolic process. This pathway regulates lipid metabolism in the liver, and the dysregulation of autophagy contributes to hyperlipidemia and atherosclerosis. This study is to investigate the regulatory role of PCSK9 in lipid metabolism, autophagy, and atherosclerosis.

Our laboratory has generated double knockout mice lacking both LDLR and Apobec1 (apoB mRNA editing enzyme), named LDb, *Ldlr*^{-/-}*Apobec1*^{-/-}. They have a lipoprotein phenotype mimics humans with hyperlipidemia; elevated levels of VLDL and LDL with low levels of HDL. They develop atherosclerotic lesions spontaneously. To investigate the role of PCSK9 in lipid metabolism, autophagy and atherosclerosis, we deleted *Pcsk9* gene from LDb mice to generate the triple knockout mice (named LTp, *Ldlr*^{-/-}*Apobec1*^{-/-}*Pcsk9*^{-/-}). In comparison to parental LDb mice, the LTp mice (n=10) showed significantly decreased levels of triglyceride and apoB as early as 2-months of age. This was reflected in decreased apoB biosynthesis rate in LTp triple knockout mice, compared to LDb mice. Importantly, the atherosclerotic lesions in LTp mice were decreased 3-fold in comparison to LDb mice (8.8%±3.5 vs. 24%±3.3, p=0.004).

We then investigated the role of PCSK9 in autophagy function. The levels of Beclin-1, p62, and LC3-II were lower in LTp triple knockout mice, which suggested that lacking of PCSK9 resulted in active autophagy process. We used an in vivo autophagic flux assay to quantify the hepatic LC3-II levels, which confirmed that the autophagic process was more active in LTp triple knockout mice, compared to LDb mice.

PCSK9 also influenced the composition of LDL particles. LDL associated with PCSK9 (LDL-PCSK9) contained relatively more cholesteryl ester, compared to LDL without PCSK9 (LDL-no). LDL-PCSK9 induced the expressions of LOX-1 and TLR-2 receptors and the proinflammatory factors of CCL-2, CCL-7, and IL-6 in endothelial cells. Importantly, LDL-PCSK9 induced the expressions of Beclin-1, p62, and TRAF6 in endothelial cells. All these factors contribute to the development of atherosclerosis. Taken together, our study demonstrated that PCSK9 regulates lipid metabolism, autophagy, and atherosclerosis.

Keywords: PCSK9, Autophagy, Atherosclerosis, Hyperlipidemia, Mice

Gene-gene interactions affecting the risk of myocardial infarction in two populations from Russia

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Genome-wide association studies (GWAS) have identified many genetic loci associated with complex traits such as lipid metabolism and coronary artery disease in the populations of European ancestry. However, these results need validation in a number of independent multi-ethnic populations. The aim of our study was to replicate the associations found in GWAS in two native populations of the Volga-Ural region (Russian Federation).

Genotyping of rs838880 (*SCARB1*, Scavenger Receptor Class B, Member 1 gene), rs6511720 (*LDLR*, Low Density Lipoprotein Receptor gene), rs2230806 (*ABCA1*, ATP-Binding Cassette, Sub-Family A (ABC1), Member 1 gene), rs9349379 (*PHACTR1*, Phosphatase And Actin Regulator 1 gene), rs4977574 (*CDKN2B-AS1*, Cyclin-Dependent Kinase 4 Inhibitor B Antisense RNA 1 gene), rs1593 (*F11*, Coagulation Factor XI gene) polymorphic loci was performed in the study group of 1233 individuals (588 Tatars and 645 Russians), originating from the Republic of Bashkortostan (Russian Federation). The study group included 639 patients with myocardial infarction and 594 healthy control subjects. Data were analyzed using IBM SPSS 21.0 program. The analysis of association between allele and/or genotype combinations and myocardial infarction was performed using a Markov chain Monte-Carlo-based approach implemented in the APSampler program (v. 3.6.0).

We detected an association of *PHACTR1* rs9349379*G/G genotype (OR=1.7, P=0.009) and *CDKN2B-AS1* rs4977574*G allele (OR=1.32, P=0.02) with myocardial infarction in the ethnic group of Tatars. In the group of Russians, the risk of myocardial infarction was associated with *LDLR* rs6511720*G/T (OR=1.79, P=0.007) and *CDKN2B-AS1* rs4977574*G/G (OR=1.46, P=0.045) genotypes. The carriers of *F11* rs1593*A/A genotype of Russian ethnicity had higher risk of early disease onset (myocardial infarction before age 39, OR=18.27, P=0.016). The analysis of genotype and allelic combinations influencing the development of myocardial infarction revealed several patterns differing significantly in frequency between the group of patients and the control group. The most significant association with myocardial infarction was observed in the group of Russians for the following gene patterns: *CDKN2B-AS1* rs4977574*G + *SCARB1* rs838880*T + *LDLR* rs6511720*T + *APOC1* rs4420638*G (5.96% vs. 1.05% in the control group, OR=6.00, $P_{FDR}=0.043$), *ABCA1* rs2230806*G/A + *LDLR* rs6511720*T + *APOB* rs1042034*G (4.89% vs. 0.7% in the control group, OR=7.33, $P_{FDR}=0.041$), *ABCA1* rs2230806*A + *SCARB1* rs838880*T + *LDLR* rs6511720*T + *APOC1* rs4420638*G (4.05% vs. 0.35% in the control group, OR=12.08, $P_{FDR}=0.041$). In Tatars, the risk of myocardial infarction was associated with *CDKN2B-AS1* rs4977574*A + *APOC1* rs4420638*G/G (5.82% vs. 1% in the control group, OR=6.14, $P_{FDR}=0.011$), *F11* rs1593*A/A + *CDKN2B-AS1* rs4977574*G (3.3% vs. 0% in the control group, OR=8.43, $P_{FDR}=0.012$).

The results of our study indicate that gene-gene interactions may affect the development of myocardial infarction in specific populations. Additional studies are required to investigate the exact mechanisms involved in the pathogenesis of the disease.

Keywords: GWAS, lipid metabolism, polymorphic markers, gene-gene interactions

The modern concept of the atherosclerosis mechanisms: the role of the innate immunity

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The outstanding experimental studies, accomplished by N.N. Anichkov in the Emperor's Military Medical Academy on the eve of World War I, showed, that targeted regulation of the diet in experimental animals provides the control of formation of the atherosclerotic vascular lesions. The worldwide recognition of N.N. Anichkov as the founder of the scientific concept of atherogenesis arose in the second half of the XXth century, when it became clear, that "atherosclerosis is generally considered to be the major disease of this era". The XXth century widened the phenomenology of atherogenesis as a process caused mostly by passive deposition of cholesterol in the vessels. However, in the last two decades of the XXth century and in the beginning of the XXIst century the research of the cellular mechanisms of atherosclerosis developed at a new, molecular-genetic level. The atherogenesis research in the end of the XXth century confirmed the results of the experimental studies, accomplished by N.N. Anichkov, that showed three main types of the cells directly involved in the atherosclerotic process: smooth muscle cells, macrophages and lymphocytes, and also allowed to identify the macrophages receptors, which play the key role in the primary atherosclerotic process involving innate immune system. These pattern recognition receptors include toll-like and scavenger receptors. According to the modern concept, the atherosclerosis is chronic progressive inflammation of the large and medium-sized arteries, which activated by the mechanisms of the innate immune system in response to endogenous molecules, morphologically characterized by deposition of the cholesterol, accompanied by disturbances of cell death, fibrosis and thrombosis as the main clinical manifestations of the disease. Due to the important role of the innate immune mechanisms in the activation of the atherogenesis, we should highlight the key aspects of the atherogenesis, which are not only of academic interest, but are also useful for the strategy of pharmacological target regulation of atherosclerotic processes:

- cellular and molecular mechanisms of the innate immunity play the key role in the early stage development of vector transformations "monocyte – macrophage – foam cells" transformation;
- molecular mechanisms of formation and development of atherosclerotic processes are regulated by the receptor mechanisms of innate immunity and are characterized by the cross-regulation and synergistic activity of toll-like and scavenger receptors;
- at the early stages of atherogenesis the activity of toll-like receptors is aimed predominantly to identify the pathogen and subsequently regulate of inflammatory processes, and scavenger receptors show mainly effector function on pathogens;
- among the toll-like receptors, TLR4 plays specific pathogenetic importance in atherogenesis, and among the scavenger receptors the key player is the receptor CD36, because the activity and cooperation of these pathogen recognition receptors largely determines the accumulation of oxidized LDL by macrophages and their transformation into foam cells;
- the complex nature of the mechanisms of activation of the innate immunity receptor system, cross-regulation of toll-like and scavenger receptors with the direct participation of their agonists (endogenous ligands) largely determines asymptomatic development of the atherosclerosis in the absence of the typically signs of inflammation (sterile inflammation).

Keywords: atherosclerosis, atherogenesis, innate immunity, pattern recognition receptors, sterile inflammation

Metabolic Syndrome (Diabetes, Obesity)

Metabolic Syndrome and Inflammatory Connective Tissue Diseases

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Inflammation is a key component of obesity and type 2 diabetes mellitus. It is also risk factor of cardiovascular diseases. Patients with chronic inflammatory diseases such as rheumatoid arthritis or systemic lupus erythematosus have an increased risk of cardiovascular diseases too. The expected higher prevalence of metabolic syndrome and its components in rheumatic diseases (such as possible cause of increased cardiovascular risk) was confirmed in rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis and psoriatic arthritis.

We conducted study to assess the relationship between the rheumatoid arthritis and the increased cardiovascular risk in the presence of risk factors involved in metabolic syndrome including prediabetic state, central obesity, atherogenic dyslipidaemia and hypertension. The prevalence of the metabolic syndrome in the cohort of patients with the rheumatoid arthritis according to IDF, AHA/NHLBI and also NCEP ATP III criteria compared with the Slovak population in all age groups are higher. The prevalence was more than 55% in patients older than 60 years according to IDF criteria. Patients treated with methotrexate had the lowest prevalence of metabolic syndrome even lower than the control group. The most often component of the metabolic syndrome was obesity (waist circumference or BMI evaluation). Patients with higher inflammatory activity (evaluated by CRP) had a higher prevalence of metabolic syndrome. Prevalence of metabolic syndrome in patients with rheumatoid arthritis does not depend on the presence of specific gene polymorphisms for the development of autoimmune diseases (PTPN-22, STAT-4, CTLA-4, TRAF1/C5).

Keywords: metabolic syndrome, cardiovascular risk, inflammatory connective tissue diseases, insulin resistance, rheumatoid arthritis

The parameters of ambulatory blood pressure monitoring and endothelial dysfunction in hypertensive patients with diabetes mellitus type 2

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Aim: Diabetic hypertensive patients have pronounced changes in ambulatory blood pressure profile and endothelial function. But the correlation between the parameters of ambulatory blood pressure monitoring (ABPM) and endothelial dysfunction in diabetic hypertensive patients have not been fully clarified. We studied ABP and endothelial function in a group of diabetic hypertensive patients.

Methods: Patients with a glomerular filtration rate (GFR) of less than 30 mL/min per 1.73 m² were excluded. 120 patients were included into the research. Of these, the first (basic) group made up diabetic hypertensive patients in which there were 34 males and 26 females, the mean age was 56.1±1.3 years, the duration of arterial hypertension (AH) was 12.3±2.1 years and the duration of type 2 diabetes mellitus (DM2) was 4.4±0.7 years. The second (control) group made up 60 non-diabetic hypertensive patients in which there were 27 males and 33 females, the mean age was 55.2±1.2 year and duration of AH was 11.1±0.9 years. The patients in both groups were similar in age, duration of AH.

Results: The analysis of the results of the 24-hour ABPM revealed that the number of patients with increased 24 hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) variability was more among diabetic hypertensive patients than in non-diabetic hypertensive patients (76.7 % versus 21.1 and 70.0 % versus 22.5 %, respectively, p <0,05). There were not any significant changes in pulse rate, SBP and DBP. The amount of non-dipper and night-peaker patients was significantly higher in the basic group than in the control one (60.0 % versus 25.4 %, respectively, p <0,05). It was established that the number of patients with DBP daily value

Conclusion: The correlation between the parameters of ABPM and endothelial dysfunction in diabetic hypertensive patients were established in this study.

Keywords: arterial hypertension, type 2 diabetes mellitus, endothelial dysfunction, ambulatory blood pressure monitoring

Effects of Chios mastic gum on cholesterol and glucose levels of hyperlipidemic, prediabetic, overweight volunteers

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Background: Chios mastic gum (CMG) is a natural resin that is excreted from the trunk and branches of the mastic bush (*Pistacia Lentiscus* var. *Chia*). CMG has shown a significant lowering effect on total cholesterol and glucose levels of healthy volunteers in previous studies.

Purpose: Our aim was to evaluate the effectiveness and safety profile of CMG on lipid and glucose levels in hyperlipidemic, overweight and obese individuals not amenable to pharmaceutical interventions according to current guidelines. We present here the preliminary results of this ongoing study.

Methods: Seventy-two hypercholesterolemic, overweight and obese volunteers with impaired fasting plasma glucose have been recruited so far. Eligibility is based on total cholesterol > 200 mg/dl and fasting plasma glucose 100-125 mg/dl and body mass index (BMI) > 25 kg/m². They are randomly and double-blindly assigned to receive either capsules of CMG in a total daily dose of 2 gr or placebo for 12 weeks. Individuals already receiving any agent with possible effect on serum lipids and glucose are excluded. No special dietary intervention is applied. Serum total, LDL and HDL cholesterol, fasting plasma glucose and HbA1c levels are evaluated at the beginning and at the end of the 12-week treatment period.

Results: Significant reductions were observed for total cholesterol levels by 6% (p=0.01, 95% CI: 208.1-231.2 mg/dl), LDL by 7.5% (p=0.01, 95% CI: 138.2-159.5 mg/dl) and fasting plasma glucose by 7.3% (p=0.01, 95% CI: 98.3-104.8 mg/dl), compared to placebo. HDL cholesterol, triglycerides and HbA1c did not demonstrate any statistically significant difference.

Conclusions: According to these preliminary results, CMG has a significant favourable lowering effect in total cholesterol, LDL cholesterol and glucose levels of hypercholesterolemic, pre-diabetic and overweight/obese volunteers.

Keywords: mastic, hyperlipidemia, impaired glucose tolerance, prediabetes, metabolic syndrome

Free but not total testosterone is inversely correlated with subclinical atherosclerosis in type 2 diabetic men

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Introduction: Men with type 2 diabetes (DM2) are often characterized by abnormal reduced plasma testosterone levels. There is evidence suggesting an inverse association between serum levels of testosterone and coronary artery disease. The aim of this study was to relate endogenous sex hormone levels of men with DM2 and subclinical atherosclerosis (SA).

Hypothesis: Free and total testosterone influence on subclinical atherosclerotic burden.

Methods: Asymptomatic non-insulin dependent diabetic men (n=45) in cardiovascular disease primary prevention were enrolled in a cross-sectional design. SA was evaluated by carotid Doppler ultrasound assessing intima-media thickness (IMT) and carotid plaques. The correlations between clinical and laboratorial characteristics, including free and total testosterone with IMT were investigated. Multivariable linear regression models were used to assess the relation between free testosterone and IMT.

Results: IMT was correlated to free testosterone, duration of diabetes, age, blood pressure and insulin resistance. IMT was not correlated to total testosterone levels. As depicted in the Table, IMT was associated with the duration of diabetes and inversely with free testosterone levels, independently of age, blood pressure or insulin resistance. For each decrease of 1 ng/dL of free testosterone and an increase of 1 year of diabetes duration there is an increase of 0,048 mm and 0,014 in IMT, respectively.

Conclusion: Our data indicate that free testosterone is a potent independent predictor of atherosclerotic burden irrespectively to age.

Table. Multivariable linear regression models to assess the relation between free testosterone and IMT

Variables	Model 1	Model 2
Age	0,004 ± 0,003	0,002 ± 0,003
Duration of diabetes	0,017 ± 0,006*	0,014 ± 0,006*
Free testosterone	-0,041 ± 0,020*	-0,048 ± 0,020*
Diastolic blood pressure	-	-0,003 ± 0,003
HOMA-IR	-	-0,027 ± 0,017

*p ≤ 0,05

Keywords: testosterone, subclinical atherosclerosis, diabetes, intima-media thickness

The connection of diabetic dyslipidemia and erectile dysfunction

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Background: Diabetes is an established risk factor for sexual dysfunction in men; a threefold increased risk of erectile dysfunction (ED) was documented in diabetic compared with nondiabetic men. Diabetic vasculopathy concerns macroangiopathy, microangiopathy, and endothelial dysfunction. Macrovascular disease in diabetes corresponds to the atherosclerotic damage in the blood vessels, which limits blood flow to the penis.

Aim: Value the connection of dyslipidemia and erectile dysfunction in men patients who are ill with diabetes.

Materials and methods: In the research, 180 patients at the age of 33-67 with type 2 diabetes mellitus were participated. According to the duration of diabetes, the patients were divided into three groups and revealed the erectile dysfunction. The lipid metabolism was revealed and HbA1c was determined in all the patients.

Results: The patients who are ill with diabetes within 1-5 years (n=41, 22,78%), the erectile dysfunction is met in 34,15% of patients (in this group n=14), those who are ill with diabetes within 5-10 years, the erectile dysfunction is met in 57,53% (in this group n=43), who are ill with diabetes within 10 years and more the erectile dysfunction is met in 69,7% of patients (n=46). The result of lipid metabolism value showed that hypercholesterinemia was met in 42,22% (n=76) of the patients, hypertriglyceridemia was met in 21,11% (n=38), combined disorder was met in 24, 44% (n=44). Thus, 87,77% of the examined patients has lipid metabolism disorder. The result of the research showed that erectile dysfunction very often accompanied with dyslipidemia. It should be noted that 60,52% of the patients (n=23) who had isolated hypertriglyceridemia, they had erectile dysfunction, 63,16% of the patients (n=48) who had hypercholesterinemia, they had erectile dysfunction and 72,73% (n=32) of the patients had combined disorder.

Conclusion: Surely, the erectile dysfunction in diabetes mellitus has a multifactorial nature and here it has meaning duration of diabetes, level of compensation, complications especially neuropathy availability and harmful habits. According to our findings, we have a lot of patients with erectile dysfunction and hypertriglyceridemia. The findings remind us once more that medical practitioners have to pay attention especially to lipid metabolism condition, triglyceridemia level in diabetic patients. So, dyslipidemia is the reason of increasing cardiovascular risks and decreasing quality of life.

Flow Mediated Dilatation (FMD) score as an effective tool for screening of CVD in T2DM

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Background: The risk of cardiovascular diseases (CVD) in T2DM patients is 4% higher than in the healthy counterparts. The first stage to CVD is endothelial dysfunction which along with vascular injury causes formation of atherosclerotic changes in the tunica intima of arteries. Endothelial dysfunction can be analysed to diagnose early atherosclerotic changes and arterial stiffness. Role of Hyperglycemia, Diabetic Dyslipidemia and Inflammation in the acceleration vascular injury can be detected earlier and treated so as avoid severe cardiac events.

Objectives:

1. To determine the efficacy of FMD as a screening tool for early stage CVD in T2DM patients
2. To determine early stage CVD risk in type 2 DM patient using FMD score – correlating it with acceleration of inflammatory process of vascular injury.

Method: A total of 100 (72 F and 28 M) patients with type 2 DM of more than 10 years with age above 50years were screened for FMD (Flow Mediated Dilatation) score along with 60 (34 F, 26 M) healthy controls (without DM same age group), using Angio defender (Everist Genomics Ann Arbor, MI, USA). Pro inflammatory cytokines- TNF alpha, IL-6, IL-1 were measured using standard ELISA kits. As surrogates for disease activity C-reactive protein and ESR levels were determined. A Framingham risk score was also assessed in order to evaluate coronary heart disease risk at 10years in percent. A Treadmill Stress Test (TMT) was done in patients showing endothelial dysfunction to correlate the results.

Result: The FMD score in 100 type 2 DM patients showed that 70% (n=70, 61F 9M) patients suffered from impaired endothelial function and increased arterial thickness; 16% (n=16, 9F 7M) patients suffered from endothelial dysfunction, arterial stiffness and atherosclerosis whereas the remaining 14% had normal endothelial function. On the other hand in the healthy counterparts, the FMD score was normal in 80% (n= 48, 26F 22M) patients. The pro inflammatory cytokines were either normal or high in the patients with impaired endothelial function. C-reactive proteins and ESR levels also varied from high to normal in patients with endothelial dysfunction. The Framingham risk score also matched with 20% high risk in patients with lower flow mediated dilatation. The TMT test done for the patients with impaired endothelial dysfunction and arterial stiffness showed positive results in 75.5% (n=65) patients.

Conclusion: The flow mediated dilatation score can be effectively used as a marker to determine the vascular injury and endothelial dysfunction in patients with type 2 DM. 70 % of patients showed impaired endothelial function and increased arterial thickness which can be considered for counseling of patients for prevention of CVD, using the FMD tool. Acceleration of Inflammatory process could also be effectively correlated with the FMD score.

Keywords: Type 2 DM, Flow mediated Dilatation score, CVD, endothelial dysfunction

Effectiveness of different treatment of metabolic syndrome

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Aim: Evaluation of the effectiveness of different metabolic syndrome (MS) treatment

Materials and methods. Two groups of patients with MS were examined. They were divided into two groups according to different types of treatment. First group (gr. 1) included 30 patients treated traditionally including diet, dose physical exercises, iatrophysics. Their mean age was 69.67 ± 2.9 years, 17 men and 13 women. The second group (group 2) consisted of 40 patients 21 men and 19 women who's mean age was 69.6 ± 1.78 years. Their treatment was added with statins and metformin. All patients underwent cardiology patient algorithm. Metabolic criteria included weight, BMI, waist measurement, glucose triglycerides, total cholesterol levels. Inflammatory markers such as C-reactive protein, fibrinogen, ESR and leukocytes were measured. The treatment effectiveness was evaluated within a month and a month after the treatment.

Results: The second group consisted of patients with the higher indexes such as weight ($p=0.005$), BMI ($p=0.01$), waist measurement ($p=0.017$), glucose level ($p=0.000$) and total cholesterol ($p=0.000$). Highly effective treatment was observed in both examined groups ($p(t)$ and $p(W) - 0.000, 0.003, 0.001$). As per weight and glucose level treatment results were greater in group 2 ($p=0.006, p=0.002$), though per BMI, total cholesterol there were only a reducing trend found ($p=0.089, p=0.065$). A month after the end of treatment most of the parameters were significantly more evident in group 2 than in group 1, but statistical difference was found only for weight, BMI and glucose level ($p=0.030, p=0.035, p=0.000$). All parameters statistically reduced in both groups within 30 days period of treatment ($p(t)$ and $p(W)$ ($0.000, 0.003, 0.001$) and remains during a month after treatment. Reduced inflammatory titers of CRP, ESR ($p=0.0001$) and decreased level of leukocytes ($p=0.001$) against treatment were observed in both groups

Conclusions:

1. All examined parameters (weight, BMI, waist measurement, glucose, total cholesterol, CRP, fibrinogen, ESR and leukocytes) reduce significantly during the treatment in both groups.
2. Complex treatment of metabolic syndrome added with metformin and statins reduce weight, BMI, glucose and total cholesterol significantly.
3. Treatment effectiveness in both groups is highly valued and lasts at least within one month.
4. Significant decrease of inflammatory tests in both groups was found during the treatment.

Keywords: metabolic syndrome, C-reactive protein, metformin

Incidence of hypercholesterolemia and other cardiovascular risk factors according to ESSE-RF research in West Siberia

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Background: It is well known that dyslipidemia is an important cardiovascular risk factor. Moreover, it is mostly well treated by statin administration. But the problem is that in general population, especially among healthy people it often stays undetected.

Aim: The aim of the study was to evaluate incidence of hypercholesterolemia and other cardiovascular risk factors in patients without any cardiovascular disease.

Materials and methods: Cross-sectional study was performed within the framework of multicentre epidemiological study Epidemiology of Cardiovascular Diseases and their risk factors in the regions of the Russian Federation (ESSE-RF) from March to October 2013. The study subject was a random population sampling of male and female adult population in the age of 25-64 years old in the Kemerovo region. Each participant provided a written informed content for performing examination. Total cholesterol over 5.5 mmol/l was considered as pathological. 1615 subjects were included at the study and were divided into 2 groups: group 1 – subjects with normal level of total cholesterol (n=1028), group 2 – subjects with elevated level of total cholesterol (n=587). We analyzed clinicoanamnesic data and laboratory characteristics in the groups depending on the presence of lipid metabolism disorders.

Results: The total amount of participants with elevated total cholesterol was 36.34% (n=587). It should be noticed that they were significantly older (50.81 ± 9.82 vs 44.48 ± 11.57 years, $p=0.0000$), mostly women (60.48% vs 54.87%, $p=0.0287$), more often had arterial hypertension, and elevated body mass index. Incidence of current smoking was almost the same in both groups and reached 12%. Incidence of type 2 diabetes mellitus also was comparable.

Conclusion: The results of this study shows us that over than 36% in general population have lipid metabolism disorders. The also mark the importance of effective preventional measures for cardiovascular risk. According to ESSE-RF data we can define most risky group: older women with overweight.

Keywords: ESSE-RF, hypercholesterolemia, lipid metabolism disorders

Effect of ADAMTS5 deficiency on the metabolic syndrome

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Background: Expression of ADAMTS5 (A Disintegrin and Metalloproteinase with Thrombospondin type 1 motifs; member 5) is enhanced in expanding adipose tissue, but little information is available on a potential role in the metabolic syndrome.

Methods: Wild-type (WT) and deficient (*Adamts5*^{-/-}) mice were kept on a high fat diet for 15 weeks, and metabolic parameters were monitored.

Results: Total body weight and subcutaneous adipose tissue mass of obese WT and *Adamts5*^{-/-} mice were not significantly different. However, visceral/gonadal fat mass was significantly lower for *Adamts5*^{-/-} mice, as confirmed by magnetic resonance imaging. Glucose levels were not different between both genotypes, but insulin levels were significantly lower for obese *Adamts5*^{-/-} as compared to WT mice, resulting in a lower HOMA index (1.1 ± 0.1 versus 2.5 ± 0.5). In separate experiments, the insulin tolerance test revealed that obese *Adamts5*^{-/-} mice are more insulin sensitive than WT mice, whereas the glucose tolerance test was comparable for both genotypes. Plasma levels of total and HDL cholesterol, free fatty acids and triglycerides were significantly higher for obese *Adamts5*^{-/-} as compared to WT mice. Plasma adiponectin levels were comparable, but leptin levels were significantly lower for obese *Adamts5*^{-/-} mice. Furthermore, plasma markers for liver function (alkaline phosphatases, AST and ALT) and overall organ damage (LDH activity) were significantly lower for obese *Adamts5*^{-/-} as compared to obese WT mice. Hepatic macrophage content was lower in obese *Adamts5*^{-/-} mice as shown by reduced F4/80 staining and expression of macrophage markers. Further analysis revealed lower expression of pro-inflammatory M1 macrophage markers (TNF alpha, IL1beta and MCP1), and higher expression of anti-inflammatory M2 macrophage markers (Arg1 and Mrc1).

Conclusion: In a diet-induced obesity model in mice, ADAMTS5 deficiency is associated with a beneficial inflammatory profile and higher insulin sensitivity, and appears to protect against diet-induced visceral fat expansion and organ damage

Keywords: ADAMTS, obesity, metabolic syndrome

The Mediterranean diet improve n-3 fatty acids index and eicosanoids profile among former athletes in comparison to caloric restriction diet (CR)

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Athletes who finished their careers often have a problem with maintaining body weight. It may lead to the development of the diseases of civilization, such as: diabetes, hypertension or arteriosclerosis. There are no “gold standards” of nutrition for this group of patients. One of the solutions is to undertake the Mediterranean diet (MD). It has been described that caloric restriction (CR) helps to extend life and fight against the diseases of civilization. CR diet is based on calorie cuts up to 30% of the value of RMR (resting metabolic rate).

The aim of the study was to examine the effect of a six-week diet (CR n=15 or MD n=15) on: biochemical parameters, fatty acids profiles and eicosanoids profiles in former athletes. The athletes were randomly divided into 3 groups: CR, MD and control (C, n=15). The CR's group showed significantly statically lower levels of BMI (p <0.05), WR (p <0.05), total cholesterol (p <0.01), LDL (p <0.01), TG (p <0.01), total lipids (p <0.01) insulin (p <0.05) and insulin resistance (HOMA-IR, p <0.05). Patients taking the MD diet had significantly decreased BMI (p <0.01) and reduced levels of total lipids (p <0.05). We not found any significant changes in control group.

The analysis of the fatty acid profile in serum reveals that CR group had a significantly decreased level of two polyunsaturated fatty acids from n-6 and n-3 families: gamma-linolenic acid (C18: 3 n6, p <0.05) and eicosapentaenoic acid (EPA n-3, p <0.05). The MD group showed accumulation of the docosahexaenoic acid (DHA, n-3) and improvement of omega 3 index and EPA+DHA/AA ratio (p <0,05) in serum. Patients following the MD showed also significantly lower concentrations of 15 – hydroxyicosatetraenoic acid (15-HETE, p <0.05)- one of most powerful proinflammatory factor. We did not notice any significant differences in eicosanoids in CR and C group.

The analysis of the biochemical parameters shows that the CR improved the profile of basic lipid parameters, and that it equalized the level of insulin and reduced insulin resistance. Most probably, this effect is the result of high restrictions of the intake of fat and carbohydrates. The analysis of the fatty acids' profile revealed that the MD has a high cardio-protective effect in comparison to the CR. The supply of polyunsaturated fatty acids, especially DHA, can be the reason for this situation. We also observe the improvement of the prognostic markers of arteriosclerosis, such as omega 3 index, and the EPA+DHA/AA ratio. The decrease of inflammation was also confirmed through the decrease of 15-HETE – the mediator of the inflammatory process. It can be assumed that the MD diet seems to be more helpful in the decrease of inflammatory processes and, therefore, it can have a long lasting protective effect on the cardiovascular system. In the case of patients with insulin resistance, the diet based on calorie restrictions is more recommended.

Keywords: Fatty acids, eicosanoids, overweight, obese, dyslipidemia

Metabolic syndrome-contribution of visceral fat and adiponectin

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Although abdominal obesity or visceral obesity is considered to be a major component of metabolic syndrome and to have an important role in a cluster of cardiovascular risks and finally the development of cardiovascular disease, there has not been a consensus about definition and diagnostic criteria for this syndrome.

In this lecture, I will show an important role of visceral fat accumulation in the development of a variety of obesity-related disease including cardiovascular disease based on our clinical studies using CT scan and also discuss the mechanism of these disorders by focusing on adipocytokines, especially adiponectin which was discovered from human adipose tissue by our group in 1995. Adiponectin is a unique collagen-like protein which has anti-diabetic, anti-atherogenic function as well as anti-inflammatory function. I would like to show that hypoadiponectinemia caused by visceral fat accumulation is a key mechanism of a variety of obesity-related diseases such as DM, hyper tension and lipid disorders and also directly cardiovascular disease.

Relationships between lipid parameters and liver markers in men with type 2 diabetes mellitus, non-alcoholic fatty liver disease and stable ischaemic heart disease, atherosclerosis of the aorta

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Background and Aim: Type 2 diabetes mellitus (DM) and non-alcoholic fatty liver disease (NAFLD) are the public health problems of epidemic proportions worldwide. The aim of this study was to investigate the associations between lipid parameters (LP) of blood serum: total cholesterol (TC), triglycerides (TG), low density lipoproteins (LDL-C), high density (HDL-C), very low density (VLDL-C), atherogenic coefficient (AC), triglyceride coefficient (TGC), sum of AC+TGC, product of AC TGC and serum liver markers (LM): alanine aminotransferase (ALT), aspartate aminotransferase (AST) in patients with type 2 DM, NAFLD and ischaemic heart disease (IHD), atherosclerosis of the aorta (AA).

Material and methods: The study consisted of sixty-seven men (mean age 52.0 ± 0.97 years) with type 2 DM, NAFLD and IHD, AA. Program of examination included general clinical examination, biochemical tests and instrumental methods. Relationships LP of blood serum: TC, TG, LDL-C, HDL-C, VLDL-C, AC, TGC, sum of AC+TGC, product of AC TGC and ALT, AST were analyzed with using multivariate correlation analysis (criteria Student-Fisher). Correlations of each individual of LP (TC, TG, LDL-C, HDL-C, VLDL-C, AC, TGC, sum of AC+TGC, product of AC TGC) and LM (ALT, AST) were analyzed in tandem:

Results: Sequential multivariate correlation analysis is shown that in men with type 2 DM, NAFLD and IHD, AA the values of the variant, ≤ 10 th and > 90 th percentiles of TC, TG, LDL-C, HDL-C, VLDL-C, AC, TGC, sum of AC+TGC, product of AC TGC were directly/positively associated ($p < 0.05 - < 0.001$) with of the variant, ≤ 10 th and > 90 th percentiles of, ALT, AST. The values of the ≤ 10 th percentile of TC, TG, LDL-C, HDL-C, VLDL-C, AC, TGC, sum of AC+TGC, product of AC TGC and of the > 90 th percentile of ALT, AST were inversely/negatively correlated ($p < 0.05 - < 0.001$), as well as between the values of > 90 th percentiles of TC, TG, LDL-C, HDL-C, VLDL-C, AC, TGC, sum of AC+TGC, product of AC TGC and ≤ 10 th percentiles of ALT, AST.

Conclusion: The associations LP: TC, TG, LDL-C, HDL-C, VLDL-C, AC, TGC, sum of AC+TGC, product of AC TGC and serum LM: AST, ALT are common key factors in the pathogenesis of type 2 DM, NAFLD in IHD, AA patients. There should be careful monitoring of lipid indicators and liver aminotransferases to evaluate the metabolism in type 2 DM, NAFLD and IHD, AA patients.

High prevalence of metabolic syndrome in rural part of Croatia. Croatian rural study

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Background: Data on prevalence of metabolic syndrome (MS) in rural regions are still inconclusive and several reports showed it to be higher in urban than in rural areas. The aim of this study was to determine the prevalence of MS in a rural, continental Croatian part comparing 3 most widely used definitions of MS (NCEP-ATPIII; IDF and WHO).

Material and methods: We enrolled 1118 (713 female, 405 male) participants from 12 continental, villages. NCEP-ATPIII, IDF and WHO definition were used. Blood pressure was measured according to the ESH/ESC guidelines.

Results: In the whole group the prevalence of MS was highest using the IDF definition (IDF vs. NCEP-ATPIII vs. WHO (48.6% vs. 44.1% vs. 20.1%, $p < 0.03$, respectively). Women had more frequently MS (NCEP-ATPIII vs. IDF vs. WHO = 47.4% vs. 57.8% vs. 21.6%;) than men (NCEP-ATPIII vs. IDF vs. WHO = 37.5,4% vs. 51.8% vs. 17.9%) regardless which definition was used (all $p < 0.05$). We failed to find significant differences between MS and non-MS groups in age. In the whole MS group pathologic waist circumference was present in 81% of examines i.e. visceral obesity was the most prominent finding. Women had pathological waist circumference and men hyperglycaemia and as the most prominent component of MS. Importantly, examinees that did not fulfil criteria for MS also frequently had risk factors: hypertension (37%), visceral obesity (28%), low HDL cholesterol (6.3%), hyperglycemia (8.1%) and hypertriglyceridemia (37.3%). Salt intake was very high in the whole group (10.6 gram) without differences between MS and non-MS groups pointing on poor lifestyle habits and inappropriate diet.

Conclusion: The prevalence of metabolic syndrome in Croatian continental rural population is high according to NCEP-ATPIII and IDF definition. WHO definition is obsolete. Visceral obesity is the main component of MS. Even farmers without MS frequently have risk factors due to bad lifestyle and diet indicating that this population need to be educated.

Keywords: Metabolic syndrome, cardiovascular risk, guidelines, NCEP-ATPIII

The intensity of metabolic alterations and the results of reconstructive interventions in patients with widespread atherosclerosis.

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The abnormality of cardiometabolic process affects the course of atherosclerosis process.

The target of this research is the exposure of association between the metabolic alterations and the development of infectious after-effects after reconstructive interventions on major arteries.

Materials and methods: The observations after 57 patients with multifocal atherosclerosis, who came through reconstructive interventions on major arteries, are the base of the work. Of those, 34 patients were registered to have an infection in the area of surgical intervention (main group). 23 of those who were operated formed the control group. The features of the course of hypertension, diabetes, abnormalities of lipid metabolism, changes of body weight, characteristics of operative approach, nidus of endogenous infection were analyzed.

Results: The presence of the critical ischemia was the main leading reason of the development of infectious after-effects ($p=0,01$). The presence of the visceral obesity also predisposed the development of infectious after-effects ($p=0,01$). Manifestation of dislipidemia associated with the development of infection in the area of surgical intervention ($p=0,01$). The presence of metabolic syndrome, especially with the decompensated diabetes on the background, increases the risk of infectious after-effects ($p=0,01$).

Conclusions: Metabolic dysfunctions in patients with atherosclerosis undermines the intensity of ischemia and predispose the development of infection in the area of surgical intervention.

Keywords: infection, results of reconstructive interventions, diabetes, critical ischemia, metabolic syndrome

Treatment of Diabetes and its Effect on Body Weight

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Weight gain during diabetes therapy can be a challenging problem mainly in already overweight type 2 diabetes mellitus patients, affecting treatment compliance and long-term prognosis. It has also undesirable physiological effects on blood pressure, plasma lipid levels, waist-to-hip ratio and on an increase in insulin resistance. Until recently, many patients had little alternative other than to accept unwanted weight gain if they were to achieve sufficient glycaemic control to reduce risk of chronic complications of diabetes. There is therefore an effort in the development of new antidiabetic therapy that combines achieving optimal glycemic control as well as minimal effect on weight gain and low risk of hypoglycemia.

The evidence and merit of glucagon-like peptide-1 receptor agonist, sodium-glucose co-transporter-2 inhibitor and basal insulin analogs regimens are reviewed in this presentation.

The impact of bariatric surgery on cardiometabolic profile and adipokine levels

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Objectives: Bariatric Surgery is associated with reduction in cardiovascular mortality but the intimate mechanism that lies behind this benefit remains unclear. We evaluated the impact of sleeve gastrectomy with transit bipartition (SGTB) on cardiometabolic parameters.

Methods: Twenty diabetic individuals with a BMI between 28–35 kg/m² were randomized to SGTB or clinical treatment and ten healthy subjects (normal BMI) represented the control group. Retinol binding protein-4 (RBP-4), fibroblast growth factor 19 (FGF-19), IGF-1 (Insulin Like growth factor -1), Omentin, Free Fatty acids, Bile Acids, Glucagon, Adispin, Adiponectin, lipid profile and glycaemia were evaluated before and 3 months after treatment.

Results: At 3 months, significant differences were observed only in the surgical group: reduction in BMI (33,4±2,6 vs. 27,4±2,8 kg/m², p<0,001), triglycerides (369,5±324,6 vs. 130,8±43,1 mg/dL, p<0,001), Pro-insulin (12,72±9,11 vs. 1,76±1,14 pM, p<0,001), glycaemia (217±103,1 vs. 102±2, mg/dL, p <0,001), glycated hemoglobin (9,26±2,12 vs. 6,18±0,63 %, p<0,001), Total Cholesterol (182,9±45,4 vs. 139,8±13 mg/dl, p<0,001), RBP-4 (9,85±2,53 vs. 7,3±1,35 ng/ml, p<0,001) and increment in HDL-cholesterol (33,1±7,7 vs. 38,4±10,6 mg/dL, p<0,001), glucagon (7,4±7,9 vs. 10,2±9,7 pg/ml, p<0,001) and FGF-19 (74,1±45,8 vs. 237,3±234 pg/ml, p=0,001). Interestingly, pro insulin, RBP-4, HbA1c and HDL-cholesterol levels in the surgical group achieved “control group” values after 3 months but FGF-19 levels were almost two fold the results in the healthy subjects (237±234 vs. 98±102,1 pg/ml). Other variables such as omentin, IGF-1, free fatty acids, bile acids, adipsin and adiponectin did not alter significantly 3 months after de surgery.

Conclusions: Our results showed that bariatric surgery was associated to changes in metabolic variables and adipokines levels that could represent significant improvement in cardiovascular risk profile.

Keywords: Bariatric Surgery, Obesity, Atherosclerosis, Cardiovascular risk, Adipokines

Metabolic syndrome complicated by coronary atherosclerosis in Arctic Circle, for example the Yakutian population: ethnicity and gender differences

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We studied the frequency of the association between metabolic syndrome (MetS) and coronary atherosclerosis (CA) in Yakutian population depending on ethnicity and gender. This study population was composed of 456 patients (396 men and 60 women) with the verified CA according to selective coronarography (SCAG) and 483 control persons (212 men and 271 women) without clinical signs of coronary heart disease (CHD). Age of the surveyed population made 45-64 years. Research period: 2007-2010. Joint Interim statement (JIS) and All-Russian Scientific Society of Cardiology (VNOK) criteria were used for diagnostics of MetS. According to SCAG the stenosis of coronary arteries of less than 50% diameter narrowing prevailed among the natives than in the non-natives (men – 38.8 vs 17%, $p=0.000$; women – 62.5 vs 41.2%, $p=0.035$ respectively). Among non-native men the frequency of coronary arteries with significant stenosis and occlusions was higher (coronary arteries stenosis of 50-75% – 34.6 vs 27%, $p=0.014$; coronary arteries stenosis of more than 75% – 24.3 vs 19.1%, $p=0.061$; occlusions of coronary arteries – 24.1 vs 15.1%, $p=0.001$ respectively). A higher rate of coronary arteries stenosis of less than 50% was noted in both ethnic groups among women in comparison with men (native – 62.5 vs 38.8%, $p=0.004$; non native – 41.2 vs 17%, $p=0.000$ respectively). More than 55% of patients with the verified CA and about 13% of control persons had MetS. MetS was higher in representatives of non-native nationality than in native people of Yakutia. MetS was higher in women in comparison with men. The results of our research showed that the lowest frequency of MetS was observed using the ATP III criteria, while highest frequency of MetS according to versions for ethnic group of Chinese and using the VNOK criteria. This proves the necessity of the development of unique regional ethnic criteria to diagnose of MetS.

Keywords: metabolic syndrome, coronary atherosclerosis, Yakutian population, ethnicity and gender differences

Cholesterol level or age is more powerful in subclinical atherosclerosis progression during 2-years follow-up of relatively healthy bank employers?

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Objective No large studies have been performed assessing dynamic changes of subclinical TOD in patients with MS, so the progression rate and contributing factors are not well determined. Aim of our study to assess association of metabolic syndrome (MS) and its components with target organ damage in follow-up study of relatively healthy bank employers.

Methods Out of 1,600 random sample of office workers, a group of 383 participants with at least one component of MS and without cardiovascular complications was selected (mean age 46.6 ± 9.0 years, 214 females (64.6%)). Follow-up visit after 2 years was performed in 331 subjects. Target organ damage (TOD) was assessed by echocardiography, carotid ultrasound, applanational tonometry, brachial-ankle index and urine albumin excretion measurements at both visits. Blood pressure (BP) was measured twice on right arm by automatic tonometer Omron (Japan) with calculation of mean value. Anthropometry, vital signs and biochemistry were performed according to standard protocols. Statistical analysis was performed using SPSS Statistics 20.

Results Presence of MS was not associated with higher probability of TOD. During follow-up proportion of patients with LVH significantly decreased (from 46.7% to 32.9%, $p=0.003$) and prevalence of patients with $IMT > 0.09$ cm increased (from 24.5% to 44.1%, $p < 0.001$) accompanying by significant declining of office blood pressure and total cholesterol from 5.9 ± 1.4 to 4.9 ± 1.0 mmol/l,

Conclusions MS per se is not related to increased probability to TOD. Surprisingly, in spite of significant decrease of total cholesterol level and number of patients with hypercholesterolemia, progression of carotid atherosclerosis was detected probably due to aging and hypertension maintenance.

Keywords: metabolic syndrome, subclinical atherosclerosis, target organ damage, hypercholesterolemia, age

Prevalence of low Testosterone among T2DM patients: symptomatic vs asymptomatic population for sexual dysfunction

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Aim: To find out the prevalence of low testosterone in Type 2 Diabetes Mellitus (T2DM) patients comparing the symptomatic vs. Asymptomatic population for sexual dysfunction

Objective: 1. To find the prevalence of low testosterone in T2DM patients between the age group of 45-60yrs:

- Asymptomatic population
- Symptomatic population

Method: It is an observational prospective study. All consecutive male T2DM patients coming to a specialised Diabetes Care centre in Western India, Ahmedabad, were included in the study matching the inclusion criteria.

Inclusion Criteria:

1. Age group 45-60years
2. T2DM \geq 5years
3. Time period 2-12-2014 to 3-12-2015

Exclusion Criteria: Pre existing hypogonadism, Critically Ill patients.

All patients matching the inclusion criteria were subjected to ADAM (Androgen Deficiency in Ageing Male) Questionnaire, BMI, WHR, a detailed history process. A routine laboratory analysis at the centre includes FBS, HbA1c, S. Creatinine, Lipid Profile, TSH, Urine RM, S.Testosterone. (All patients are explained and counselled about the necessity and requirement of the tests for the management of their condition). We defined symptomatic patients as having atleast one of the symptoms of erectile dysfunction, inability to penetrate, reduced morning erections. Low testosterone was defined as S.testosterone $<$ 262ng/dl.

Result:

1. 180 patients matched our inclusion criteria
2. Out of these there were:
 - 115 asymptomatic patients
 - 65 symptomatic patients
3. 27 patients out of the asymptomatic pool could not undergo the blood analysis due to economic reasons.
4. 19.3% (n=17) patients of the asymptomatic pool had a result of low s. Testosterone.
5. 38.4% (n=25) patients out of the symptomatic pool had a result of low s. Testosterone.

Conclusion: The study showed that there is high prevalence of low testosterone in not only symptomatic DM patients but also asymptomatic DM patients. It poses a bigger challenge to make up guidelines for the treatment and screening of DM patients with low testosterone levels and the benefits of further evaluation and treatment need to be further studied.

Keywords: Low Testosterone, Sexual Dysfunction, Type 2 Diabetes Mellitus (T2DM)

Coronary Artery Disease as a Risk for Developing Type 2 Diabetes Mellitus

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Diabetes mellitus is a major risk factor for coronary artery disease (CAD); whether conversely CAD confers an increased risk for diabetes is unclear.

We prospectively recorded incident diabetes over 6.1 ± 3.7 years in 829 consecutive non-diabetic Caucasian patients undergoing coronary angiography for the evaluation of stable CAD, covering 5057 patient years.

During follow-up, diabetes was newly diagnosed in 133 patients, i.e. in 16% of the study population or in 2.6% per year. Patients with significant CAD ($n=444$) when compared to subjects who did not have significant CAD at the baseline angiography were at a strongly increased diabetes risk (20.3 vs. 11.2%; $p < 0.001$). The relationship between CAD and incident diabetes was confirmed after multivariate adjustment including metabolic syndrome status (OR 1.85 [1.23-2.79], $p=0.003$).

We conclude that the presence of CAD indicates a strongly increased risk for incident diabetes. Repeated diabetes screening of coronary patients and targeted programs to prevent diabetes in these high-risk patients are warranted.

Keywords: coronary artery disease, risk prediction, type 2 diabetes mellitus, epidemiology

GQ-11: A novel PPAR α agonist with beneficial effects in high fat diet-induced obesity

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Introduction: Thiazolidinediones (TZDs) comprise a class of hypoglycemic drugs that reduces insulin resistance in peripheral tissues, mediated by peroxisome proliferator-activated receptors (PPARs) activation. Actually, new TZDs have been developed aiming to obtain beneficial effects and minimize side effects found with known TZDs. It has been shown not only the typical hypoglycemic action of these new compounds, but also additional effects on adipokines and lipid metabolism, besides anti-inflammatory properties.

Aims: This study aimed to investigate the effects of GQ-11, a novel PPAR α agonist, on adipose tissue and liver of obese LDLr^{-/-} mice fed a high fat diet.

Methods: High-fat diet-fed C57BL/6J LDLr^{-/-} mice were treated with GQ-11 (20 mg/kg/day), pioglitazone (20 mg/kg/day) or vehicle for 4 weeks. Relative gene expressions in adipose tissue and liver were quantified by RT-PCR ($\Delta\Delta$ ct analysis method), Glucose tolerance test (GTT) was done to study dynamic glucose activity. Serum adiponectin and insulin were measured by ELISA and lipid profile was measured by enzymatic/colorimetric assays. In addition, inflammatory biomarkers in serum were evaluated by flow cytometry and by western blot in adipose tissue.

Results/Conclusion: GQ-11 showed hypoglycemic effects similar to pioglitazone besides other beneficial effects on lipid metabolism and anti-inflammatory action. A significant increase (28%) of HDL-cholesterol and decrease (39%) of VLDL-cholesterol promoted by GQ-11 was found. Accordingly, up regulation of ABCA1, SBR1 and APOA1 mRNA was observed in the liver. In addition, GQ-11 induced IL-10 increase and MCP-1 decrease in blood serum and in adipose tissue (mRNA and protein), indicating an important anti-inflammatory action.

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Keywords: obesity, PPARs, thiazolidinediones, adipose tissue

Aging and Diet Interactions in Atherogenesis of Nonhuman Primates

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Background: Epidemiological studies indicate that aging is the largest risk factor for morbidity and mortality due to atherosclerotic associated events such as coronary heart disease and stroke in patients with dyslipidemia. However, the molecular and cellular interactions between aging and a high cholesterol diet remain elusive due to the lack of an optimal animal model. In this study, rhesus monkeys of variable age were given a high cholesterol diet. Subsequently, the aorta, common carotid, and common iliac arteries were studied to explore how interactions between aging and a high cholesterol diet contribute to the pathogenesis of atherosclerosis.

Methods and Results: 26 rhesus monkeys (from 5.86 to 27.48 years-old) were divided into standard diet (SD; n=10) and high cholesterol diet (HCD; n=26) groups. They were then subdivided into young (< 15-year-old: for SD, n=5; for HCD, n=8) and old (>15-year-old: for SD, n=5; for HCD, n=8) subgroups. Lipid profile testing demonstrates that circulating plasma cholesterol levels were stably increased by 2-fold in both young and old HCD monkeys starting from 6 months of the diet compared to that of SD monkeys. Histopathology showed that the atherosclerotic plaque burden (the ratio of plaque circumference to the corresponding lumen circumference) was markedly increased in HCD vs SD group, in particular within abdominal aorta and common iliac artery. Importantly, the degree of increase was greater in the old HCD compared to that of the young HCD (two-way ANOVA, $p < 0.001$). Morphometric analysis also indicated that atherosclerotic plaque size in old HCD was significantly increased compared to young HCD group ($p < 0.05$). Proteomic analysis showed a significant increase in angiotensin II associated inflammatory signalling network within the arterial wall is closely associated with an increase in abdominal aortic atherosclerotic plaque burden in monkeys fed a HCD. Furthermore, in vitro studies demonstrated that early passage endothelial cells (ECs) from old SD monkeys in culture, have not only lower migratory, adhesive, and replicative capacities, but also higher gelatin metalloproteinase (MMP-2/9) activity compared to young cells. Early passage vascular smooth muscle cells (VSMCs) in culture from SD monkeys showed similar proinflammatory phenotype with a higher invasive/proliferative capacity as well as increased MMP-2/9 activity in old compared to that of young cells. Interestingly, both ECs and VSMCs from old versus young SD monkeys have a higher capacity for uptake of oxidatively modified low-density lipoprotein (ox-LDL) (ECs, $p < 0.05$; VSMCs, $p < 0.01$).

Conclusions: The aging arterial wall suffers from a chronic proinflammatory state that is exacerbated by a high cholesterol diet, resulting in an acceleration of arterial wall inflammation and attendant increase in atherosclerotic plaque burden. Thus, therapies aimed at mitigating arterial aging could be an effective approach for prevention of or delaying the onset of atherosclerosis that accompanies advancing age in primates.

Keywords: Aging, Atherosclerosis, High cholesterol diet

Effects of physical exercises on WAT characteristics in DIO rats

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Background: Excess of white adipose tissue (WAT), extensive visceral fat depot and adipose cell hypertrophy apparently play role as metabolic disorders key risk factors.

Objective: The present study was designed to determine WAT allocation in rats received hi-fat diet combining with continuous and intermittent exercises.

Methods: Adult male rats with diet-induced obesity (DIO) were divided into three subgroups performing physical exercises as follows: 1) continuous swimming carrying 4 % body weight load, 2) intermittent swimming carrying 8 % body weight load and 3) non-trained control. Training period lasts six weeks. Body weight, WAT total weight, fat depots (mesenteric, epididymal, retroperitoneal, subcutaneous) absolute and relative weight, adipocytes mean size and size distribution were measured and calculated.

Results: All rats have increased body weight. However trained rats have lower amount of WAT, with greater effect in first subgroup. Non-trained rats have larger subcutaneous and retroperitoneal fat depots and high amount of subcutaneous small-size adipocytes. Continuous swimming animals have small-size subcutaneous adipocytes and relatively low portions of subcutaneous and retroperitoneal fat depots and high portion of epididymal one comparing with non-trained rats. Intermittent swimming rats have small-size mesenteric adipocytes and relatively high portions of subcutaneous and epididymal fat depot, high portion of mesenteric and retroperitoneal ones comparing with non-trained rats.

Conclusion: Hence this study shows that continuous swimming exercises have a greater effect on WAT total weight decrease. Intermittent swimming exercises increase subcutaneous fat depot and decrease visceral fat depot. It might play positive role in metabolic disorders.

Keywords: swimming rats, diet-induced obesity, adipose tissue, adipocytes, physical exercises

Nonpharmacol treatment of HLP

Characterization of patients who started or stopped a lipoprotein apheresis (LA) at our center in 2014 and 2015

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Background: Up to 2013 the majority of new patients in the apheresis centers in Saxony (Germany) exhibited high lipoprotein(a) levels (Emmrich, U., et al. *Atheroscler. Suppl.* 2015; 18:215-25). We wanted to evaluate whether this trend continued also in the following years by characterizing the new patients at our center. Moreover the reasons why some patients stopped being treated with the extracorporeal method were analyzed.

Patients and Methods: 25 patients (16 males, 9 females; mean age 57 years (range: 31 to 77 years) started apheresis. We subdivided the patients based on their LDL-cholesterol (LDL-C) and lipoprotein(a) (Lp(a)) levels before the first apheresis session (3 groups). Cardiovascular events (mean CVE per patient) in different vascular territories have been documented. 10 patients (7 males, 3 females; mean age 64.7 years (range: 52 to 84 years) stopped LA.

Results: Data obtained in the 3 groups are given in a table:

	Group 1	Group 2	Group 3
n	8	13	4
males/females	5 m / 3 f	8 m / 5 f	3 m / 1 f
mean age (years)	61	53	61
range	31 – 73	34 – 77	36 – 77
mean LDL-C (mmol/l)	3.64	2.03	4.88
range	1.96 – 5.93	1.35 – 3.03	3.71 – 7.10
mean Lp(a) (nmol/l)	48.38	223.15	264.75
range	19 – 110	127 – 503	185 – 371
coronary arteries	1.8	1.6	2.3
carotids, stroke	0.1	0.3	0.3
aorta	0.0	0.2	0.3
leg arteries	0.6	1.0	0.8

Reasons for discontinuation were (number of patients in brackets): bad tolerability (1), death (2), multimorbidity (1), instable arteriovenous fistula (2), bronchial carcinoma (1), continuation at another center (1), switch to PCSK9 inhibitor (2).

Discussion: Two thirds of the new patients had clearly elevated Lp(a) levels. In these patients more often interventions at the aorta and the leg arteries had to be performed. The LA reduces CVE more effectively than in patients with hypercholesterolemia. Health problems were the major reasons for stopping LA therapy, the compliance of the patients was excellent.

Keywords: lipoprotein(a), hypercholesterolemia, lipoprotein apheresis, cardiovascular events

Different lipids apheresis systems. Pro and contra.

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Therapeutic apheresis is fast developing area of the modern medicine, indications for use of these techniques are expanding. Dyslipidemia is one of the main indications for the use of lipid apheresis – LDL apheresis. It has been accumulated more than 30 years' experience in the treatment of patients with FH. Positive clinical results were obtained during the lipid apheresis in patients after coronary artery bypass surgery to avoid occlusions in auto venous bypasses in the early postoperative period.

Lipid apheresis currently involves the removal of various fractions of atherogenic apoB100 containing lipoproteins, such as: low density lipoprotein (LDL), very low density lipoproteins (VLDL), and lipoprotein(a) [Lp(a)]. The range of systems for lipid apheresis is the widest among other areas of therapeutic apheresis. For the extracorporeal removal of lipids have been developed and applied multiple use highly specific immunoadsorption columns such as «LDL TheraSorb» (Miltenyi Biotec, Germany), «LDL Lipopak» and «Lp(a) Lipopak» (POCARD Ltd. Russia), selective adsorption columns, such as «Liposorber»® (Kaneka, Japan), «Lipocollect» (Medicollect, Germany), «DALI»® (Fresenius, Germany). In addition to the sorption technologies methods cascade filtration are used with the hollow fiber filters «Evaflux»® (Kuraray Medical, Japan) and heparin precipitation technique «HELP»® (B.Braun, Germany).

The use of highly specific multiple use systems, such as the immunosorbents, has the advantage for the long-term and regular of LDL apheresis treatment of FH patients. The results of the specific Lp(a) apheresis procedures with «Lp(a) Lipopak» columns have demonstrated the stabilization and regression of atherosclerotic lesions in the coronary and carotid arteries in patients with chronic ischemic heart disease with increased concentration of Lp(a) and normal LDL cholesterol level. For the short term LDL apheresis courses in patients before and after CABG surgery it is justified the treatment with single-use absorption, filtration or precipitation devices. The use of apheresis systems designed for the whole blood significantly simplifies the procedure, but somewhat less efficient than systems adapted for the regeneration during the procedure.

Recently it has been demonstrated the positive effect of lipid apheresis techniques not only for the reduction of target lipid components levels, but also on the hemodynamic parameters and inflammation in the vascular wall.

The successful development of therapeutic apheresis methods and lipid apheresis, in particular, and the expansion of the indications for their use in the cardiology, gives the prospects of these approaches in the treatment of severe drugs resistant patients with lipids abnormalities.

Keywords: LDL apheresis, immunoadsorption columns, lipoprotein(a)

Pharmacol treatment of HLP

The Role of Aggressive Statin Therapy On Morphological Changes of Venous Grafts in Patients After Surgical Myocardial Revascularisation

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The increasing number of CABG surgeries demands to develop new options and methods of treating this category of patients. According to up to date concepts patients after CABG are exposed to different risk factors and needed to be treated using modern approaches to reduce the progression of CAD and its complications.

Objectives: The aim of study was to evaluate the influence of aggressive statin therapy prescription before aorto-coronary artery bypass graft surgery in coronary artery disease patients on the LDL cholesterol and morphologic characteristics of venous conduits being used as coronary grafts.

Methods: The study was an investigator-initiated, prospective, single-center, single-blind, randomized study which enrolled 88 patients suffering CAD and angina pectoris from 2 to 4 functional class with planned CABG surgery (mean age 64,2±9,4 years). Included patients were divided on two groups using computerized randomisation process 28 days before CABG surgery: control statin therapy (Simvastatin 20 mg daily, n=44) and aggressive statin therapy treatment group (Rosuvastatin 40mg daily, n=44). The samples of the great saphenous vein were obtained during the CABG surgery. Histological examination was performed on paraffin slices stained with hematoxylin and eosin. Immunohistochemistry test was performed by kit of a monoclonal mouse antibodies to a marker of proliferating cells – Ki-67.

Results: The control treatment (Simvastatin 20 mg daily) group showed no change in total or LDL cholesterol. Patients in the aggressive treatment group (Rosuvastatin 40mg daily) showed a mean LDL reduction of 20mg/dl. This finding was highly significant and was also present for total cholesterol. Aggressive statin therapy treatment during 28 days before CABG results in to reduced desquamation of the endothelium, intimal hyperplasia and reduce the number of layers of smooth muscle cells in the medial parts of the great saphenous veins. A significant difference between groups in terms of epithelial desquamation was established (48% of cases in the control group and 15% – in the aggressive group, P <0,05). In addition Rosuvastatin 40mg daily reduces the proliferation index of the value of the Ki-67 expression in endothelial and smooth muscle cells of the great saphenous vein.

Conclusions: Beneficial effects of Aggressive statin therapy on hyperplastic processes in venous grafts suggest potential well long-term effects of CABG.

Keywords: Rosuvastatin, CABG, venous grafts

Anti-inflammatory and anti-atherogenic effects of the inflammasome NLRP3 inhibitor, arglabin, in ApoE₂.Ki mice fed a high fat diet.

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Background: This study was designed to evaluate the effect of arglabin on inflammasome NLRP3 inhibition and atherosclerotic lesion in ApoE₂.Ki mice fed a high fat Western-type diet (HFD).

Methods and Results: Arglabin was purified and its chemical identity was confirmed by mass spectrometry. It inhibited, in a dose-dependent manner, IL-1b and IL-18 production, but not IL-6 and IL-12, in cultured mouse peritoneal macrophages with a maximum effect at ~50 nM and EC₅₀ values for the both cytokines of ~ 10 nM. LPS and cholesterol crystal-activated Nlrp3^{-/-} macrophages did not induce IL-1b and IL-18 production. In addition, arglabin activated autophagy as evidenced by the increase of LC3-II protein. Intraperitoneal injection of arglabin (2.5 ng/g of bw, twice daily, 13 weeks) into female ApoE₂.Ki mice fed a HFD resulted in a decreased IL-1b plasma level *vs* vehicle-treated mice (4.64 ± 1.43 pg/ml *vs* 11.61 ± 3.05 pg/ml, *P*<0.01). Surprisingly, arglabin also reduced plasma levels of total cholesterol by ~56% (*P*<0.01) and triglycerides by ~ 55% (*P*<0.05). Moreover, arglabin oriented the pro-inflammatory M1 macrophages into the anti-inflammatory M2 phenotype in spleen and arterial lesions. Finally, marked reductions in mean lesion areas in the sinus (45 ± 19%, *P*<0.05) and whole aorta (60 ± 2%, *P*<0.01) were observed.

Conclusions: Arglabin reduces inflammation, plasma lipids, increases autophagy and orients tissue macrophages into an anti-inflammatory phenotype in ApoE₂.Ki mice fed a HFD. Consequently, a marked reduction of atherosclerotic lesions was observed. Thus, arglabin may represent a new promising drug to treat inflammation and atherosclerosis.

Keywords: Inflammasome, Atherosclerosis, Cytokines

Hypolipidemic effects of a novel compound in an animal model of hypercholesterolemia (WHHLMI rabbits)

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Aim: Although statin is the first-choice drugs for hypercholesterolemia, the prevention effect on cardiovascular events has a limit. Therefore, a compound having different mechanism from statin will contribute to further reduction of cardiovascular events. We developed a new compound showing potent hypolipidemic effects. In this study, we examined hypolipidemic effects of our newly developed compound and the mechanism.

Methods: WHHLMI rabbits, an animal model for hypercholesterolemia and coronary atherosclerosis, were administered a new compound-supplemented chow for 5 weeks at a dose of 30 mg/kg (treated group). In control group, WHHLMI rabbits were administered standard chow. Chow was administered to rabbits 120 g per day. Lipid levels and serum levels of AST (GOT) and ALT (GPT) were assayed with enzymatic methods. Lipoproteins were fractionated with an ultracentrifuge. Expression of mRNA of enzymes relating to lipid metabolism was analyzed with real-time qPCR at the end of the treatment. In addition, lipid content in the liver and fat accumulation in adipose tissues were measured.

Results: In drug treated group, serum lipid levels were decreased markedly in total cholesterol, triglyceride, and phospholipid. These decreases in the treated group were mainly due to a decrease in VLDL fraction. In addition, triglyceride content in LDL fraction also decreased markedly. In liver of drug treated group, expression of mRNA was significantly decreased in fatty acid synthase (FAS) and in microsomal triglyceride transfer protein (MTP), but was increased in cholesterol 7 alpha-hydroxylase (CYP7A1) compared to the control group. In addition, expression of mRNA was increased in lipoprotein lipase (LPL) in mesenteric adipose tissue, and decreased in Niemann-Pick C1 like 1 protein (NPC1L1) in ileum. Compared to the control, lipid content in the treated group was decreased in liver, and fat accumulation was decreased in pericardial fat and in mesenteric fat. There were no differences in serum levels of AST and ALT between treated and control groups, and each rabbit did not show any symptoms about side effects including chow consumption.

Conclusions: Our newly developed compound is a potent hypolipidemic compound and the mechanism was different from that of statins. Furthermore, this compound may be a medicine for steatohepatitis and metabolic syndrome.

Keywords: hypolipidemic compound, VLDL, FAS, LPL, WHHLMI rabbit

Varia

The low molecular weight apolipoprotein(a) phenotype as the important risk factor for coronary atherosclerosis

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Background. In accordance with European Atherosclerosis Society Consensus Lipoprotein(a) [Lp(a)] statement the desirable level of Lp(a) should be less than 50 mg/dL. In this study we learned the relationship between apo(a) phenotypes and Lp(a) concentration with coronary atherosclerosis and myocardial infarction (MI).

Methods. The study population consisted of 540 patients (mean age 54.0±8.8 years, 82% men) with results of coronary angiography. Atherosclerosis severity was assessed by the number of diseased major coronary arteries. Patients with 50% stenosis of only one coronary artery consisted 127(24%) cases, multivessel coronary arteries diseases had 356(66%) patients, 57(10%) patients had no atherosclerotic lesions. Lipids profile, glucose, Lp(a) and apo(a) phenotyping were analyzed in these patients. All patients were divided into 4 groups: with Lp(a)<50 mg/dL [normal Lp(a)] or ≥50 mg/dL [high Lp(a)], and as low-molecular weight (LMW) and high-molecular weight (HMW) apo(a) phenotypes.

Results. Baseline clinical and biochemical characteristics were similar in all groups. In groups with LMW apo(a) regardless of Lp(a) levels odds ratio (OR) (95% confidence interval (CI)) for the multivessel coronary atherosclerosis was significantly higher [OR=2.2 (95% CI 1.0-4.9), p=0.05 for normal Lp(a) and 10.1 (95% CI 3.1-33.5), p<0.005 for high Lp(a)], than in group with high Lp(a) in presence of HMW apo(a) OR=1.1(95% CI 0.3-3.3), p=0.92. In multiple regression model after adjustment for age, sex, hyperlipidemia and hypertension both Lp(a) and LMW apo(a) correlated with the angiographic burden of disease (p<0.001).

Conclusion. LMW apo(a) isoforms are associated with multivessel coronary artery diseases and MI independently of high Lp(a) levels. The Lp(a) level less than 50 mg/dL in patients with LMW phenotype apo(a) should be corrected in order to prevent the atherosclerosis progression and its complications.

Keywords: lipoprotein(a), apolipoprotein(a), atherosclerosis

Clinical features and risk factors of coronary artery diseases in rheumatoid arthritis

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Introduction: Coronary artery disease (CAD) is one of the causes of cardiovascular (CV) mortality in rheumatoid arthritis (RA). The assessment of the risk factors of CAD and interpretation of clinical and instrumental signs of the CAD in RA are difficult.

Materials and Methods: 90 pts with RA (on the ACR/EULAR criteria 2010) and hypothetical CAD was examined. Clinical manifestations of the CAD were typical angina in 32 pts (35%), atypical chest pain 47(52%), dyspnoea in 5 (6%). 6 pts had not got any signs of angina.

The stress-tests results were: positive in 9 pts (12%), negative in 25 (34%), questionable in 8 pts (11%), not adjusted to the criteria of ischemia in 32pts (43%). 26 pts hadn't underwent the stress-test due to strong joint damages. To verify the CAD 62 pts had underwent coronary angiography. By the results of which pts were divided into 2 groups. Group 1 stress-test was negative or coronary arteries had stenosis<50%; group 2 pts with >50%stenosis. RA-related factors, parameters of inflammation did not differ in pts of both groups.

Clinical characteristics of groups

	Group 1(n=67)	Group 2(n=23)	P
Men/women(n)	28/71	65/34	0.02
Smoking(n%)	14,9	39,1	0,001
Strain of CV diseases(n%)	28	47	0,045
Hypertension(n%)	77,6	78,3	0,00001
Myocardial infarction(n%)	1	7	0,0002
Typical angina(%)	23	78	0,01
Atypical chest pain(%)	61	17	0,003
Silent ishemia(%)	8,9	1	0,03
Dyspnoea(%)	5,9	4	0,04
Cholesterol M(mmol/l)	5,5[4,9;6,5]	4,8[4,4;5,9]	0,04

In 44% of patients with RA stress-test result was questionable or was not brought to the criteria of ischemia. We used the SPECT with 99mTc-MIBI with physical activity stress-test. Summed rest scores (SRS) in both groups did not differ. Summed stress scores (SSS) and difference scores (SDS) were significantly lower in patients without coronary lesions.

Results: It is necessary to perform a stress-test with additional visualization using the SPECT with 99mTc-MIBI for verification of myocardial ischemia in RA pts. CAD and significant coronary lesions in RA are often marked by the presence of traditional risk factors such as hypertension, heredity. RA pts without obstructive coronary lesions have atypical forms of pain or painless form of myocardial ischemia more often. **Keywords:** coronary artery disease, rheumatoid arthritis, stress-test with visualization, SPECT with 99mTc-MIBI, atherosclerosis risk factors

Anitschkow's Expanding Legacy: Porosity of the "Liver Sieve" influences Atherosclerosis and many other Maladies.

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Anitschkow's pioneering studies of the cholesterol-fed rabbit have continuing implications regarding the causes of atherosclerosis. His seminal observations stimulated our experiments, dissecting the balance of dietary cholesterol with that synthesised by the liver. Over the last fifty years the electron-microscope and ultra-centrifuge have enabled the exploration of nature's nanotechnology, explaining many familial and life-style factors influencing cholesterol-related atherogenesis, as reported to the International Atherosclerosis Society (IAS) in Tokyo, 1976.

NZ white rabbits are exquisitely sensitive to dietary cholesterol, rapidly increasing their serum cholesterol from the double-whammy of circulating dietary chylomicron remnants, as well as in smaller liver- synthesised lipoproteins (VLDL and LDL). We first thought that the distribution of cholesterol in large compared to small chylomicrons (intestinal VLDL) might explain the rabbits' sensitivity to food cholesterol.

Wisse, a pioneer in the study of the hepatic micro-circulatory ultrastructure, hypothesised that the fenestrated liver sinusoidal endothelial cells (LSEC) might filter chylomicrons from their smaller chylomicron remnants, VLDL and LDL. We confirmed this ultra-filtration (but in rat livers) by both electron microscopy and radio-labelling of dietary lipoproteins. Only small chylomicrons or their remnants traverse the LSEC fenestrae to contact the underlying hepatocytes.

Subsequently we determined a lower porosity of rabbit LSEC, with fenestrae in the order of only about 50nm diameter, compared to that of the rat with fenestrae of about 100nm. The lower LSEC porosity in rabbits (vegans) inhibits the liver's uptake of much of the food-cholesterol transported by chylomicron remnants, thus rabbit hepatocytes continue to synthesise cholesterol. This is exported as hepatic VLDL and LDL to the blood mainly via the thoracic duct lymph. Conversely, rats (omnivores) with larger fenestrae, balance dietary cholesterol by inhibiting hepatocyte HMG Co A Reductase, the enzyme synthesising hepatic cholesterol.

Many human life-styles related to atherosclerosis have also been shown in animals to affect both serum cholesterol and LSEC porosity. Thus nicotine decreases LSEC porosity in rats to resemble that in rabbits, while the drug 'pantethine' increases rabbit's LSEC porosity to resemble rats: with as predicted, concurrent serum cholesterol changes. Other lifestyles have been shown by us and others to decrease LSEC porosity and raise serum cholesterol: these include alcoholism, detergents and surfactants, dimethyl-nitrosamine and cocaine. Arsenical ground water from some wells and fracking of some shale seams relate to defenestration, concurrent with changes in the gut's microbiome. Ageing also relates to a decreased LSEC porosity.

Thus Anitschkow's cholesterol-fed rabbits led us to confirm the role of the "Liver Sieve" in atherogenesis. This ultra-filter regulates the balance of dietary cholesterol with that synthesised by the liver, thus influencing the circulating lipoproteins relating to atherogenesis. However the LSEC's porosity also has been shown to influence diverse hepatic and general maladies such as viral hepatitis, cirrhosis, autoimmunity by trans-endothelial lymphocyte hepatocyte interactions (TEHLI), diabetes, genetic diseases, therapy by epigenetics, endotoxins, sepsis and hepatic malignancies.

Keywords: Hypercholesterolaemia, Chylomicrons, Liver, Nanotechnology, Ultrafiltration

The Impact of existent cardiovascular diseases, traditional risk factors, systemic inflammation on N-Terminal pro-brain natriuretic peptide level in patients with early rheumatoid arthritis

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Background: Rheumatoid arthritis (RA) is a disease with proven high cardiovascular risk. High cardiovascular mortality associated with accelerated progression of atherosclerosis in patient with RA, resulting in chronic heart failure (CHF) and sudden cardiac death.

Purpose: to determine the level of NT-proBNP in patients (pts) with early RA prior to therapy with basic anti-inflammatory drugs (BAID), examine its relationship with traditional risk factors (TRF), cardiovascular disease (CVD) and markers of inflammation.

Methods: A total of 66 early RA pts (ACR/EULAR criteria, 2010) were included in the study: 71% of women, age 56 [46;61] years, disease duration 6 [4;8] months; DAS28 5.3 [5.0;6.2], positive for ACCP (100%), RF (87%), without prior administration of BAID and glucocorticoids. All pts were assessed for TRF of CVD (ESC guidelines, 2011), ECG, 24-h ECG and blood pressure monitoring, echocardiography, tissue Doppler imaging, carotid artery ultrasound. Coronary calcium index was determined by 64-slice computed tomograph (the Agatston score). Antihypertensive therapy was administered in 51 (77%) pts: ACE inhibitors, ARBs, beta-blockers, calcium antagonists, diuretics. The normal range for NT-proBNP was less than 125 pg/ml.

Results: At baseline the concentration of NT-proBNP in early RA pts (125 [65; 208] pg/ml) was higher than in control group (52,0 [40,5;69,1] pg/ml) ($p < 0,0001$). In 32 (49%) RA pts NT-proBNP level were higher than normal. Pts with elevated NT-proBNP level compared to pts with normal one were older (60 [56;65] vs 50 [35;55] years), have a higher frequency of carotid atherosclerosis (ACA) (85% vs 43%), coronary artery calcinosis (69% vs 22%), chronic heart failure (CHF) (20% vs 0%), ischemic heart disease (28% vs 5%), as well as a higher body mass index (BMI) (28 [24;31] kg/m² vs 24 [22;29] kg/m²), left carotid intima-media thickness (cIMT) 0.93 [0.87;1.04] mm, right cIMT 0.92 [0.85;0.98] mm, CRP (34[13;78] mg/l vs 14[3;41] mg/l) ($p < 0,05$ for all cases). The frequency of dyslipidemia, abdominal obesity, diabetes mellitus were not obtained between the groups. There were correlation between NT-proBNP level, erythrocyte sedimentation rate (ESR) ($r = 0,6, p < 0,01$), CRP ($r = 0,4, p < 0,01$), activity index SDAI ($r = 0,4, p < 0,05$) and CDAI ($r = 0,3, p < 0,05$). NT-proBNP related factors that remained associated on a multivariable linear regression analysis were CHF, ACA, CRP, BMI and LDL. Multiple coefficient of determination (R^2) was 53% ($p = 0,001$).

Conclusion: NT-proBNP level in early RA pts higher than in control group. Presence of CHF, ACA, higher CRP level and lower level of LDL strongly associated with higher NT-proBNP level.

Keywords: NT-proBNP, rheumatoid arthritis, chronic heart failure

Notch signaling is differently altered in smooth muscle and endothelial cells of thoracic aortic aneurysm patients.

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Purpose: Thoracic aortic aneurysm (TAA) develops as a result of complex series of events that alter the cellular structure of the aortic wall. It has been shown in our and others previous studies, that patients with defects of left ventricular outflow tract may have mutations in *NOTCH1* gene. Notch signaling between endothelial and smooth muscle cells plays an important role for smooth muscle differentiation, which is altered in patients with thoracic aortic aneurysm. The aim of this study was to assess the expression level of Notch signaling components in endothelial and smooth muscle cells derived from aneurysms in patients with bicuspid aortic valve (BAV) and tricuspid aortic valve (TAV).

Methods: Human aortic endothelial cells (HAECs) and smooth muscle cells (SMC) were isolated from tissue fragments of BAV- and TAV-associated thoracic aortic aneurysm patients and from healthy donors used as controls. The baseline level of Notch receptors, ligands and target genes was estimated by qPCR.

Results: Endothelial cells of TAA patients had significantly lower mRNA levels of *NOTCH1*, *NOTCH2*, *NOTCH4* and *DLL4* comparing to controls. However the mRNA level of direct Notch target *HEY1* was higher in HAEC of TAA patients. On the contrary, SMC of the patients had significantly higher mRNA levels of Notch receptors: *NOTCH1*, *NOTCH2*, *NOTCH3* comparing to controls, while levels of direct Notch target genes, such as *HEY1*, *HES1*, was not changed in SMC of the patients.

Conclusions: Expression level of Notch receptors, ligands and effectors is altered in HAEC of TAA patients. In contrast, in SMC of the patients the level of Notch receptors is changed comparing to controls, but not the level of Notch effector genes such as *HEY1* and *HES1*. Our results show that Notch signaling is differently altered in endothelial and smooth muscle cells of TAA patients. This corresponds to the hypothesis that Notch-dependent differentiation of SMC is governed by endothelial cells. We suppose that alterations of key Notch pathway elements in HAEC population may cause an impairment of SMC differentiation in patients with thoracic aortic aneurysm.

Keywords: thoracic aortic aneurysm, Notch signaling, smooth muscle cells, endothelial cells

Arterial stiffness in rheumatoid arthritis and coronary artery disease

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Introduction: Cardiovascular (CV) diseases are the main cause of the increased mortality in rheumatoid arthritis (RA) in comparison with general population. A purpose of this investigation is arterial stiffness parameters researching in RA and RA with coronary artery disease (CAD).

Materials and Methods: 41 pts included. 31 pts were with RA according on the ACR/EULAR criteria 2010. 10 pts without RA with CAD according on the diagnostic tests and coronary angiography data as control. All RA patients underwent the examination included ECG, Echo, stress-tests, coronary angiography. 20 patients` stress-tests proved negative and/or coronary angiography didn`t indicate stenosis more than 50%. They had formed into a group 1. Group 2 included RA pts with CAD who had stenosis in the one or more coronary arteries more than 50%.

	Group 1(n=20)	Group 2(n=11)	Control(n=10)	p
Men/Women	4(20%)/16(80%)	7(64%)/4(36%)	5(50%)/5(50%)	N/A
Hypertention	19 (95%)	8 (73%)	8 (80%)	N/A
Diabetes mellitus	3 (15%)	0	0	N/A
Myocardial infarction(n,%)	-	3 (27%)	3 (30%)	N/A
Mean blood pressure	128,7 /79.0	124,2/77.8	125.3/78.4	N/A
Smoking(n,%)	4(20%)	3(27%)	3(30%)	N/A
Cholesterol,mmol/l	5,44±0,71	4,82±0,92	5.2±0.9	N/A
LDL,mmol/l	3.46±0.46	2,89±0.64	3.5±0.9	N/A
RA duration(years)	10.0±0.5	10.5±1.2	-	N/A
RA activity(DAS)	4.47±1.3	3.8±0.8	-	N/A
ACCP,RF positives	15(75%),10(50%)	9(82%),7(64%)	-	N/A

All included pts underwent the non-invasive study of arterial stiffness: measurement of carotid-femoral pulse wave velocity (PWV) by applanation tonometry (by SphygmoCor device, "AtCorMedical", Australia).

Results: PWV in all RA pts (n=31) was higher than PWV in control (n=10): 14,8 ± 2,3 m/sec versus 8,2 ± 1,9 m/sec, p = 0,007.

	Group 1(n=20)	Group 2(n=11)	Control(n=10)	p(1,3)	p(2,3)	p(1,2)
PWV(m/sec)	13,6±0,9	15,6±1,9	8,2±1,9	0,02	0,0015	0,07

Conclusion: Arterial stiffness in RA pts both groups is higher than in control. Arterial stiffness rising besides the hypertension, dyslipidemia and smoking might be an additional factor of atherosclerotic lesion in this group of patients.

Keywords: coronary artery disease, rheumatoid arthritis, arterial stiffness, atherosclerosis, coronary angiography

Immunopathological mechanisms of the destabilization of atherosclerotic plaque by human

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The complex immunohistochemical, morphological and immunobiochemical study of the role of autoimmune mechanisms in formation and development the unstable, characterized by the progressive increase, atherosclerotic lesions of the arteries of human made it possible to establish a number of new facts.

On the basis its own experimental data is realized the analysis of the structural special features of different atherosclerotic lesions, which made it possible to create the classification, at basis of which lie the generalized types of the taken place unstable and stable atherosclerotic plaques. Is for the first time isolated the separate progressive form of the unstable plaque, in which is observed a constant alternation of layers of the new formation lipid deposits with the layers of fibrous connective tissue (change of the phases of progression and remission). Earlier this type of damage by anyone was not considered as the unstable.

Is for the first time discovered the possible connection between the deep destructive and degenerate changes in the elastic and collagen matrix, which are observed with the formation of unstable atherosclerotic plaque and by the strong expression of proinflammatory interleukin -18 in cells and structures of the same form of damage. Its role in the destabilization of atherosclerotic plaque remained, until now, of unknown. On the basis obtained given is expressed hypothesis about the defined by example action of interleukin -18 on the studied process due to its ability to induce the synthesis of interferon-gamma in the T-lymphocytes and the macrophages, which finally leads to the inhibition of the synthesis of collagen and elastin in the smooth-muscle cells of vascular wall and to the destruction of the strength of the fibrous cap of plaque. It is possible that use further of the inhibitors of interleukin -18 will be able to limit the formation of unstable lesions and to thus prevent the progression of atherosclerotic process in the arteries of human.

Is revealed the close connection between the infiltration of vascular wall by immunoinflammatory cells and by processes of the destabilization of atherosclerotic plaque. It is shown that the most massive and numerous infiltrations are located in the zone of erosions and breaks of the cap of unstable atherosclerotic plaque.

As a result the analysis of aorta and coronary arteries (earlier carotid arteries) are for the first time acquired data, which show the important role of the infectious agents of bacterial (Chlamydia of pneumoniae) and virus (cytomegaloviruses) nature to the formation of the unstable, progressive atherosclerotic lesions in human. In this case the hypotheses about source and ways of the penetration of obligatory parasites into the vascular wall of human, and about their possible influence on the progressive increase of the atherosclerotic plaques and on the development of immunoinflammatory processes by atherogenesis as a whole are formulated.

Keywords: unstable and stable atherosclerotic plaques, T-lymphocytes and macrophages, infectious agents

Anichkov's ideas today

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Nikolai Anichkov in 1913 showed the role of cholesterol in atherogenesis. No cholesterol, no atherosclerosis was his main idea. No one has proved Anichkov made a mistake. Modern science formulated risk factor theory and cholesterol became one of the other factors. Do we use the Anichkov's idea in our practice enough? I do not think so. Doctors and their patients are oriented to use surgical procedures and pharmaceutical drugs. They are not inclined to think that reducing the consumption of cholesterol is much more impotent. An overwhelming majority does not want to change their lifestyle to become healthy.

Atherosclerosis is an accumulation disease. Cholesterol is deposited inside arteries. Why? Russian scientist Lomonosov is the one who discovered the law of mass conservation. It implies that matter cannot be created or destroyed. The main components of atherosclerotic plaques is cholesterol. It builds up in the walls of arteries. Where does it come from? Anichkov showed it was food cholesterol. Another Russian scientist Kapitolina Volkova found that regression of atherosclerosis is possible in humans if they don't eat food cholesterol.

There is a lack of clinical trials properly organized to investigate the impact of consumption of cholesterol. For example I could not find any information about CAD among vegans. According to Anichkov's idea they must not have any signs of atherosclerosis. It would be very important evidence to prove the truth of his theory.

We have to come back from idea of risk factors to monocausal theory. If we eliminate the cause of atherosclerosis (food cholesterol) it will regress. As it was with the infectious disease earlier. Anichkov gave us the key to a mystery of atherosclerosis. We must take it and go that way.

Keywords: Anichkov, atherosclerosis, cholesterol

Anti-Atherogenic Role of c-Kit/SCF Signaling in Hyperlipidemic Mice

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This study provides our novel evidence that stem cell factor (SCF) receptor c-Kit regulates vascular smooth muscle cell (SMC) phenotype and is potently anti-atherogenic. Atherosclerotic plaque was quantified in transgenic mice deficient for c-Kit ($c\text{-Kit}^{W/W^v} \text{ApoE}^{-/-}$) or SCF ($c\text{-Kit}^{sl/+} \text{ApoE}^{-/-}$) after 16 weeks of high fat diet (HFD). Both mutant strains displayed substantially greater atherosclerosis compared with control ($\text{ApoE}^{-/-}$) littermates ($pW/W^v \text{ApoE}^{-/-}$ mice failed to rescue the atherogenic phenotype indicating that increased atherosclerosis was associated with reduced arterial c-Kit. The key role of vascular c-Kit in preventing atherosclerosis development was further proved after specifically knocking down c-Kit in SMC of a $\text{ApoE}^{-/-}$ conditional knockout mouse after tamoxifen pulses. $\text{ApoE}^{-/-}$ mice with defective expression of c-Kit in SMC developed three times more disease than their littermate control ($p < 0.01$). To investigate the mechanism, SMC organization and morphology were analyzed in aorta by histopathology and electron microscopy. Remarkably, SMCs were more abundant, disorganized and vacuolated in aortas of c-Kit mutant mice compared with controls ($p < 0.05$). Markers of the “contractile” SMC phenotype (Calponin, SM22 α) were downregulated in parallel with decreased c-Kit ($p < 0.05$). Reconstitution of c-Kit in synthetic cultured SMCs conferred increased spindle-shaped morphology, reduced proliferation and elevated levels of contractile markers Calponin and SM22 α , each characteristic of a resumed contractile phenotype ($p < 0.05$). Deregulation of contractile markers in c-Kit deficient cells was secondary to increased expression and activity of Kruppel-like factor 4 (KLF4), a potent transcriptional factor which suppresses the VSMC contractile phenotype. In conclusion c-Kit/SCF expression prevents phenotypic switching of contractile SMC to the pro-inflammatory, synthetic phenotype and markedly suppresses atherosclerosis in this murine model.

Keywords: atherosclerosis, experimental, C-Kit

Early use of therapeutic apheresis reduces the incidence of angiographic in-stent restenosis and major cardiovascular events in patients with stable coronary artery disease after coronary stenting

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Along with a variety of publications on the effects of therapeutic apheresis (TA) in disorders of lipid metabolism, there are few reports on the clinical effectiveness of the TA in the prevention of complications of percutaneous coronary intervention (PCI).

Objective: To investigate the effect of TA on the incidence of both angiographic in-stent restenosis, and the composite endpoint that included: all-cause mortality, non-fatal myocardial infarction, stroke, repeat revascularization in patients with stable coronary artery disease (CAD).

Methods: 84 patients with stable CAD and those in whom initial class II-III angina subsequently stabilized medically were included in the study. All patients underwent coronary stent implantation and received aspirin, clopidogrel, statins and other medications in accordance with accepted treatment guidelines and established practice standards. Patients were randomly assigned to undergo TA and optimal medical therapy (TA group, n=44) or optimal medical therapy alone (OMT group, n=40). Drug-eluting stents were implanted in 34 (85%) patients OMT group and in 35 (80%) patients TA group, the remaining patients used the bare metal stents. It should be noted, OMT group had more patients with 1-vessel lesions (12 (30%) vs. 5 (11%) in the TA group ($p=0,03$)). Conversely, the TA group had more patients with 3-vessel lesions (28 (64%) vs. 16 (40%) in the OMT group ($p=0,01$)). 2 methods of TA were used: double filtration plasmapheresis (DFPP) by Cascadeflo EC50 and EC40 (26 patients), Cryoprecipitation with active coal plasma adsorption (CPA) (18 patients). CPA does not apply to LDL apheresis but it is a procedure which improves the rheological properties of blood and reduces the levels of pro-inflammatory mediators. TA treatment was started on 3-5 days after PCI. 3 procedures were conducted with intervals of 2-3 days. Perfused plasma volume was 100-120% of the circulating plasma volume. Heparin was used as an anticoagulant. The follow-up period was $11,8 \pm 4$ months. All patients underwent control coronary angiography or multilayer spiral CT coronary angiography at the end of the follow-up period.

Results. There were verified 8 (20%) cases of the angiographic ISR. Four patients required repeated revascularization in the OMT group during follow-up. The rates of the combined endpoint that included: death from any cause (5%), nonfatal myocardial infarction (2.5%), stroke (2.5%), repeated revascularization (15%) were significantly higher in the OMT group compared to the TA group (25% vs. 4,5%, $p=0,02$). By contrast, only one case of angiographic in-stent restenosis (2.3%) was verified in the TA group, which did not require implementation of target lesion revascularization. Two (4.5%) patients had a new atherosclerotic lesion (they all received CPA) and underwent target vessel revascularization. In this group, all patients are alive and there are no indications of myocardial infarctions or strokes.

Conclusions. Early use of TA reduces the incidence of angiographic ISR and major cardiovascular events in patients with stable CAD when added to optimal medical therapy.

Keywords: coronary artery disease, percutaneous coronary intervention, therapeutic apheresis, in-stent restenosis, treatment outcome

Clodidogrel binds to lipoprotein-associated phospholipase A₂ (Lp-PLA₂) and inhibits the enzyme activity in patients with an acute coronary syndrome

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Background-Aim: Lipoprotein-Associated Phospholipase A₂ (Lp-PLA₂) circulates in plasma in active form bound primarily to low-density lipoprotein (LDL). Lp-PLA₂ catalyzes the hydrolysis of platelet activating factor (PAF) and oxidized phospholipids. These phospholipids are formed during oxidative modification of LDL in the arterial intima and may play important roles in the pathophysiology of atherosclerosis. Many clinical studies have demonstrated that elevated Lp-PLA₂ levels in plasma are correlated with increased cardiovascular risk. Clopidogrel still remains an antiplatelet drug of choice for cardiovascular patients, despite the availability of new more potent antiplatelet drugs in the daily clinical practice. Apart from potent antiplatelet activity, clopidogrel exhibits various pleiotropic effects. Aim of the study was to investigate the possible effect of clopidogrel on the activity of Lp-PLA₂, *in vitro* and *ex vivo* in patients with an acute coronary syndrome (ACS).

Methods: The possible interaction of clopidogrel with recombinant Lp-PLA₂ (rLp-PLA₂) was studied using fluorescence spectroscopy whereas the possible degradation of clopidogrel by rLp-PLA₂ was evaluated with LC-MS/MS (LC/MSD Trap SL). Also, the effect of clopidogrel on recombinant Lp-PLA₂ (rLp-PLA₂) activity as well as on the enzyme activity in total plasma, and on LDL was determined by the trichloroacetic acid precipitation method using [³H]JPAF as a substrate. We also determined the circulating levels of Lp-PLA₂ activity in 50 ACS patients before the administration of clopidogrel and 5-days afterwards.

Results: Titration of clopidogrel concentrations (0.5-20 μM) to the solution of rLp-PLA₂ (2 μM) revealed a gradual decrease in fluorescence, thus providing strong evidence that clopidogrel binds to Lp-PLA₂. However, according to the results obtained by LC/MS-MS, clopidogrel is not degraded by Lp-PLA₂, since the spectrum of clopidogrel (m/z 322) was the same either in the presence or absence of Lp-PLA₂. Clopidogrel inhibits the enzymatic activity of rLp-PLA₂, LDL and plasma Lp-PLA₂. Lp-PLA₂ activity levels in ACS patients were significantly reduced (p<0.01) at 5 days post treatment with clopidogrel compared to baseline whereas lipid parameters did not alter from the baseline to 5-days post treatment.

Conclusions: Clopidogrel binds to Lp-PLA₂ and inhibits the enzyme activity suggesting a new pleiotropic (antiatherogenic) effect of this antiplatelet drug.

Keywords: Lp-PLA₂, Clopidogrel, Pleiotropic effect

Implementation of the Treat-to-Target strategy in early rheumatoid arthritis patients could not prevent an atherosclerosis progression in carotid arteries.

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Background: Treat-to-Target (T2T) strategy is early and aggressively rheumatoid arthritis (RA) treatment for reaching the remission or low-disease activity, aimed to achieve the optimal therapeutic outcomes in RA.

Objectives: Examine changes in carotid artery duplex ultrasound results in early RA patients (pts) following 18 months antirheumatic therapy using “T2T” strategy.

Methods: 74 pts (73% women, age 56[47;61] years) with early RA (ACR/EULAR criteria, 2010) with moderate/high activity (DAS28-ESR 5.4[4.9;6], positive for ACCP (100%), RF (87%) without prior administration of disease-modifying antirheumatic drugs, glucocorticoids. Methotrexate therapy (MT) was started in all pts with an escalation of the dose up to 30 mg/week SC. In case of no remission 3 months later, MT was added with biologic therapy (BT): Anti-TNF agents, Abatacept, Rituximab. Arterial hypertension (AH) have been detected at 46 pts (62.2%), ischemic heart disease (IHD) – 12 (16.2%), dyslipidemia – 65 (88%). Some pts have been treated with statins (n=34;46%) (median Atorvastatin and Rozuvastatin dose=10mg/d). After 18 months RA remission (DAS28-ESR<2.6) have been detected at 31 pts (42%): on MTX – 17 (55%), on MTX+BT – 14 (45%). All pts underwent Extracranial cerebrovascular duplex scanning to evaluate of intima-media thickness (IMT) and detect of atherosclerotic plaques (AP).

Results: The following baseline results have been detected: IMT max sin 0.9 [0.76;1] mm, IMT max dex 0.85 [0.73;0.94] mm; among pts with AP (55%) number of AP (NAP) was 2[2;3]. IMT has been higher in menopausal women, pts with AH and IHD, correlated positively with age, body mass index, arterial blood pressure, level of TC, TG, LDL (p<0.05). Correlation IMT with DAS28-ESR, ESR, CRP has not been detected. Events of AP have been most frequently in older pts, menopausal women, pts with AH and IHD (p<0.05). After 18 months, significant decrease of DAS28-ESR, ESR, CRP accompany with increase of TC, LDL, HDL levels was achieved. IMT did not significantly changed. Among pts with baseline AP, NAP was increased (3[2;4]; p<0.05). NAP increased independently from achieved decrease of RA activity (DAS28-ESR<2.6/≥2.6). Among pts without baseline AP, newly onset AP have been detected in 8 pts (p<0.05), independently from reached decrease of RA activity (DAS28-ESR<2.6/≥2.6). Correlation ΔNAP with ΔTC, ΔTG, ΔLDL, ΔHDL and ΔDAS28-ESR, ΔESR has not been detected. However, the events of new AP were more frequent in those with greater baseline CRP level (r=0.35; p<0.01). Statin therapy has not resulted in change of lipid levels and progression of atherosclerosis in carotid arteries (ACA).

Conclusions: There was very high prevalence of ACA in early RA pts. ACA has relation to traditional risk factors. There was an increase of NAP (but not IMT) and onset of newly events of AP among early RA pts despite use of the “T2T” strategy. High baseline CRP levels were associated with more prominent ACA progression on treatment. Achieving of RA remission as judged by a DAS28-ESR did not translate into slowing of ACA progression.

Keywords: Rheumatoid arthritis, atherosclerosis, treat-to-target strategy, carotid artery duplex ultrasound

Poster Presentations

“From everyday clinical practice”

Myocardial revascularization in the elderly patients

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Purpose: based on the retrospective observational cohort study to assess the feasibility of the application of isolated coronary artery bypass grafting (CABG) in patients over 70 years old.

Material and methods: from January to December, 2015 at single center 200 CABG performed in patients older than 70 years. The average age of patients was 74.4 ± 2.4 years. Among operated was 26% of women, 74% of men. The proportion of patients with a BMI of 30 kg/m^2 – 30%, diabetes – 19%, atherosclerosis of carotid arteries – 66%, arterial hypertension – 91.5%, stroke history – 8.5%, kidney failure (GFR < 60 ml/min/1,73 m²) – 16.5% and myocardial infarction (MI) in the history of 74%. Were classified as stable angina 64.5% patients, as unstable angina 15% and 7.5% – as acute MI. Reduced left ventricular ejection fraction (< 30%) has had 5% patients. Left main coronary artery stenosis were in 11.5% of patients. All operations are performed using standard technique, with internal mammary arteries and vein, with cardiopulmonary bypass (61%) or on a beating heart (39%). The average number of distal anastomoses was 2.97 ± 0.8 , average number of proximal anastomoses with aorta was 1.5 ± 0.8 , average number of grafts was 2.5 ± 0.7 .

The results: In-hospital mortality from patients over 70 years old was 1.5%: one patient died as a result of postoperative bleeding, another cause of death became cardiogenic shock, the third – pneumonia and pleural empyema. The incidence of peri-operative stroke occurred in 1% of patients in cases after operations with cardiopulmonary bypass. Serious complications were common after CABG (bleeding-1.5%, respiratory failure-2.5%, sepsis – 1.0%). Paroxysmal atrial fibrillation after operations was registered in 27% of patients. The average time spent by patients in the intensive care 32.7 ± 41.2 hours, in hospital stay 11.2 ± 3.9 days.

Conclusions: coronary artery bypass an attractive option for the management of older people with ischemic heart disease. Mortality and complications in peri-operative period were satisfactory. However, were high postoperative atrial fibrillation and increase duration of stay in intensive care.

Keywords: coronary artery bypass grafting, older people, mortality, atrial fibrillation

Lipid profile in adolescents with focus on family history

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As atherosclerosis is a lifelong process that begins in childhood, it is important to discover risk factors in children's age. Among the significant risk factors are increased lipids and lipoprotein levels and positive family history.

Aim: To Determine the lipid and lipoprotein values in the serum of children aged 10 to 19, by sex, the percentage of children with values of lipids and lipoproteins, which are a high risk factors for cardiovascular disease in adult age, with special emphasis on family history

Material and methods: 1826 adolescents (957 boys and 869 girls) aged 10 to 19 were examined. They were classified into 4 groups. Children from families with risk factors for coronary heart disease without myocardial infarction (RG1), where one of parents suffered from myocardial infarction before the age of 55 (RG2), where grandparents suffered from myocardial infarction (RG3) and children without a family history of coronary heart disease and risk factors, the control group (CG)

Fasting plasma concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride were measured., low-density lipoprotein cholesterol (LDL-C) was calculated. The assessment of these values was in accordance with NCEP classification for children and adolescents (1991) and recommendation of New York Academy of Science (1991).

Results: Average values of lipids and lipoproteins were within normal limits. Relative to sex, TC, HDL-C, LDL cholesterol values were significantly higher in girls ($p < 0.01$, < 0.001 , < 0.10), triglycerides in boys (< 0.05). Non-HDL was higher in girls, but without significant difference ($p > 0.05$). The percentage of adolescents with TC and LDL cholesterol values which are high risk for cardiovascular diseases (CVD) in adulthood were higher in girls (13.12% 12.2% / 11.91%, 11.29%). The percentage of HDL-C, non-HDL and Tg were higher in boys (18:29%. 16:51%. 9:40% / 12:43%. 16.11%, 6.67).

Among 66 boys, whose one of parents suffered from myocardial infarction or stroke, in 31 (46.97%) of the boys, grandparents also suffered from myocardial infarction or stroke, and among 50 girls whose one of parents suffered from myocardial infarction or stroke in 20 (40%) girls grandparents also suffered from myocardial infarction or stroke.

The values of TC, LDL, non-HDL cholesterol and TG were significantly higher, and HDL-C significantly lower in the risk groups (RG1, RG2 and RG3) of adolescents than in the control group (< 0.001). The percentage of adolescents with lipids and lipoproteins values, which are a high risk factor for developing cardiovascular disease in adulthood were higher in adolescents with positive family history than in the control group.

Conclusion: Determining lipid and lipoproteins values in adolescents is very important especially in those with risk factors and positive family history. Children from families with coronary heart disease history and risk factors, are at increased risk of increased levels of lipids and lipoproteins and developing cardiovascular disease in adulthood.

Early identification of risk factors for atherosclerosis in children is the reason to take appropriate prevention measures.

Keywords: lipid profile, adolescent, family history, cardiovascular disease, risk factors

Matching of order rank over time measurements of blood pressure fluctuation and pulse wave velocity of the day using a wristwatch-type blood pressure meter in hemiplegics of the maintenance phase

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This study is part of a study aimed at to be used in the management of arteriosclerosis of hemiplegics of the maintenance phase using the pulse wave velocity.

Purpose: The aim is to clarify the match rate of rank the between the pulse wave velocity and wearable wristwatch-type blood pressure mete in 24 hours of hemiplegia in the maintenance phase.

Participations: Hemiplegia after cerebral vascular disorders, for people (n = 44), which uses the elapsed welfare facilities from the onset of more than two years. Enrolement is to walk alone. They agreed to the described.

Methods: We measured the blood pressure of 24 hours every 15 minutes in the paralysis measurement of the wrist of the participants by a wristwatch-type blood pressure meter. It used BPro (Healthstat, Singapore) of data of ambulatory blood pressure monitoring (ABPM). To measure the affected brachial-ankle pulse wave velocity by BP-203(Nihon Corin) every 6 hours. The analysis of the order match rate in the time zone in which the peak value of baPWV exists. Evaluation was order matching rate the between the order of PWV value of 24 hours indicating the good of the vessel hardness (slow speed) and the order of value of ABPM of the same point in time. Statistical analysis, descriptive statistics and from the data in this period, ABPM, to determine the degree of matching of the time zone in which the peak value of the time zone and baPWV which showed a peak value of the acceleration is present, was verified by Goodness fitness test. Using by the IBM-SPSS v20.

Results: Successive values of baPWV every 6 hours and charts concordance rate ABPM at each time was 60%. Linearity of one group is 80%, non-linearity group was 55%. The average value and standard deviation of the time distribution ratio of the activity-rest, sleep time (2SD), 1SD, 2SD, were divided into 2SD above three groups, to determine the time zone coincidence of the peak value in each group. Those who showed the ABPM that matches the baPWV variation of every 6 hours in the 24 hours is 60%, and the remaining 40% showed a peak value independent of the ABPM. Time zone for each of ABPM, matching degree of acceleration peak value time zone and PWV peak value time zone is ABPM60%, acceleration peak was 55%. Concordance rate of 68% within 1SD of each classification by the degree away from the mean value of the time distribution ratio of the activity-rest, sleep, 1 ~ 2SD within is 9%, 2SD or more was 22%.

Conclusion: baPWV and cross-order match rate of ABPM showed 60% of the match. In the future, if the application of the analysis of biological information, can be expected to monitor the inhibiting the deterioration vascular function of hemiplegics of maintenance phase from ABPM using a wristwatch-type blood pressure meter.

Keywords: Matching of order rank, pulse wave velocity, ABPM, hemiplegics, wristwatch-type blood pressure meter

Personalized approach to evaluate of the long-term prognosis of acute coronary syndrome with persistent ST-segment elevation

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Aim: Prediction of long-term (annual) negative and favorable outcomes of acute coronary syndrome with persistent segment elevation ST for optimal rehabilitation, secondary prevention and personalized treatment approach.

Material and methods: The study included 145 patients with STEMI (106 men and 39 women) who were hospitalized in Clinical Hospital No. 1 in Novosibirsk during 2010. The average age of patients was $59,1 \pm 6,1$ years. The diagnosis of ACS was installed on the set of criteria developed by the European Society of Cardiology and the American College of Cardiology (2000). All patients underwent clinical and instrumental study with the following program: clinical examination, electrocardiography, echocardiography, holter monitoring, the study of inflammatory cytokines and molecular genetic studies. The methods of factor and correlation analysis of the impact has been identified in each of the studied parameters on the probability of an unfavorable annual prognosis.

Results: The result of the study was an innovative method of multivariate prediction remote (annual) negative and favorable outcomes of acute coronary syndrome with persistent ST-segment elevation. Model includes determining whether or not a patient of diabetes mellitus (DM), the value of left ventricular ejection fraction (LVEF), a concentration of high-sensitivity C-reactive protein in serum (vchSRP) genotype for the polymorphic variant rs1376251 TAS2R50 gene. The sensitivity of the method for predicting adverse outcomes was 82% and success rate – 80%.

Conclusion: The proposed model is based on research performance in Russian patients and takes into account the activity of the atherosclerotic inflammatory process and the patient's genotype. The formula for calculating the probability of an adverse outcome shows how the weight factor with this or that factor affects the probability of an adverse outcome. The model is easy to use and allows you to personalize the secondary prevention in these patients.

Keywords: long-term outcomes, STEMI, multivariate prediction, atherosclerotic inflammatory process, rs1376251

Coronary stenting results in elderly patients with acute coronary syndrome

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Nowadays there is a demographic trend towards to global ageing of the population. Morbidity and mortality from ischemic heart disease (IHD), acute coronary syndrome (ACS)/myocardial infarction (MI) increase with age. A leading cause of total and cardiovascular mortality is IHD, ACS/MI. Invasive revascularisation in ACS improves treatment outcomes, reduces mortality rate. Research on ACS has shown the best results of active approach (urgent revascularisation) in patients with the highest risk of adverse outcomes. In elderly patients the risk of adverse outcomes in ACS is very high. However, for elderly patients there is the paradox «risk -treatment» – the greater the risk, the more a conservative approach is preferred by doctors in clinical practice due to the high risk of invasive intervention complications itself. There are a number of randomized studies with NNT- index using demonstrated the advantages of the active approach in the elderly patients with both versions of ACS. In our research we explored the efficiency of invasive revascularization, coronary stenting in elderly patients with ACS. The study included 919 patients, 213 of those aged 65-74 years, 224 – older than 75 years. In fact, according to the obtained data thrombolytic therapy (TLT) is performed less often in elderly patients over 75 years (5% against 11% in patients under the age 65 years). The number of cases of coronary angiography (CAG) also less with them due to higher frequency of renal dysfunction, high risk of x-ray contrast nephropathy, the bleedings (25% against 50% in patients under the age 65 years). However, in cases of a CAG, the proportion of emergency surgical revascularization – PCI, stenting of the coronary vessels had no difference between those in the group of patients younger than 65 years. An obtained data on the impact of invasive treatment on in-hospital outcomes of ACS undoubtedly indicate the best survival rates in elderly and senile age patients with a high risk of death in NSTEMI (in patients over 75 years from the group with PCI mortality rate is 0 % vs. 13% from the group without PCI, in patients aged 65-74 years – 0 and 5% respectively). These results are very important, because NSTEMI dominates among the elderly group of patients. Consequently, the invasive interventions with the abundance by precaution rules are preferable in that patient category.

Keywords: acute coronary syndrome, not ST elevation ACS (NSTEMI), coronary stenting, revascularisation, invasive intervention

EECP

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Background: The incidence of angina pectoris and congestive heart failure (CHF) continues to increase in the United States and in the rest of the world. EECP therapy is a novel and potentially beneficial adjunct clinical tool which is used in the treatment of patients (pts) who remain symptomatic despite maximum medical therapy.

Purpose: The study was undertaken to evaluate the beneficial results of EECP therapy in pts who remained symptomatic despite maximum medical management.

Methods: 84 consecutive pts referred for EECP were included; of this cohort, 52 pts were recruited and 42 completed a full course of therapy (35 sessions). Pre and post treatment results for changes in functional capacity and severity of symptoms were evaluated. A paired t-test was utilized to evaluate significance of results. A p-value of

Results: The mean age of the pts was 72 years (range: 49-94 years.) We looked at the 6 minute walk test (6MWT), Duke Activity Status Index (DASI), exercise tolerance in METs, mean anginal episodes per week, systolic blood pressure (SBP), diastolic blood pressure (DBP), and functional class of CHF and angina pectoris. The McNemar's test for comparison of CCVS/NYHA functional class was performed by combining functional class 1 and 2 (mild) and functional class 3 and 4 (moderate to severe). Pre and post treatment results were obtained. 6MWT: 386.1 vs 426.8 (SE: 7.9), $p < 0.0001$; DASI: 4.10 vs 6.3 (SE:0.57), $p < 0.0003$; exercise tolerance in METs 2.90 vs. 4.0 (SE 0.23), $p < 0.0001$; mean anginal episodes 12.3 vs. 2.4 (SE: 2.18), $p < 0.0001$; NTG use 2.45 vs. 0.47 (SE: 0.78), $p < 0.01$; SBP: 117 vs. 114 (SE: 1.5), $p < 0.05$; DBP: 67 vs 66 (SE: 0.687), $p = \text{NS}$; angina pectoris and CHF (CCVS/ NYHA functional class: 95 percent vs 25 percent, $p < 0.0001$.

Conclusions: There was significant improvement of anginal and CHF symptoms in pts completing a full course of EECP therapy. In addition, there was statistically significant improvement in the number of anginal episodes, DASI score, decreased NTG use, increased exercise tolerance in METs, mild decrease in SBP and improvement of angina/CHF functional class. However, no significant difference in DBP was observed. More research is needed to confirm these findings.

Keywords: Cardiac Rehabilitation, Ischemic Heart Disease, Congestive Heart failure, Angina Pectoris, Counter pulsation therapy

Cognitive deficits, dyslipidemia and patterns of statin therapy in patients with non-hemorrhagic stroke

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Objective: Stroke is a common long-term condition with an increasing incidence as the population ages. Stroke symptoms often include cognitive deficits. Dyslipidemia is a well-known risk factor for stroke. The aim of the study was to investigate the cognitive impairment, lipid profile characteristics and patterns of statin therapy in patients with non-hemorrhagic stroke.

Methods: In 178 patients with acute ischemic stroke (42.7% male, 69.2±8.9 (M±SD) years, current smoking 33.1%, abdominal obesity 71.9%, arterial hypertension 96.1%, myocardial infarction 16.3%, previous non-hemorrhagic stroke 35.4%, diabetes mellitus 19.7%, brachiocephalic atherosclerosis 79.2%, atrial fibrillation 24.2%, chronic heart failure NYHA II/III 32/4%, chronic kidney disease 21.9%, estimated glomerular filtration rate 67.1±17.1 ml/min/1.73 m², alcohol abuse 13.5%, anemia 12.9%, previous statin therapy 9.6% the cognitive impairment, lipid profile characteristics and frequency of statin therapy were assessed. Cognitive functions were evaluated by using the Montreal Cognitive Assessment (MoCA) scale.

Results: 171 (96%) patients had cognitive dysfunction: 20.1±4.3 scores by MoCA scale. 153 (86%) patients had dyslipidemia. The mean levels of lipids were 5.5±1.3 mmol/l for total cholesterol (TC), 1.1±0.3 mmol/l for HDL-C, 3.6±0.9 mmol/l for LDL-C and 2.1±0.6 mmol/l for triglycerides (TG). 18 (18%) patients were treated by statins during hospitalization. All of them took a *low-dose statin*.

Conclusion: 96% of patients with non-hemorrhagic stroke have cognitive impairment according to MoCA scale, 86% of patients have dyslipidemia, only 9.6% and 18% of patients receive low-dose statin therapy ambulatory and at hospital respectively. There is a substantial gap between the guidelines and real practice of statin therapy.

Anticoagulant Therapy (NOAC)

Prevention of thromboembolic disease in elderly hospitalized patients

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The document "Safe Practices for Better Health Care", from the National Quality Forum US, summarizes the high priority practices to be implemented based on the evidence of effectiveness for patient safety. It is based on a set of indicators which have been adapted to our Hospital and integrated in a plan for monitoring patient safety. A first evaluation of these indicators was carried out showing an opportunity to improve the indicator D01, which investigates the adequate assessment of the risk for deep vein thrombosis (DVT) and pulmonary embolism in medical patients and the correct use of prophylaxis. As a basis for this cycle, a study was performed to determine the adequacy of prophylactic anticoagulation in these patients, by measuring both the risk of DVT using the Padua Scale and the risk of bleeding using the IMPROVE Scale. The study included stays of two or more days in medical patients aged 65 or more years.

The LQAS technique was used to identify the clinic units having space for improvement. In this technique uniform lots of products are tested (in this case the units) according to reach or not pre-established quality standards using a small sample of each lot. The practice was considered as correct when explicitly assess the risk (all necessary items for scoring scales are registered) and the prophylaxis (anticoagulation) was given to the patient if both the Padua value is ≥ 4 and the IMPROVE value is < 7 , or do not receive it otherwise. (confidence 95%, power 80%). A proper practice standard level of 95% and a threshold of 55% (minimum level) were fixed. Every lot required to evaluate 6 patients, demanding a compliance of 5 patients of higher

A total of 54 cases (9 units / lots) were evaluated. Overall, 72% of the actions were correct ($95\text{CI} \pm 12\%$). Prophylaxis was initiated in 21 patients (39%), although only 17% needed it according to the scales values. A total of 25% of needed prophylaxis were not prescribed, while 71% of prescribed prophylaxis were not needed. No difference were found by patient gender or age. The correlation between prescribed prophylaxis and proper practice was high, reverse ($R = -0.86$) and significant ($p < 0.01$), so the more prophylactic prescribed alower percentage of proper practice should be expected. In 6 units the lot was accepted (67%).

The results indicate that the handling and safety of these patients can be improved.

Biomarkers

Arterial stiffness detected by different methods in population-based sample of Saint-Petersburg inhabitants

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Objective: Different diagnostic procedures of arterial stiffness are now suggested but the problem of more precise and simple evaluation is still discussed. The aim of our study is to determine the correlation between different methods of arterial stiffness assessment.

Design and methods: 452 apparently healthy participants aged 25–65 years were randomly selected from 1600 Saint-Petersburg inhabitants (a sample from ESSE-RF study). All participants signed informed consent and filled in the questionnaire regarding risk factors, concomitant diseases and therapy. Fasting lipids, glucose (Abbott Architect 8000 (USA)), anthropometry and BP measurement (OMRON, Japan) were performed. Cardio-ankle vascular index (CAVI) and carotid-femoral pulse wave velocity (cfPWV-V) were measured by VaSera VS-1500 (Fukuda, Japan), carotid-femoral pulse wave velocity (cfPWV-S) was measured by SphygmoCor (Atcor, Australia). Statistical analysis was performed using SPSS Statistics 20.

Results: Most of patients 341 (75,4%) did not have subclinical vascular damage by both methods and only 3 patients (0,7%) had. Increased arterial stiffness detected by CAVI assessment (33 (7,3%)) was found out significantly more often ($p < 0,005$) in comparison with cfPWV-S assessment (21 (4,6%)). Spearman's coefficient of correlation for cfPWV-S and CAVI was 0,74, coefficient of concordance "kappa" was 0,04. Spearman's coefficient of correlation for cfPWV-S and cfPWV-V was 0,10, coefficient of concordance "kappa" was 0,06. Spearman's coefficient of correlation for CAVI and cfPWV-V was 0,28, coefficient of concordance "kappa" was 0,03.

Conclusion: There was no significant correlations between different methods of arterial stiffness assessment. Probably, applanational tonometry and volumetric sphygmography are detecting slightly different pathological mechanisms.

PCSK9 level in male population and its association with atherosclerosis risk factors

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Concentration of atherogenic LDL cholesterol is often elevated in patients at high risk of cardiovascular disability and death. Proprotein convertase subtilisin/kexin type 9 [PCSK9] is a protein made by the liver which increases the removal of LDL receptors from the surface of liver cells. There is lack of population studies measured concentration of PCSK9, especially in Russia.

The aim of the study was to investigate blood levels of PCSK9 in males of different population subgroups and its associations with cardiovascular risk factors and with unfavorable 7-years long-term prognosis.

The study included three subgroups of males from a population sample of residents of Novosibirsk, 44-73 years old, not receiving lipid-lowering drugs: the population subgroup (183 males), the subgroup with a hypercholesterolemia (46 males) and a subgroup with hypocholesterolemia (18 males). Blood level of PCSK9 was determined by ELISA using the test-systems «Human Proprotein Convertase 9/PCSK9 Immunoassay» (R&D Systems). Long-term results of the endpoint (myocardial infarction, cardiovascular death) were studied for 7 years after the examination of population subgroups of males using the data of the Registers of myocardial infarction and cardiovascular mortality.

The results revealed a normal distribution of the protein PCSK9 in male population subgroups with hyper- and hypocholesterolemia and the abnormal distribution deposited to the left in the population group of males. PCSK9 protein concentration in the subgroup of males with hypercholesterolemia is 1.2 times higher than in the population group of males. Statistically significant correlations of PCSK9 protein level with total cholesterol, LDL cholesterol, glucose were presented. PCSK9 variability due to the influence of other factors is only 15% (R Square =0,155, $p < 0,001$). Significant influences of HDL-cholesterol levels (Beta =0,238, $p = 0,023$), TG (Beta =0,253, $p = 0,049$) and LDL cholesterol (Beta =0,751, $p = 0,009$) to protein PCSK9 blood level were showed. Multivariate regression analysis revealed a significant independent association of PCSK9 protein levels with the cardiovascular death in a 7-year long-term period ($p = 0,048$, OR =1,01). The results revealed increasing of the relative risk for cardiovascular death within 7 years after the examination independently of the other parameters by 1% in men by increasing blood levels of PCSK9 protein at 1 ng/ml.

Keywords: PCSK9, male population, hypercholesterolemia, hypocholesterolemia, long-term results

Markers of myocardial necrosis and acid-base balance parameters after beating-heart coronary bypass grafting in type two diabetes patients

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Aim: To study the relationships of myocardial necrosis markers dynamics with perioperative glucose-lowering treatment regimen, glucose metabolism and acid-base balance parameters during beating-heart coronary artery bypass grafting in type two diabetes patients.

Material and methods: The study included 71 patients with ischemic coronary disease (ICD) with type two diabetes mellitus (DM) treated by oral hypoglycemic agents undergoing off-pump coronary artery bypass grafting (CABG). The mean age was 59 [56–64]. There were 51 (71.8%) males. Up to 7 days before surgery the patients were randomized to continuing of oral hypoglycemic agents (n=34) or to switching to rapid-acting insulin (n=37). In the study groups we compared glycemetic parameters, markers of myocardial necrosis (troponin T and creatine phosphokinase-MB (CPK-MB)) and acid-base balance, as well as their dynamics during the perioperative period. The relationships of myocardial necrosis markers dynamics with glucose metabolism and acid-base balance parameters were investigated.

Results and conclusions: Baseline parameters of glucose metabolism did not differ between the groups. Before the surgery in switched to rapid-acting insulin patients serum glucose, its daily variability and the proportion of blood glucose values less than recommended perioperative range (6.1–10.0 mmol/l) were higher than in those at oral hypoglycemic agents. The myocardial necrosis markers at the day before and 24-h after surgery as well as lactate level and blood acidity during and at 24 hours after surgery were higher in the insulin-group. The insulin-group was characterized by greater increase of troponin T during 24-h after surgery (0.36 [0.25–0.40] vs. 0.2 [0.1–0.25] ng/ml, $p < 0.001$) and CPK-MB (14 [8.0–17.0] vs. 7.3 [1.5–8.7] U/L, $p < 0.001$). Troponin T and CPK-MB dynamics correlated with serum glucose during surgery ($r = +0.81$ and $r = +0.66$, respectively), daily serum glucose variability at the day before surgery ($r = +0.71$ and $r = +0.63$) and the first day of admission to hospital ($r = +0.37$ and $r = +0.31$).

Conclusion: In diabetes patients undergoing off-pump coronary artery bypass grafting the switching to rapid-acting insulin in comparison to those who continued oral glucose-lowering agents taking the higher perioperative increase of troponin T and creatine phosphokinase-MB was revealed.

Keywords: coronary artery bypass surgery, diabetes mellitus, troponin T, creatine phosphokinase-MB, acid-base status

Postprandial hyperlipidemia correlates with a degree of coronary atherosclerosis.

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Aim: To examine relationship between postprandial lipemia (PL) and severity of angiographic manifestations of coronary atherosclerosis.

Materials and Methods: 239 patients (pts, <65 yrs), which underwent the coronary angiography. Among them 72 patients had no the signs of coronary atherosclerosis (group 1), 60 patients had coronary stenosis < 50% (group 2) and 107 patients had stenosis >50% of a lumen. All patients underwent standard fat load (FL) by J. Patch (65 g of 20% milk fat cream per square meter of body surface) with venous blood samples drawn at fasting, 3 and 6 hours after the FL.

Results: Six hours after fat load the levels of triglycerides (TG) increased in group 1 by 91%, in group 2 by 131% and in group 3 by 180% ($p < 0,001$). In patients of group 2 and 3 we observed the rise of levels of LDL-C and apo B ($p < 0,01$, $p < 0,01$), while in group 1 patients these parameters decreased by 6% ($p < 0,01$). HDL-C and apo AI had significantly decreased in group 2 ($p < 0,01$) and 3 patients ($p < 0,01$), while in group 1 the levels of HDL-C and apo AI increased significantly. The apo B/apo AI ratio increased in group 2 ($1,03 \pm 0,02$ vs $1,28 \pm 0,01$, $p < 0,01$) and in group 3 ($1,35 \pm 0,02$ vs $1,59 \pm 0,02$, $p < 0,01$), while in group 1 (without coronary stenosis) apo B/apo AI ratio significantly decreased ($0,88 \pm 0,03$ vs $0,72 \pm 0,04$, $p < 0,02$). We observed the tight correlation between the coronary score (by G. Gensini) and square under the curve of TG ($r = 0,40$, $p < 0,02$) and TG in chylomicrons + VLDL cholesterol ($r = 0,69$, $p < 0,01$).

Conclusion: There is a tight correlation between the degree of coronary stenosis and postprandial abnormalities of lipids and lipoproteins.

Keywords: postprandial lipemia, coronary atherosclerosis, lipids, lipoproteins

Paraoxonase-1 overexpression prevents experimental abdominal aortic aneurysm progression.

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Abdominal aortic aneurysm (AAA) is a permanent dilation of the aorta due to excessive proteolytic, oxidative and inflammatory injury of the aortic wall. We aimed to identify novel mediators involved in AAA pathophysiology, which could lead to novel therapeutic approaches. For that purpose, plasma from 4 AAA patients and 4 controls were analyzed by a label free proteomic approach. Among identified proteins, paraoxonase-1 (PON1) was decreased in plasma of AAA patients compared to controls. Confirming the proteomic results, PON1 concentration was lower in AAA patients (N=52) compared to control subjects (N=29) (369.9 ± 25.1 vs 467.7 ± 30.4 ng/ml, $p < 0.05$). Since PON1 enzymatic activity must be determined in serum, serum samples were obtained from another cohort of AAA patients [N=58] and controls subjects [N=60]. Decreased PON1 activity was observed in AAA patients as compared to controls subjects (39.1 ± 1.7 vs 47.1 ± 2.1 UI/ml, $p < 0.001$). Multivariable logistic regression analysis showed that PON1 concentration and activity below the media were independent predictors for the presence of AAA. Similar to humans, PON1 activity was also decreased in serum of elastase-induced AAA mice (n=10) as compared to control (n=10) healthy mice (47.7 ± 2.6 versus 58.6 ± 3.9 UI/mL, $p < 0.05$). To address the potential role of PON1 as a mediator of AAA, elastase-induced AAA was performed in human transgenic PON1 mice (HuTgPON1) and wild type mice (WT). Interestingly, overexpression of PON1 was accompanied by smaller aortic dilatation and higher elastin and vascular smooth muscle cell content in the AAA of HuTgPON1 compared to WT mice. Moreover, HuTgPON1 mice display decreased oxidative stress and apoptosis, as well as macrophage infiltration and monocyte chemoattractant protein-1 expression, in elastase-induced AAA. In conclusion, decreased circulating PON1 activity is associated to human and experimental AAA. PON1 overexpression in mice protects against AAA progression by reducing oxidative stress, apoptosis and inflammation, suggesting that strategies aimed at increasing PON1 activity could prevent AAA.

Keywords: biomarkers, HDL, oxidative stress, abdominal aortic aneurysm

Inflammation enhances mortality in patients on renal replacement therapy

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Introduction: Atherosclerosis, a major problem in patients on chronic hemodialysis, has been characterized as an inflammatory disease. C-reactive protein (CRP), is a predictor of cardiovascular mortality in the general population. The aim of this study was to evaluate the relation of the inflammatory markers with mortality in patients with end stage renal disease on renal replacement therapy.

Methods: A case control study was conducted in the University Hospital Center “Mother Teresa” enrolling all patients on chronic dialysis (Hemodialysis and Peritoneal Dialysis) older than 18 years who had more than 3 months in therapy. Plasma levels of albumin (S alb) C-reactive protein (CRP), fibrinogen were measured using routine methods. All patients had been followed up for 2 years and the end point was overall and cardiovascular mortality.

Results: Our dialysis population studied consisted in 122 pts, 78 pts (61%) on hemodialysis, mean age 53.4 ± 14.5 years and mean time on therapy was of 40.4 ± 14.4 months. S alb result 3.28 ± 0.46 g/dl, CRP 8.4 ± 8.36 mg/L, fibrinogen 551.2 ± 116.1 . Overall mortality was 27 events (22 %) while cardiovascular mortality was 15.5% (19 events). The main causes of CV death were sudden deaths (31.5%), deaths from ischemic heart disease and stroke with 26.4% respectively. Binary logistic regression analysis showed that CRP [OR= 1.06 (1.01-1.10) p=0.011], was independent risk factor for cardiovascular mortality. It was found an increase of 6% of cardiovascular mortality for each unit increase of CRP [OR=1.06(1.01-1.10) p=0.011]. Meanwhile albumin levels below 3g/dl represent an independent risk factors with a risk 3.7 higher for overall mortality (p=0.024)

In Conclusion: End stage renal disease represent a high inflammatory profile where amongs its markers CRP and serum albumin are independent predictor of cardiovascular mortality and overall mortality respectively.

Keywords: Inflammation, mortality, end stage renal disease

Circulating myeloid-related protein-8/14 is related to thromboxane-dependent platelet activation in patients with acute coronary syndrome, with and without ongoing low-dose aspirin treatment

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Platelet activation is involved in acute coronary syndromes (ACS). Incomplete suppression by low-dose aspirin treatment of thromboxane (TX) metabolite excretion (urinary 11-dehydro-TXB₂) is predictive of vascular events in high-risk patients. Myeloid-related protein (MRP)-8/14 is a heterodimer secreted on activation of platelets, monocytes, and neutrophils, regulating inflammation and predicting cardiovascular events. Among platelet transcripts, MRP-14 has emerged as a powerful predictor of ACS. We enrolled 68 stable ischemic heart disease (IHD) and 63 ACS patients, undergoing coronary angiography, to evaluate whether MRP-8/14 release in the circulation is related to TX-dependent platelet activation in ACS and IHD patients and to residual TX biosynthesis in low-dose aspirin-treated ACS patients. In ACS patients, plasma MRP-8/14 and urinary 11-dehydro-TXB₂ levels were linearly correlated ($r=0.651$, $P<0.001$) but significantly higher than those in IHD patients ($P=0.012$, $P=0.044$) only among subjects not receiving aspirin. In aspirin-treated ACS patients, MRP-8/14 and 11-dehydro-TXB₂ were lower versus those not receiving aspirin ($P<0.001$) and still significantly correlated ($r=0.528$, $P<0.001$). Higher 11-dehydro-TXB₂ significantly predicted higher MRP-8/14 in both all ACS patients and ACS receiving aspirin ($P<0.001$, adj $R(2)=0.463$ and adj $R(2)=0.497$) after multivariable adjustment. Conversely, plasma MRP-8/14 ($P<0.001$) and higher urinary 8-iso-prostaglandin F_{2α} ($P=0.050$) levels were significant predictors of residual, on-aspirin, TX biosynthesis in ACS (adjusted $R(2)=0.384$). Circulating MRP-8/14 is associated with TX-dependent platelet activation in ACS, even during low-dose aspirin treatment, suggesting a contribution of residual TX to MRP-8/14 shedding, which may further amplify platelet activation. Circulating MRP-8/14 may be a target to test different antiplatelet strategies in ACS.

Keywords: Platelet, 11-dehydro-TXB₂, MRP-8/14

Endothelial dysfunction markers in liver and kidney transplant recipients

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Research Objective: a continuous monitoring of endothelial dysfunction markers in liver and kidney transplant recipients (L&KTRs) at two stages: when selected for the waiting list and throughout the long-term postoperative period.

Materials and Methods: 164 patients of the (RTPCOTT), RB, were examined: 75 recipients after orthotopic liver transplantation (Group 1), and 89 patients after kidney transplantation (Group 2). The research had a prospective nature, including patients into the research groups at the waiting list stage.

Results: L&KTRs in the long-term postoperative period showed a verifiable increase in the level of nitric oxide metabolites (NOM): in Group 1 it was 45.83 ± 3.57 micromole on average; in Group 2 – 54.4 ± 4.33 micromole, $p < 0.05$. At the waiting list stage the level of NOM in potential donor L&KTRs was 49.9 ± 4.77 micromole and 51.8 ± 5.12 micromole accordingly. After the liver transplant operation the recipients showed a lower level of NOM than the kidney transplant recipients, which may be linked with a more pronounced endothelial dysfunction, prior to the surgery. A comparison of endothelin-1 levels in L&KTRs confirms a verifiable increase in endothelin-1 content in the blood serum of kidney transplant recipients in the long-term postoperative period (37.6 ± 1.8 ng/ml on the waiting list and 47.7 ± 4.3 ng/ml 12 months after the surgery, $p < 0.05$). The statistical processing of the data ascertained that the endothelin-1 level in kidney transplant recipients also considerably exceeded the normal figures. At the waiting list stage it was considerably lower than in the postoperative period (38.3 ± 6.1 ng/ml and 51.3 ± 8.5 ng/ml accordingly, $p < 0.05$). Mean concentration of the adhesion molecule VCAM in kidney transplant recipients in the long-term postoperative period was 980.4 ± 128.4 ng/ml, while in the group of donor liver recipients it was 565.24 ± 46.26 ng/ml, $p < 0.01$. At the waiting list stage this index was 550.06 ± 25.86 ng/ml and 542.39 ± 41.58 ng/ml accordingly. Thus, the mean concentration of VCAM was verifiably higher in the long-term postoperative period in the group of donor kidney recipients, despite the lack of difference at the waiting list stage in both the groups under study. Mean concentrations of P-selectin in the postoperative period were for Group 1 – 251.43 ± 14.28 ng/ml, for Group 2 – 309.47 ± 10.18 ng/ml, $p < 0.05$. Before the transplantation these indices were comparable in both the groups: 289.54 ± 9.12 ng/ml, and 299.17 ± 11.45 ng/ml accordingly. Mean levels of E-selectin were practically the same in both the groups: 59.39 ± 4.37 ng/ml and 69.87 ± 6.37 ng/ml in Group 1 before and after the surgery; 54.47 ± 2.98 ng/ml and 67.34 ± 8.12 ng/ml in dynamics in Group 2.

Conclusion: L&KTRs in the long-term postoperative period showed a verifiable rise in the level of NOM, of endothelin 1, of cell-cell adhesion molecules VCAM and of P-selectin, which means that organ transplantation does not solve the problem of reducing cardiovascular risk for patients on the whole and of endothelial dysfunction in particular.

Keywords: endothelial dysfunction markers, liver and kidney transplant recipients, cardiovascular risk

Apolipoprotein B versus non-high-density lipoprotein cholesterol: Association with markers of endothelial dysfunction and subclinical atherosclerosis

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Background: Both apolipoprotein B (apoB) and non-HDL-cholesterol (non-HDL-C) are accepted as alternative risk factors or targets for lipid lowering therapy, which correlate more strongly with cardiovascular events than LDL-cholesterol.

Objective: The aim of the study was to evaluate the differences in plasma levels of plasminogen activator inhibitor-1 (PAI-1) and of von Willebrand factor (vWF) as markers of endothelial dysfunction and intima-media thickness (IMT) of the common carotid as a marker of subclinical atherosclerosis between dyslipidemic individuals with apoB levels higher or lower than predicted from regression equation of apoB versus non-HDL-C.

Methods: 594 dyslipidemic subjects without atherosclerotic manifestation were divided into these groups: H-apoB group (n=222), L-apoB group (n=239) with higher or lower apoB levels than predicted and group (n=133) with apoB levels within $\pm 15\%$ predicted levels from regression equation of apoB versus non-HDL-C. Differences in variables between groups were analyzed by ANOVA after adjustment for age, gender and smoking. Multivariate regression analyses were used for testing for an independent association between variables.

Results: Significantly higher levels of diastolic blood pressure ($p < 0.001$), total ($p < 0.05$) and LDL-cholesterol ($p < 0.001$) were detected in H-apoB individuals. They also had higher levels of PAI-1 ($p < 0.001$). No significant differences were found in vWF, IMT and markers of insulin resistance. PAI levels were independently predicted by apoB ($p < 0.0001$) and non-HDL-C ($p < 0.001$). Neither apoB, nor non-HDL-C was independently associated with IMT.

Conclusion: ApoB measurement beyond non-HDL-C calculation can identify the subjects with signs of endothelial damage, but not those with subclinical atherosclerosis.

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Keywords: apolipoprotein B, non-HDL-cholesterol, plasminogen activator inhibitor-1, von Willebrand factor, intima-media thickness

The relationship of FGF-21 and A-FABP to markers of insulin resistance and endothelial dysfunction in individuals with dyslipidemia

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Introduction: Fibroblast growth factor 21 (FGF-21) mediates a number of positive metabolic effects, and maybe protects cardiovascular cells. In contrast, adipocyte fatty acid binding protein (A-FABP) is a factor with many adverse metabolic effects and is considered as an indicator (or even the mediator) of obesity-related cardiovascular diseases. The aim of the pilot study was to compare the levels of FGF-21 and of A-FABP in dyslipidemic or normolipidemic individuals and to determine the relationship of these factors to the selected markers of insulin resistance and endothelial dysfunction.

Methods: 148 asymptomatic dyslipidemic individuals (DLP; 70 men, 78 women) and 66 healthy controls (NLP; 38 men, 28 women) were included in the study. In addition to FGF-21 A-FABP, lipid and anthropological parameters, some indicators of insulin resistance – insulin, C-peptide, fasting glycemia, and markers of endothelial dysfunction – von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (t-PA), thrombomodulin and soluble vasoactive molecules (s-VCAM-1, s-ICAM-1) were also examined.

Results: In comparison with healthy controls DLP individuals had higher levels of FGF-21 [234.6 (134.6-419.3) versus 128.4 (63.7-225.5) ng/l, $p < 0.001$]. Levels of A-FABP were significantly higher only in individuals with metabolic syndrome [26.9 (21.6-40.1) versus 20.4 (15.6-419.3) $\mu\text{g/l}$, $p < 0.01$]. FGF-21 was independently associated with vWF ($\beta = 0.421$, $p < 0.01$), t-PA ($\beta = 0.110$, $p < 0.01$), fasting glycemia ($\beta = 0.266$, $p < 0.01$) and the waist circumference ($\beta = 0.534$, $p < 0.001$). A-FABP was associated with vWF ($\beta = 0.686$, $p < 0.001$), C-reactive protein ($\beta = 0.076$, $p < 0.05$) and with a body mass index ($\beta = 0.525$, $p < 0.01$).

Conclusion: Asymptomatic dyslipidemic individuals have significantly higher levels of FGF-21 which are independently associated with markers of endothelial dysfunction. A-FABP could participate in damage of endothelium. Conversely, the increase of FGF-21 could be a secondary result as a protection against of the endothelial injury.

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Keywords: Fibroblast growth factor 21, Adipocyte fatty acid-binding protein, Endothelial dysfunction, Dyslipidemia

Age and gender properties of protein growth factors and damages in acute coronary syndromes

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Introduction: Worldwide deaths from cardio – vascular disease ranks first among all causes of overall mortality. To improve the diagnosis and risk stratification of acute coronary syndrome and opened actively studied new protein growth factors and damage, pregnancy-associated plasma protein-A (PAPP-A) and insulin-like growth factor 1 (IGF-I).

Objective: analysis of PAPP-A and IGF-I in the blood plasma in patients with acute coronary syndrome. The identification of gender, age, property, confirm the biological role of proteins. The ability to predict disease at the protein level.

Material and methods: The study included 71 patients with acute coronary pathology (ACS), the mean age was $57 \pm 8,5$ years. The blood plasma of patients measured PAPP-A and IGF-I. Blood sampling was carried out at the time of admission of the patient to verify a definitive diagnosis. The concentration of PAPP-A was determined by immunofluorescence («Diagnostic Systems Laboratories», USA). The concentration of IGF-I was determined by enzyme immunoassay (ELISA) using the kits of the company «Diagnostic Systems Laboratories» (USA). The control group consisted of 20 healthy individuals. The comparison group consisted of 40 patients with hypertension and coronary heart disease with stable forms of angina. Statistical analysis of the material held by a package “Statistics 8.0”.

Results: PAPP-A in patients with myocardial infarction with Q wave were the highest $27,75 \pm 11,75$ and close to the cases of mortality $27,7 \pm 7,1$. In patients with myocardial infarction without Q wave PAPP-A concentrations were slightly lower than $22,12 \pm 7,69$, but fairly significant ($p < 0.05$) higher than that of patients with a diagnosis of unstable angina $-8,22 \pm 3,16$. Increasing concentrations of IGF-I also noted in all patients with acute myocardial infarction. However, compared to PAPP-A, the concentration of IGF-I in patients with acute myocardial infarction with Q wave was $156,53 \pm 45,31$, and was slightly lower than in patients with acute myocardial infarction without tooth Q $-172,28 \pm 31,59$ and unstable angina. The highest concentration of IGF-I was in patients with unstable angina $179,68 \pm 44,09$. There was a negative correlation IGF-I and PAPP-A in the case of death from acute myocardial infarction – the concentration of IGF-I declined and amounted to $126,06 \pm 15,12$, while the levels of PAPP-A was the highest. Identified gender differences IGF-I in patients with ACS, men $175,54 \pm 45,73$, women $150,60 \pm 37,18$ ($p = 0,024$). PAPP-A group of heart attacks in men was $29,64 \pm 10,64$, women – $21,62 \pm 10,76$ ($p = 0,021$). In the other categories of studies gender differences are not revealed. Differences between levels of PAPP-A and IGF-I may be explained by the heterogeneity of groups. Analysis of the gender feature of 2x2 test showed in the outcome of myocardial infarction – $\chi^2 = 0,08$, $p = 0,77$, in unstable angina – $\chi^2 = 0,16$, $p = 0,69$, the probability of death – $\chi^2 = 1,64$ $p = 0,20$. Three variations of the endpoints of ACS the likelihood of disease outcome does not depend on gender, $p > 0,05$.

Correlation of IGF-I levels and indicators of age in patients with ACS in the form of negative communication moderate ($r = -0,3$, $p = 0,01$). PAPP-A has no correlation with patient age ($r = -0,1$, $p = 0,38$, this acute phase protein, indicating deterioration and instability of an atherosclerotic plaque.

Conclusions: The concentrations of PAPP-A and IGF-I was significantly higher in the acute coronary disease compared with healthy individuals, patients with hypertension and coronary heart disease (stable form of angina).

The present study shows that the levels of IGF-I and PAPP-A does not have the gender properties, and is confirmed by their biological role, PAPP-A – a protein damage, acute phase, and IGF-I – a marker of vascular growth or repair when damaged. Interaction of IGF-I and PAPP-A is considered as the mechanism of injury and protect the vessel wall in atherosclerosis.

Keywords: pregnancy-associated plasma protein-A, insulin-like growth factor-1, acute coronary syndrome, myocardial infarction, unstable angina

Clinical significance of the protein growth factors and injury in acute coronary syndrome

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Introduction: PAPP-A and IGF-I – markers, the biological role of which – activation damage and protect the vessel wall. In cardiology, for predicting the outcome of acute coronary syndrome applied scale Grace.

The purpose of the analysis of PAPP-A and IGF-I acute coronary syndrome, prognostic significance.

Material and methods: In a study of 71 patients with acute coronary syndrome, the average age of 57 years. The plasma was determined PAPP-A and IGF-I. The blood sampling was performed at admission. Indicators calculated Grace scale program Ask risk model. A control group of 20 healthy individuals. A comparison group of 40 patients with hypertension and coronary heart disease with stable forms.

Results: PAPP-A, IGF-I acute coronary syndrome higher compared with controls and comparison. PAPP-A unstable angina higher than in the control group to 3.6 times, and PAPP-A myocardial infarction of 11.6 times. PAPP-A myocardial infarction is 3.2 times higher than in unstable angina. IGF-I unstable angina highest, 1.2 times higher than in the control group. Lowest IGF-I in the cases of mortality figures – 1.27 lower than in the control group. All patients with myocardial infarction had symptoms of complications of acute period. Correlation of IGF-I with the outcome of myocardial infarction and Grace in a hospital statistically significant ($p < 0.05$) negative, moderate, $p = 0.004$, $r = -0.42$, with Grace in 6 months a statistically significant ($p < 0.05$) negative, moderate, $p = 0.001$, $r = -0.46$.

Conclusion: PAPP-A and IGF-I-protein growth factors and damage, can be used as the analyzer unstable atherosclerotic plaque in acute coronary conditions. A significant increase in PAPP-A, reduced IGF-I adversity and negative outlook, indicating the massive development of vascular inflammation and low vascular repair. IGF-I and PAPP-A – a modern biochemical markers of early and six-month prognosis of acute coronary disease.

Keywords: Unstable angina, myocardial infarction, pregnancy-associated plasma protein-A, insulin-like growth factor-1, acute coronary syndrome

Hypercortisolaemia as a biomarker of long-term prognosis in patients with myocardial infarction

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Aim: to assess plasma cortisol levels in patients with acute myocardial infarction (AMI) and glucose abnormalities (GA) and to study the relationships between hypercortisolaemia and the long-term prognosis of AMI.

Methods: In all, 360 subjects (63.6% of men) during 1st-5th day of AMI were included. All patients without diabetes mellitus type 2 (DMT2) passed the oral glucose tolerance test (OGTT) during the second AMI week. Plasma levels of insulin and cortisol during OGTT, leptin and adiponectin were defined in 113 consecutive patients. Differences in patients' anthropometrical data, blood level of biomarkers were analyzed by Kruskal-Wallis and χ^2 tests and post-hoc tests with Bonferroni correction ($p=0.0167$). Associations of hypercortisolaemia (>600 nmol/l) with the occurrence of adverse events during two-year follow-up period after AMI were studied by logistic regression analysis.

Results: All patients had increased basal level of cortisol (>600 nmol/l) despite the presence of GA. Patients with hypercortisolaemia had significantly higher levels of basal glycaemia (5.5 (5.05-5.78) vs 5.3 (5.10-5.83) mmol/l, $p=0.006$) and adipokines (leptin (131.9 (74.3-157.0) vs 127.0 (69.5-162.0) ng/ml, $p<0.001$) and adiponectin (3.83 (2.61-4.25) vs 3.82 (3.44-4.28) ug/ml, $p=0.001$). There were significant associations between hypercortisolaemia and long-term prognosis of AMI. It was an independent predictor of repeated AMI (OR=2.97, 95% CI=1.16-7.59, $p=0.023$) with adjustment for previous AMI on admission ($p=0.038$), glycaemia on admission ($p=0.054$), and GA ($p=0.475$), and a predictor of combined end point of cardio-vascular events (OR 1.88, 95% CI=1.03-3.43, $p=0.039$), but had insignificant independent association ($p=0.166$) after adjustment for other risk factors.

Conclusions: Basal cortisol levels were abnormally high in all patients with AMI. Basal hypercortisolaemia was associated with poor long-term prognosis after AMI.

Keywords: hypercortisolaemia, myocardial infarction, long-term prognosis

Investigating the underlying mechanisms in high risk CAD by studying patient specific iPSCs derived hepatocyte models in vitro

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Coronary artery disease (CAD) remains asymptomatic for decades and conventional laboratory tests such as LDL-C are known as poor predictors of chronic diseases. At least 10% of the chronic events occur in apparently healthy individuals in the absence of traditional risk factors. In addition, while some of the atherosclerotic plaques remain stable during the lifetime, others can be highly vulnerable and lead to heart attack and sudden death. In this study we investigate if molecular lipid species such as distinct phospholipids and sphingolipids could be better predictors of clinical outcome for CAD. Here, we aim to develop an *in vitro* model of CAD patient's hepatocytes to study key lipids involved in formation of vulnerable atherosclerotic plaques. To achieve our aim, induced pluripotent stem cells (iPSCs) have been developed from the skin biopsies of three patient groups: acute, stable CAD and control. Then iPSCs have been differentiated to functional hepatocyte-like cells. Three hepatic differentiation methods were tested to find the best protocol for our purpose and results have been compared. The gene expression of SOX17, FOXA2, AFP, and ALB was evaluated by qPCR and confirmed by Immunocytochemistry. We show that hepatocyte-like cells were able to uptake LDL, store lipids, and secrete LDL, TG, albumin, as well as urea. However, we did observe that various methods produced hepatocytes with different morphology and functionality. Lipidomic data by mass spectrometry revealed that lipid profile varies between hepatocytes produced by different methods. In conclusion, we have successfully set up an *in vitro* patient specific hepatocyte model which is functional and is capable of secreting lipids. This model can be an invaluable platform to investigate the underlying mechanisms in CAD which can lead us to discover novel lipid biomarkers for high risk CAD. We already have nominated some candidate lipids as reliable predictors of risky CAD.

Keywords: Atherosclerosis, Induced pluripotent stem cells, Hepatocyte-like cells, In vitro model, Lipidomics

Inflammation markers and lipid profile analysis in the patients after myocardial revascularization

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The inflammation and lipoprotein levels are the main factors of atherogenesis. The aim was to determine atherogenic factors correlation in the patients underwent myocardial revascularization.

Materials and methods: The study included 130 patients with non-ST elevation acute coronary syndrome (non-ST ACS) underwent coronary artery bypass grafting (CABG). The average age of patients was 58.4 years±0.8 years. Inflammation markers (IL-6, TNF- α , ICAM-1, TGF- β 1, C-reactive protein, fibrinogen, white blood cells) and lipid panel were measured in blood serum at the 6, 12, 24 and 48 months of follow-up. Immune-enzyme analysis was used to measure ICAM-1, cytokines and C-reactive protein levels in blood serum samples. The lipid panel was determined by direct homogenous enzymatic colorimetric method. Correlation analysis was used to process the results.

Results: It was shown a significant positive correlation between total cholesterol, low-density lipoprotein levels and fibrinogen ($r_s=0,54$; $p<0,05$ and $r_s=0,85$; $p<0,01$, respectively), C-reactive protein ($r_s=0,33$; $p<0,05$ and $r_s=0,55$; $p<0,01$, respectively) and leukocyte concentrations ($r_s=0,24$ and $r_s=0,35$; $p<0,05$, respectively). ICAM-1 and TNF- α levels were positively correlated with the triglyceride values ($r_s=0,43$ and $r_s=0,40$; $p<0,05$, respectively). Atherogenic coefficient had a statistically significant relationship with the TGF- β 1 ($r_s=0,35$; $p<0,05$), TNF- α ($r_s=0,66$; $p<0,05$), C-reactive protein ($r_s=0,85$; $p<0,05$) and leukocytes levels ($r_s=0,68$; $p<0,05$). A negative correlation of IL-6 and fibrinogen levels was detected for high density lipoprotein ($r_s= -0,33$ and $r_s= -0,78$; $p<0,05$, respectively) values.

Conclusions: Correlation analysis showed a close relationship between systemic inflammation markers and blood lipid levels and confirms an important role of atherosclerosis prevention among patients underwent CABG.

Keywords: inflammation, atherogenesis, revascularization, lipoprotein

Evaluation of Uromodulin as new serum marker for renal function and the incidence of chronic kidney disease

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Uromodulin is exclusively produced in the kidney by cells lining the thick ascending limb and the most abundant protein excreted in urine under physiological conditions. Apart from a recently demonstrated link between low serum uromodulin and decreased kidney function, merely anything is known about the potential of uromodulin as renal biomarker in blood.

In this study we evaluated the association between serum uromodulin and the incidence of chronic kidney disease (CKD) in 529 angiographically characterized patients. Clinical parameters including renal function have been determined at baseline and reassessed at a 4-year follow-up (FU) visit.

In our study, patients' uromodulin levels were significantly correlated with eGFR ($r=0.242$, $p<0.001$) and, in an inverse way, with ACR ($r=-0.108$, $p=0.020$) as well as urea ($r=-0.314$, $p<0.001$). We thus observed significantly different serum uromodulin concentrations in our patients with respect to presence or absence of CKD (stage ≥ 3 ; 71.9 ± 29.0 vs. 169.1 ± 76.1 ng/ml, $p<0.001$), albuminuria (>30 mg/g; 148.7 ± 72.2 vs. 167.9 ± 77.6 , $p=0.008$), and hypertension (160.9 ± 74.0 vs. 181.8 ± 87.8 ng/ml, $p<0.037$). Moreover, low serum uromodulin concentration was not only an indicator for the prevalence of kidney disease but also a predictor for future decline of renal function (CKD stage ≥ 3) during the 4-year follow-up (126.8 ± 42.3 vs. 177.2 ± 80.3 ng/ml, $p=0.007$). That risk for getting CKD stage ≥ 3 was inversely associated with serum uromodulin concentration, even after adjustment for patients' age, sex, blood pressure or the diabetic or CAD status (OR=0.348 [95%CI 0.146-0.832], $p=0.018$).

We conclude that serum uromodulin is a novel predictive biomarker for renal disease.

Keywords: uromodulin, biomarker, chronic kidney disease

Markers of vascular inflammation in patients with coronary artery disease and arterial hypertension

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Purpose: To study the vascular inflammatory response in coronary artery disease (CAD) patients with arterial hypertension (AH).

Methods: A total of 396 patients with significant coronary artery stenosis >75% were examined and divided into two groups: 1 – patients with CAD (n=44, mean age 54.5 ±8.2 years); 2 – patients with CAD and AH (n=352, mean age 57.4 ±8.3 years). Lipid profile parameters; vascular inflammatory markers (uric acid, hs-CRP, TNF-alpha, homocysteine, interleukine (IL)-1β, IL-6, IL-8; sCD40, CD40L, MMP-9, TIMP-1); endothelial dysfunction markers (endothelin-1, nitrites) were measured.

Results: Value of MMP-9 and TIMP-1 was significantly higher than the norm in both groups, but a higher level of TIMP-1, IL-8 was registered in group 1; MMP-9 and uric acid were higher in group 2.

In group 1 TIMP-1 was associated with the level of nitrites ($r=0.65$, $p<0.001$), MMP-9 ($r=-0.34$, $p=0.016$), FNO-a ($r=0.31$, $p=0.035$) and VLDL ($r=0.43$, $p=0.004$). In group 2 MMP-9 correlated with age ($r=0.16$, $p=0.003$) and HDL ($r=-0.12$, $p=0.029$). The regression analysis revealed the following factors associated with MMP-9: hs-CRP ($\beta=0.22$, $p=0.001$), age ($\beta=0.20$, $p=0.003$) in group 2.

Conclusion: In patients with CAD and AH the imbalance of MMP-9/TIMP-1 prevailed. It may be associated with the higher risk of development of atherosclerotic plaques instability in this group.

Keywords: vascular inflammatory response, coronary artery disease, arterial hypertension

Tissue RAS activity in hypertensive patients with atherosclerosis

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Introduction: It is known that expression of tissue rennin-angiotensin system (RAS) components significantly increases in arterial hypertension and associated conditions independently of circulating RAS activity.

Study objective was to compare the activity of tissue RAS on the basis of estimation of expression level of angiotensin II receptor type 1 (AT1R) in the smooth muscle cells (SMCs) in intact and atherosclerotic arteries of patients with arterial hypertension and atherosclerosis.

Methods: We investigated 31 resected medium caliber arteries. 17 arteries of patients with low extremity atherosclerosis collected during vascular reconstructive operations made the first study group. The second group consisted of 14 intact mammary arteries collected during coronary bypass in subjects with multivessel coronary disease. The groups did not differ significantly by age, gender, arterial hypertension severity, concomitant disorders (diabetes mellitus, obesity etc.). AT1R localized in SMCs were detected by immunohistochemistry with specific polyclonal antibodies to AT1R (polyclonal antibodies to Anti-AGTR1, DAKO Company, visualization system DAKO Envision Flex+). In each case of immunohistochemistry research the expression of Anti-AGTR1 marker as brown cytoplasmic or membrane staining was studied in 30 fields of view with magnification x200. Staining intensity of AT1Rs in muscular layer of arteries was assessed semiquantitatively by percentage of positive cells according to 3-level scale: «-», negative (lack of positively stained cells); «+», focal or weak expression (<50% of positive cells); «++», diffuse or strong positive reaction (>50% of positive cells).

Results: Similar results were achieved in both groups. In 8 arteries of the first group (47.05%) the low expression (+) of AT1R was found, in other 8 arteries the AT1R expression (47.05%) was strong. There was no AT1R expression (-) in 1 case (5.9%). Thus, significant tissue expression was observed approximately in 50% of patients with atherosclerotic arteries, moreover it did not depend on the studied vascular bed (affected or intact).

Conclusion: The study results suggest that the tissue RAS activity increases inhomogeneously among patients with arterial hypertension and high cardiovascular risk. AT1R expression levels in intact arteries does not differ of those in atherosclerotic arteries ($p>0.05$). AT1R expression in SMCs is negative in patients with severe atherosclerosis that puts under the doubt the key role of RAS in pathogenesis of vascular remodeling in some cases.

Further researches of mechanisms that influence the level of RAS tissue components expression are needed. The studies of low susceptibility cause of mammary arteries to atherosclerosis in high RAS activity in the presence of severe lesions of arteries at other sites are required (for example, severe coronary atherosclerosis).

Probably the study of efficacy of RAS inhibitors in patients with various AT1R tissue expressions will allow to develop the prognostic methods of therapy efficiency and to individualize the treatment.

Keywords: rennin-angiotensin system, atherosclerosis, angiotensin II receptor type 1

Simvastatin and omega-3 polyunsaturated fatty acid in connective tissue dismetabolism correction in the cerebral vessels in experimental tobacco model.

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The aim: to examine the influence of omega-3 polyunsaturated fatty acids and simvastatin to metabolism of connecting tissue in cerebral vessels with experimental modeling of smoking.

Materials and methods: The material are male rats Wistar kind. The rat's model of experimental smoking was recreated by protocol H. Zheng. The first group got the simvastatin by dose 5 mg/kg/day, the second group got the drug omega-3 of polyunsaturated fatty acids (omega-3PUFAS). The third group got both drugs. The fourth group did not get a therapy. Drug of omega-3PUFA is a mixture of purified to 95% eicosapentaenoic acid and docosapentaenoic prepared from pollack liver in the Pacific Institute of Marine Biology Far Eastern Branch of the Russian Academy of Science. The control group were rats which breathe atmospheric air. After experiment histological preparations were prepared from brain tissue. We direct localization and assessment of expression of matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9) and their inhibitors (TIMP-1 and TIMP-2). We quantified the expression level by method measurement of the total density of the precipitate immunohistochemical reaction. The result was expressed in units of optical density (UOP). The significance of differences between groups ($p < 0,05$) was assessed using the Mann- Uitni coefficient.

Results: Precipitates of MMPs and their inhibitors were detected in the capillaries of parenchymal and meningeal vessels. In the group of smokers showed an increase in the intensity of sediment precipitate both MMPs. (MMP-9_{control} 41,44±13 and MMP-9_{smokers} 65±18; MMP-2_{control} 44±13,5 and MMP-2_{smokers} 53,5±16 UOP; $p < 0,05$). Also found to decrease the activity of tissue inhibitors, more TIMP-1 (TIMP-1_{control} 65,9±26 and TIMP-1_{smokers} 34,9±15; TIMP-2_{control} 28,4±14 and TIMP-2_{smokers} 11,6±4,9 UOP; $p < 0,05$).

After treatment with simvastatin showed reduced levels of MMP-2 and MMP-9 activity and increase their inhibitors (MMP-9_{simv.} 51,6±13, MMP-2_{simv.} 41,2±16, TIMP-2_{simv.} 21,39±12, TIMP-1_{simv.} 38,2±14 UOP; $p < 0,05$).

In animals treated with monotherapy omega-3PUFAs showed a reduction in the level of MMP-2 and increased expression of inhibitors. (MMP-2_{pufa} 40,2±13, MMP-9_{pufa} 65±20, TIMP-2_{pufa} 19,8±10, TIMP-1_{pufa} 48,5±16 UOP; $p < 0,05$)

After the combination therapy was found to decrease the activity of MMP-2 and MMP-9. (MMP-9_{pufa+simv.} 57±24, MMP-2_{pufa+simv.} 42,5±18, TIMP-2_{pufa+simv.} 27,2±10, TIMP-1_{pufa+simv.} 49±16 UOP; $p < 0,05$)

Conclusion: The signs of connective tissue dismetabolism are observed in the vessels of the brain of rats with long tobacco, as evidenced by the increase in tissue expression and MMP-9, MMP-2 and decrease their inhibitors TIMP-1 and TIMP-2. When we tied to corrective therapy have a maximum efficiency of the combined effects of omega-3 polyunsaturated fatty acids and simvastatin. Simvastatin monotherapy and omega-3 PUFAs were less effective.

Keywords: smoking, metalloproteinases, simvastatin, omega-3 polyunsaturated fatty acids, rats

Lipoprotein-associated phospholipase A2 and carotid atherosclerosis in patients with coronary heart disease and hypoalphalipoproteinemia

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Aim: Assessment of the relationship lipoprotein-associated phospholipase A2 [Lp-PLA2] serum level with carotid atherosclerosis in patients with coronary heart disease [CHD] and hypoalphalipoproteinemia.

Subjects and methods: The examined number 172 patients with CHD: 133 – with hypoalphalipoproteinemia, 39 – with normal levels of high-density lipoprotein-cholesterol [HDL-C]. Patients with hypoalphalipoproteinemia were divided into 2 groups in turn: 95 – with carotid atherosclerosis, 38 – without atherosclerotic carotid arteries [CA]. A clinical examination has been conducted, lipid profile, Lp-PLA2 mass in serum has been defined. The diagnosis of CHD was determined by the standard criteria. Presence CA atherosclerosis evaluated by ultrasound duplex scanning.

Results: Correlation analysis of the concentration of Lp-PLA2 with lipid cardiovascular risk factors and indicators CA duplex scanning in patients with hypoalphalipoproteinemia found that elevated levels of Lp-PLA2 was significantly associated with total cholesterol [TC] ($r = 0,402$, $p < 0,000$), low-density lipoprotein-cholesterol [LDL-C] ($r = 0,444$, $p < 0,000$), and with a total of atherosclerotic plaques [ASP] in CA ($r = 0,237$, $p < 0,005$). Furthermore, only in the group with hypoalphalipoproteinemia, unlike the group of patients with normal HDL-C, the mean level of Lp-PLA2 serum of patients with CHD and carotid atherosclerosis was $284,5 \pm 88,9$ ng/ml and was significantly higher, along with levels of TC and LDL-C ($p < 0,025$ and $p < 0,025$ respectively) than in the group without atherosclerotic lesions of CA ($245,9 \pm 89,5$ ng/ml, $p < 0,025$).

Conclusion: An interrelation was found of Lp-PLA2 levels with the severity of carotid atherosclerosis in group of patients with CHD and with the low values of HDL-C. Elevated levels of Lp-PLA2 was significantly associated with an increase in TC, LDL-C and total number of ASP in CA.

Keywords: lipoprotein-associated phospholipase A2, coronary heart disease, carotid atherosclerosis, hypoalphalipoproteinemia

Relationship between risk factors and parameters of the lipid profile and markers of the inflammatory response in patients with hemodynamically significant coronary artery disease

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Objective: To trace the interrelation of the factors of obesity, smoking and alcohol consumption with parameters of the lipid profile and markers of inflammatory response in coronary artery disease (CAD) patients with hemodynamically significant stenosis.

Methods: A total of 396 patients with CAD and significant coronary stenosis (>75%) aged 60.3 ± 9.8 years were studied. 92.7% of patients had a weight above normal including 33.3% with overweight and 59.4% with obesity (body mass index (BMI) 31.06 ± 5.15 kg/m²): 39.1% – 1 degree of obesity, 15.2% – 2 degree, 5.1% – 3 degree). In 71.9 % of cases, patients were smokers (duration 12.67 ± 6.55 years): 29% ex-smokers, 4.3% – light smokers, 38.6% – heavy smokers, 28.1% – never smokers. 70.0% of patients had alcohol consumption (43.2% – a few drinks per year, 19.7% – a few drinks per month, 6.6% – a few drinks per week, 0.5% – a few drinks every day). All patients received standard medical therapy: ACE inhibitors, beta-blockers, antiplatelet therapy, statins, nitrates. Serum laboratory studies were performed on admission to the hospital. Lipid profile parameters (total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol, lipoprotein (a), Apo-A, Apo-B; inflammatory markers (hs-CRP, TNF-alpha, homocysteine, interleukine-1 β , 6, 8, sCD40 L, MMP-9, TIMP-1); endothelial dysfunction markers (nitrites, endothelin-1) were measured.

Results: All patients had elevated levels of atherogenic lipids (total cholesterol, LDL cholesterol, Apo-B, lipoprotein (a)), and inflammatory markers (hs-CRP, homocysteine, interleukin-1 β , 6) compared with the reference values of the studied parameters. In patients with obesity larger number of significant correlations between BMI and endothelin-1, LDL cholesterol, homocysteine was obtained. Smoking significantly correlated with interleukine-1 β , 6 and Apo-A. Alcohol consumption significantly correlated with the level of interleukin-1 β and LDL cholesterol. By regression analysis it was indicated that increase in the severity of risk factors associated with increased levels of certain markers of lipid and inflammatory response. In particular, by increasing degree of obesity the level of interleukin-1 β and VLDL cholesterol increases, the more a patient smokes, the lower level of Apo-A is; the more a patient drinks, the higher VLDL cholesterol level is.

Conclusion: Association between risk factors such as obesity, smoking and alcohol consumption and the parameters of the lipid profile and markers of inflammatory response in patients with CAD and hemodynamically significant stenosis was detected.

Keywords: coronary artery disease, risk factors, markers of inflammatory response

Levels of osteocalcin, osteoprotegerin and calcitonin in atherosclerotic plaques of the coronary arteries

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The aim of our study was to identify the associations of osteocalcin, osteoprotegerin, and calcitonin with markers of inflammation in the vascular wall in men with coronary atherosclerosis, and assess the impact of these markers on calcification of atherosclerotic lesions of the coronary arteries.

Materials and methods: the study included 65 men aged 46-79 years with coronary atherosclerosis. The patients were hospitalized at Clinical of Federal State Institution Academician E.N. Meshalkin for coronary shunting. The endarterectomy material was longitudinally and transversely symmetrically divided into fragments for histological and biochemical studies. Of 193 samples selected 19 fragments conditionally normal intima, 102 – stable and 72 – unstable plaques. There was also a division of samples into three types: 1) without calcification, 2) with fine and pulverized calcifications, 3) with large calcifications. For biochemical studies, samples were homogenized in a solution of phosphate-buffered saline. In the homogenates was determined immunoassay methods: osteoprotegerin, calcitonin, osteocalcin, hsCRP and inflammatory markers: IL6, IL8, TNF α , IL1 β .

Statistical analysis was performed with the program SPSS 13.

Results: in unstable plaques showed higher levels of calcification compared with stable plaques. Calcified was 77% of unstable plaques, 39% identified large calcifications. Among the stable was calcified 52% of plaques, large calcifications accounted for 23%. The levels of IL-6, IL-8 and TNF α were increased in lesions with dust and small calcifications, which indicates the presence of active inflammatory process.

In our study revealed a trend towards increased levels of calcitonin and osteoprotegerin in plaques with large calcifications. Showed a significant ($p < 0.05$) increase in the level of osteocalcin in the lesions with calcifications, 2,6 times higher than in areas without calcification.

When performing correlation analysis revealed moderate relationship of osteoprotegerin, osteocalcin and calcitonin with markers of inflammation. So the osteoprotegerin showed a direct relationship with IL6, and osteocalcin and calcitonin – IL1 β . The identified associations of inflammatory markers between them. Most pronounced was the relationship between Pnoa and IL1 β .

Conclusions: the initial stage of formation of the calcification of atherosclerotic lesions is characterized by increased inflammatory processes. Instability of atherosclerotic lesions is associated with higher levels of calcification and increased production of osteoprotegerin, osteocalcin and calcitonin.

Keywords: osteocalcin, osteoprotegerin, calcitonin, atherosclerotic plaques, inflammation

Role of interleukin-18 in estimation of hospital complications in subjects with coronary artery disease who underwent coronary artery bypass grafting

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Purpose. To estimate the clinical significance of interleukin – 18 (IL-18) in blood serum for predicting the risk of hospital complications development in subjects with coronary artery disease (CAD) who underwent coronary artery bypass grafting (CABG).

Materials and methods. The study included 720 subjects who underwent CABG in RI for CICVD in the period since March 2011 till April 2012. All the subjects before performing CABG and on the 7-th day after surgical intervention were measured the blood serum creatinine concentration, glomerular filtration rate (GFR) by MDRD formula and also interleukin – 18 concentration in blood serum. We evaluated the incidence of adverse outcomes of surgical interference (myocardial infarction, stroke, acute or chronic renal disease progression, remediastinotomy) during in hospital period. All the subjects were measured a score by EuroSCARE -II risk scale.

Results. In the present study we did not receive significant differences in blood serum creatinine level and GFR both as before surgery and on the 7-th postoperative day among subjects different risk groups by EuroSCORE-II, as well as in subjects with complicated and uncomplicated course of postoperative period. Whereas the IL-18 level in the blood serum before surgery and on the 7-th postoperative day was significantly higher in subjects of high and medium risk groups by EuroSCORE-II scale, as compared to low-risk subjects. Detection of IL-18 in the blood serum in preoperative period proved to be useful for estimation the risk of certain cardiovascular complications development in postoperative period. It was found out that in subjects with development of myocardial infarction or stroke after CABG preoperative IL-18 values were definitely higher as compared to subjects without MI or stroke. IL-18 values in the blood serum of subjects with the development of acute renal failure were also higher as compared to subjects without acute renal failure (ARF). Analysis of IL-18 levels in subjects with the development of postoperative adverse outcomes also showed its statistically significant higher values, both in preoperative and in postoperative periods, while such indicators of renal dysfunction as creatinine and GFR didn't show any significant differences in subjects with favorable and adverse outcomes.

Conclusion. Thus preoperative quantitative estimation of IL-18 in the blood serum which is a preclinical marker of acute kidney injury, allows to predict more accurately the hospital risk of development of adverse cardiovascular and renal complications of CABG.

Keywords: coronary artery bypass grafting, prognosis, interleukin – 18

Significant biochemistry lipid and non-lipid biomarkers of coronary atherosclerosis in Siberia

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The aim of the study was to reveal significant biochemistry lipid and non-lipid biomarkers of coronary atherosclerosis in blood in men of Siberia.

Laboratory lipid-lipoprotein (cholesterol, CH, triglycerides, TG, low-density and high-density cholesterol, LDL-CH, HDL-CH, apolipoproteins B and A1, apoB, apoA1, lipoprotein (a)), carbohydrate (plasma glucose, basal insulin, c-peptid), inflammatory (high sensitive C-reactive protein, hsCRP, cytokines, TNF-alpha, IL-6, IL-1-beta, IL-8), oxidative (basal level of LDL lipid peroxidation (LPO) products, LDL resistance to oxidation, oxidative modification of apoLDL) and antioxidative (LDL alpha-tocopherol, retinol, beta-karotene contents) biomarkers were studied in 200 men with coronary angiography documented coronary atherosclerosis compared with 1024 men of population simple of Siberia citizens.

Increased levels of blood TG, apoB, basal insulin, hsCRP, IL-6, basal level of LPO products in LDL and decreased levels of HDL-CH, apoA1 and LDL resistance to oxidation were typical for coronary atherosclerosis men compared to control group. Significant independent associations ($p < 0,01$) of coronary atherosclerosis with laboratory diagnostic biomarkers such as blood levels of HDL-CH, TG, apoB, apoA1, basal insulin, hsCRP and basal level of LPO products in LDL and LDL resistance to oxidation were also revealed.

In conclusion, this biochemical panel, including indicated biomarkers, may be important for laboratory diagnostics of coronary atherosclerosis in Siberia.

The study was supported by Grant of RFBI 16-34-00128.

Keywords: Biomarkers, Coronary atherosclerosis, Lipids, Inflammation, Oxidative LDL modification

Features of the cytokine profile, ST2 level and markers of endothelial dysfunction in patients with acute myocardial infarction and different methods of myocardial revascularization

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Objective: To study the dynamics of proinflammatory cytokines, markers of endothelial dysfunction and myocardial fibrosis in patients with acute myocardial infarction (AMI) and its association with invasive or non-invasive treatment.

Methods: 142 patients (age 64 ± 11 years) with AMI with ST-elevation (1st group, n=74) and without ST-elevation (2nd group, n=68) were included in the study. There was valued standard risk factors in both group. In all cases echocardiography was performed. Primary percutaneous coronary intervention (PCI) was performed in 50 cases from 1st group and 60 cases from 2nd group, thrombolytic therapy (TLT) was used in 21 cases, the non-invasive strategy was used in 11 cases in both groups. After PCI or TLT within the 1st day of admission and in 10th day serum levels of high-sensitivity C-reactive protein (hsCRP), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), vascular endothelial growth factor (VEGF) and a member of the interleukin-1 receptor family ST2 were measured. We used Mann-Whitney U-test, chi-square tests, Spearman's rank correlation coefficient with a significance threshold of $P=0.05$.

Results: The groups were matched by sex, age, smoking, total cholesterol, body mass index. In 1st group PCI was accompanied by increased concentrations of IL-6 ($p=0.042$), ST2 ($p=0.035$) and endothelin-1 (0.045) compared with conservative treatment's patients. Among patients from 1st group with PCI or TLT correlations between creatine phosphokinase-MB and ST2 ($R=0.63$ $P=0.039$), creatine phosphokinase-MB and IL-1 β ($R=0.85$ $P=0.016$) and MCP-1 and VEGF ($R=0.73$, $P=0.0068$) were found. 2nd group after PCI also demonstrated IL-6 ($p=0.045$) and endothelin-1 ($p=0.043$) increase, in addition, there was an increase of VEGF ($p=0.047$) and hsCRP ($p=0.0051$), but no ST2 ($p=0.44$), compared with conservative treatment's patients. In patients from 2nd group with PCI correlations between IL-1 β and MCP-1 ($R=0.70$, $P=0.035$), ejection fraction of left ventricle and IL-1 β ($R=-0.78$, $P=0.012$). Levels of ST2, VEGF, IL-6 and endothelin-1 decreased to 10th day ($p<0.05$) in both group after PCI. Non-invasive treatment was accompanied by increased levels of VEGF, IL-6, MCP-1, hsCRP in 1st group ($p<0.05$) to 10th day but in 2nd group the levels did not show statistically significant differences.

Conclusions: PCI in patients with AMI accompanied by a rapid increase of proinflammatory cytokines and markers of endothelial dysfunction and myocardial stress but it was normalized to the 10th day after the reperfusion. In non-invasive treatment there was increasing inflammation and endothelial dysfunction to 10th day. Relationship between markers of inflammation, endothelial dysfunction, myocardial fibrosis and classical markers of myocardial necrosis, parameters of echocardiography demonstrate the correlation between the inflammation and the myocardial remodeling during AMI.

Keywords: acute myocardial infarction, ST2, inflammation, vascular endothelial growth factor

Association of matrixmetalloproteinase-9, pentraxin-3 and galectin-3 with risk for cardiovascular disease development in chronic renal disease patients

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Background: Inflammation, apoptosis, and extracellular remodeling play significant role in cardiovascular disease, which present the major cause of mortality in renal patients. In the present study we compared concentration of pentraxin-3, galectin-3, MMP-9 and TIMP-1 in pre-dialysis and hemodialysis patients with healthy controls. We have also assessed association between plasma concentration of pentraxin-3, galectin-3, MMP-9, TIMP-1 and glomerular filtration with the Framingham risk score, as a measure of cardiovascular disease risk in the future.

Design and methods: In 40 renal patients and 20 controls, concentrations of pentraxin-3, galectin-3, MMP-9, and TIMP-1 were determined by ELISA method. The predicted 10-year cardiovascular risk was calculated according to the Framingham risk score algorithm.

Results: Pentraxin-3 concentration was significantly increased in renal patients compared to the healthy controls ($p < 0.001$). On the other hand, galectin-3 concentration was reduced in dialysis patients compared to pre-dialysis and control group ($p < 0.001$). In addition, concentrations of MMP-9 and TIMP-1 were elevated in renal patients compared to the controls ($p < 0.01$ and $p < 0.001$, respectively). Logistic regression analyses disclose significant associations of galectin-3, MMP-9, pentraxin-3, and glomerular filtration with calculated CVD risk score.

Conclusion: Our study demonstrated that combined testing of pentraxin-3, galectin-3, MMP-9 and glomerular filtration rate has ability to discriminate renal patients with high and low risk for coronary event in the next ten years.

Keywords: matrixmetalloproteinase-9, pentraxin-3, galectin-3, chronic renal disease

Nutritional, inflammation and oxidative stress parameters: mortality risk in hemodialysis patients

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Chronic renal failure (CRF) occurs after the destruction of nephrons due to various etiologies. It is characterized by changes in lipid status, nutritional status, oxidative stress, antioxidant protection and inflammation parameters. In this study, we investigated the relationship of these parameters in hemodialysis patients who survived and those who died one year after sampling. Lipid status, nutritional status parameters (total protein, albumin, prealbumin, retinol-binding protein), high sensitive C-reactive protein (hsCRP) were determined by routine automatized methods. The prooxidant-antioxidant balance (PAB), total oxidative status (TOS) and activity of superoxide anion dismutase (SOD) were determined by spectrophotometry, and resistin by ELISA. There were no significant differences in lipids, oxidative status and inflammation parameters between two groups, except for the concentration of PAB and hsCRP which were higher among deceased patients ($p < 0,05$ vs. $p < 0,05$). The parameters of nutritional status were significantly lower in the patients who died ($p < 0,001$). A significant positive correlation between prealbumin, total cholesterol and LDL-cholesterol was proven in both groups, but positive correlation between prealbumin and triglycerides was found only in the group of survived patients. Prealbumin concentration was negatively correlated with PAB and hsCRP concentration in survivors, and with resistin in patients who died. Based on these results, we can conclude that deceased patients were in a state of more intense oxidative stress and inflammation, compared to surviving patients and their nutritional status was worse. A significant correlation of prealbumin and resistin concentrations was observed in patients who died one year after sampling, suggesting that the resistin could potentially be an association of malnutrition and inflammation in HRI patients.

Keywords: lipid status, inflammation, prooxidant-antioxidant balance, total oxidative status, C-reactive protein

sApo-1/Fas and sBcl-2 as markers of apoptosis in acute coronary syndrome

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Apoptosis plays an essential role in atherosclerosis. Soluble forms of the Apo-1/Fas and Bcl-2 play an important role in the regulation of endothelial cell apoptosis in atherosclerosis. sApo-1/Fas inhibits Fas-mediated apoptosis of endothelial cells by blocking the interaction of the Fas-receptor and Fas-ligand. sBcl-2 inhibits the expression of VCAM-1 on activated endothelium.

Objective: The general aim of this thesis was to measure soluble markers of apoptosis sApo-1/Fas and sBcl-2 in peripheral venous blood for the investigation of the mechanism of thrombophilia in acute coronary syndrome.

Methods: 190 patients with acute coronary syndrome, ranging in age from 48 to 72 years were included in study. Markers of apoptosis sApo-1/Fas and sBcl-2 was determined by ELISA using appropriate test systems («human sApo-1/Fas ELISA» and «Protein Bcl-2 ELISA», Bender MedSystems, Austria).

Results of the study: It was found that patients with acute coronary syndrome showed a significant increase in levels of soluble forms sBcl-2 and sApo-1/Fas, most pronounced in acute myocardial infarction. Thus, unstable angina content sApo-1/Fas was $1980,4 \pm 112,62$ pg / mL, in acute myocardial infarction – $2670,0 \pm 162,34$ pg / ml, $p < 0,05$, sBcl-2 – $29,1 \pm 8,16$ IU / ml and $57,8 \pm 11,41$ IU / ml, respectively, p

Conclusions: Apoptosis in acute coronary syndrome is a systemic process, as a source sApo-1 / Fas and sBcl-2 may be cardiomyocytes, monocytes, lymphocytes, endothelial cells. The increase of sApo-1/Fas and sBcl-2 indicates the activation of anti-apoptotic and anti-inflammatory mechanisms aimed at reducing the thrombophilia in acute coronary syndrome.

Keywords: Acute coronary syndrome, apoptosis, sApo-1/Fas, sBcl-2

Cardiology/Hypertension

LDL and HDL subclasses in relation to intima media thickness in coronary artery disease

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Background: In addition to high plasma levels of low-density lipoprotein (LDL) cholesterol, and low plasma levels of high-density lipoprotein (HDL) cholesterol, small dense LDL and HDL particles have been linked with pathogenesis of atherosclerosis. On the other hand, data from many studies indicate that intima media thickness (IMT) of the carotid artery is reflecting the extent of subclinical atherosclerosis. Increased IMT represents a risk of myocardial infarction or cerebrovascular disease.

Objective: In our study, we investigated whether LDL particle size, or HDL particle size are associated with intima-media thickness (IMT) of the common carotid artery (CCA) in 106 patients with CAD at baseline and after 12 months.

Methods: Intima media thickness of the common carotid artery was quantified by B-mode ultrasound. Separation of LDL and HDL subclasses was performed by 3-31% polyacrilamide gradient gel electrophoresis. Conventional plasma lipid and apoprotein concentrations were determined with commercial tests.

Results: LDL3 was dominant subclass at baseline and after 12 months, but there was statistically significant difference in the distribution of $\approx 4,796$; p2 dominant LDL subclasses ($X < 0,01$). HDL2b was dominant subclass at baseline and after 12 months and there was no statistically significant difference in the distribution of dominant HDL subclasses. The mean IMT was significantly increased ($0,83 \text{ mm} \pm 0,02$ vs. $0,91 \text{ mm} \pm 0,01$; $p < 0,001$), and LDL size was slightly decreased ($25,7 \pm 0,56 \text{ nm}$ vs. $25,11 \pm 0,93$; N.S.) in CAD patients after 12 months period. There was significant negative correlation between IMT and LDL size at baseline and after 12 months ($r = -0,22$, $p < 0,05$; $r = -0,26$, $p < 0,05$, respectively). Although plasma lipid concentrations were significantly increased after 12 months, IMT was not significantly correlated with plasma lipid concentrations at baseline neither after 12 months. The plasma level of HDL cholesterol was not elevated and no significant correlation was observed between IMT and HDL size.

Conclusion: LDL particle size is independently associated with carotid IMT in CAD patients with normal levels of traditional lipid risk. These results imply that small, dense LDL subclasses are an important indicator for assessing atherosclerosis in CAD patients.

Keywords: LDL subclasses, HDL subclasses, intima media thickness, CAD

Comparative efficacy of antihypertensive drugs in patients with metabolic syndrome

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Background: Metabolic syndrome (MS) is a condition linking insulin resistance, dyslipidemia, hyperglycemia, and hypertension that increases the risk of developing diabetes, cardiovascular disease, and subsequent cardiovascular morbidity and mortality. High blood pressure is considered one of the key features of metabolic syndrome. It is a very prominent feature of the metabolic syndrome, present in up to 85% of patients.

Aim of the study was to compare the efficacy and tolerability of perindopril 4 mg + amlodipine 5 mg combination (P+A) versus losartan 50 mg + amlodipin 5 mg (L+A) combination in patients with MS.

Material and Methods: We investigated 84 hypertensive patients with metabolic syndrome with mild-to-moderate arterial hypertension not adequately controlled by a monotherapy with ACE inhibitors or calcium channel blockers or ARB entered this work, randomized, parallel-group study. After a two week placebo run-in, all patients with sitting diastolic blood pressure (DBP) > 95 mmHg and/or sitting systolic (BP > 160 mmHg) were randomized to receive either P+A (42 patients) or L+A (42 patients) once daily for 12 weeks. Main outcome measure was sitting DBP and SBP values at the end of active treatment. The response rate was defined as the proportion of patients with either a final sitting DBP < 90 mmHg or decreased by at least 10 mmHg or a sitting SBP < 150 mmHg or decreased by at least 20 mmHg from baseline.

Results: The DBP and SBP values obtained with P+A were, respectively, 1.9 and 2.6 mmHg lower than those obtained with L+A (both $p < 0.002$). The response rate in the L+A group (90.6%) was better than that observed in the P+A group (88.4%, $p = 0.01$). The incidence of adverse events was similar with the 2 treatment groups (14.2% vs. 16.6%, $p < 0.02$).

Conclusions: These data suggest a higher antihypertensive efficacy of the fixed combination L 50 mg + A 5 mg as compared with P 4 mg + A 5 mg. Further investigations are required with a large amount of patients.

Keywords: hypertension, metabolic syndrome

Subclinical carotid atherosclerosis in female rheumatoid arthritis patients

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Objectives: Patients with rheumatoid arthritis (RA) have increased risk of atherosclerotic cardiovascular diseases compared with general population. We assessed prevalence of subclinical atherosclerosis in a sample of female rheumatoid arthritis patients and to determine the influence of traditional and RA-related cardiovascular risk factors on atherosclerosis.

Materials and methods: It was a cross-sectional, retrospective study. A total of 47 female patients (median of age 50 yr, range from 33 to 61 yrs) with RA were included. 76% of RA patients were RF-positive and 79% had moderate-to-high disease activity according to DAS values. All patients were on non-steroidal anti-inflammatory drugs treatment, 45% patients were being treated with disease-modifying antirheumatic drugs and 19% were taking prednisolone. All study subjects underwent careful clinical examination, high-resolution carotid ultrasound. The intima-media thickness (IMT) was measured at the level of the carotid bifurcation.

Results: All RA patient were at low-to-moderate total cardiovascular risk (SCORE from 0.02 to 3.18%, median 0.52%). Subclinical atherosclerosis was found in 21 (45%) RA patients. From these, increased IMT (>0.9 mm) was detected in 11 (23%) RA patients; presence of atherosclerotic plaque along with increased IMT was revealed in 6 (13%) patients, without increased IMT – in 4 (9%). There were positive correlations of IMT with traditional risk factors (age [$r=0.30$; $p=0.03$]; smoking [$p=0.005$], total cholesterol [$r=0.33$; $p=0.004$]). Only two RA-related risk factors were correlated with IMT (ESR [$r=0.29$; $p=0.03$] and health assessment questionnaire (HAQ) [$r=0.3$; $p=0.03$]).

Conclusions: Subclinical carotid atherosclerosis was found in 45% our female RA patients with low-to-moderate total cardiovascular risk. Increased IMT correlated with traditional risk factors (age, smoking, total cholesterol) and RA-related risk factors (ESR and HAQ) as well. Thus, carotid ultrasound can improve cardiovascular risk evaluation in middle aged female patients with RA.

Keywords: Rheumatoid arthritis, Carotid intima-media thickness, Cardiovascular risk evaluation

Atherosclerosis and arteriosclerosis in men with prehypertension

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Aim. Rate vascular remodeling (atherosclerotic, characteristic of the pulse wave) in men under the age of 55 years with prehypertension.

Material and methods. The study involved 92 patients with prehypertension. The 1st group – 55 men with an isolated elevation of peripheral blood pressure to high normal levels, the 2nd – 37 men with the increase of central aortic and peripheral blood pressure to high normal levels. We performed the estimation of anthropometric indices, blood pressure, heart rate, blood lipids, ankle-brachial index (ABI). Intima-media thickness of brachiocephalic vessels was assessed on the ultrasound device Philips EnVisor C, pulse wave velocity and central blood pressure were assessed on Sphygmocor (AtCor Medical).

Results. Mean central aortic pressure (CAP) in the 1st group was $109,0 \pm 2,5$ mmHg, the 2nd group – $125,0 \pm 3,5$ mmHg ($p < 0,05$). Correlation analysis showed the existence of links of smoking ($r = 0,8$; $p < 0,001$), IMT ($r = 0,7$; $p < 0,001$) and the presence of dyslipidemia ($r = 0,4$; $p < 0,01$) with the central BP.

The average value of IMT in the 1st group was $0,8 \pm 7,4$ mm, in the 2nd – $0,9 \pm 2,1$ mm. ABI – $0,9 \pm 5,6$ and $0,9 \pm 7,8$ in the 1st and 2nd group, respectively. Frequency of brachiocephalic atherosclerosis (IMT > 0.9 mm) was 43.3% and 31.8% of patients of the first and second groups, respectively. Arteriosclerosis of the lower limbs (ABI < 0.9) – 64.7% and 25.5% of patients in the first and second groups, respectively. Men with increased central aortic pressure had increased IMT 1.3 times ($p < 0,05$) 3 times more frequently, ABI < 0.9 – 2.5 times more frequently, compared with normal central aortic pressure patients. PWV > 10 m / s was found in 3% and 5% in the first and second groups, respectively, the differences between the groups did not reach statistical significance. Stiffness index of large conductive arteries (SI) in the first group was $7,1 \pm 1,89$ m / s, in the second – $8,3 \pm 1,74$ m / s. The average value of the reflection index of small arteries (RI) – $35,6 \pm 14,5\%$, $36,5 \pm 15,43\%$. Augmentation index in the treatment groups were comparable.

Conclusions. Men with preHt with elevated central pressure have a greater incidence of brachiocephalic or lower extremities atherosclerosis, but comparable indicators of PWV. The data allow us to consider an increased level of central blood pressure as a more powerful predictor of adverse effects on the development of vascular atherosclerosis.

Use of statin in ischemic heart failure

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Aim of study. Investigation of efficacy and safety of statin use in ischemic chronic heart failure with impaired systolic function.

Methods. 84 angiography confirmed CAD patients (53 male and 31 female, 40 with NIDDM and 44 without metabolic disorders, all with post MI cardiosclerosis) with CHF NYHA II-IV functional class, LV EF<40% and LV EDD>55mm were included into study. Rosuvastatin in appropriate dose (titrate by LDL level) had been added to standard therapy of ischemic CHF (ACEI, beta-blockers, torasemide, spironolactone, aspirin, anticoagulants and antiarrhythmics – optional) in 64 patients (statin group). After 6 months clinical, hemodynamic state of patients of both groups (statin and non-statin) were checked as well as serum LDL level, estimated glomerular filtration rate (eGFR), new onset NIDDM cases and primary end-points (cardiovascular and other cases mortality and hospitalisation rate).

Results. Mean dose of rosuvastatin was 11.64±0.84mg/d. In statin group EchoCG parameters were stable during course of treatment (LV EF was 34.56±3.97% at the beginning and 33.97±2.99% at the end of treatment, p>0.05). In the non-statin group LV end systolic diameter non-significant increased with significant lowering of LV EF (36.85±3.86% and 31.56±2.85%, p<0.05). 3 patients in non-statin (15%) and 1 patient (1.56%) in statin group increased NYHA functional class (hi square=6.07, p<0.05). Serum LDL level lowered in non-statin group from 2.36±0.04 to 2.01±0.02mmol/l (p<0,05) and from 2.42±0.03 to 1.66±0.02mmol/l in statin group (p<0,01 with initial level and p<0,05 with non-statin group's 6-months level). EGFR was not changed in both group (76.22±5.86ml/min to 72.97±3.77ml/min in non-statin and 75.68±4.75 to 73.77±6.05% in statin group). There were no new-onset NIDDM, Alzheimer disease, rabdomiolysis. Mortality was 2 cardiovascular cases in non-statin (10%) and 3 (2 cardiovascular and 1 pancreatic necrosis) in statin group (4.69%, hi square=0.77, p>0.05). 1 patient in non-statin group (5%) had stroke, 5 patients in non-statin (25%) and 4 in statin group (6.25%) were hospitalised because of CHF decompensation (hi square=5.74, p<0.05).

Conclusion. Rosuvastatin is safe in treatment of ischemic CHF with low LV systolic function. It helps to preserve LV EF and CHF NYHA functional class compared with non-statin treatment. Taking into attention antyatherosclerotic property (confirmed in this study by lowering of atherogenic LDL) as well as safety, we can recommend to include rosuvastatin into standard therapy of ischemic CHF. No cases of new-onset NIDDM, rabdomiolys, Alzheimer disease, kidney function deterioration were registered in this study.

Keywords: statin, chronic heart failure, estimated glomerular filtration rate, low LV systolic function

Indicators of ambulatory blood pressure monitoring in patients with neurocirculatory dystonia

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Purpose: To determine the features of indicators of ambulatory blood pressure monitoring (ABPM) in young patients with neurocirculatory dystonia (NCD).

Methods: 178 patients (44 male, 134 female) with NCD aged (21.3 ± 0.76) years were included in this study. ABPM was performed using a portable device AVRМ-04 (Meditech, Hungary). Verification criterion of increased blood pressure (BP) by ABPM was the average daily BP $\geq 130/80$ mmHg, at period of wakefulness – BP $\geq 135/85$ mmHg and during the nighttime – BP $\geq 120/70$ mmHg according to the recommendations of the European Society of Hypertension and the European Society of Cardiology (2013).

Results: The increase of mean daily blood pressure levels were found in 17.4% patients with NCD. The mean daily levels of systolic blood pressure (SBP) in males – (129.3 ± 1.8) mm Hg, in females – (118.7 ± 3.2) mm Hg, $p=0,004$, and mean daily levels of diastolic blood pressure (DBP) in males – (72.0 ± 1.3) mm Hg, in females – (70.9 ± 2.8) mm Hg, $p>0,05$. It was revealed a significant increase of heart rate during the whole period ($r_s=0.519$, $p=0.003$) and during the day ($r_s=0.501$, $p=0.004$) in combination with elevated levels of DBP, while as the average levels of SBP had no effect on heart rate. Significant difference was established by comparing the time index of hypertensive SBP in the hypertensive group (62.8 ± 3.8)% ($n=31$) and normotensive group ($17,3 \pm 2,4$)% ($n=147$), $p<0,001$. Comparison of time index of hypertensive DBP had a similar picture: in the hypertensive group ($40,3 \pm 4,6$)% and normotensive group ($12,4 \pm 2,0$)%, $p<0,001$. The optimum daily biorhythm of blood pressure («dipper») was observed only in 1/3 of the surveyed persons. Insufficient night decrease of SBP («non-dipper») was observed in 33.9% and of DBP – 11.3% of patients. Attention is drawn to relatively high percentage of persons with excessive nocturnal reduction («over-dipper») of DBP (21%). In group with increased blood pressure at night («night-peaker») was found 8.1% persons according to SBP and as much according to DBP. With increased SBP it was observed high variability of its level during the whole period of monitoring ($r_s=0.587$, $p=0.001$).

Conclusions: 17.4% patients were regarded as hypertensive type of NCD. The increase of mean daily blood pressure levels were associated with tachycardia, increase of time index of hypertension, violations of the daily biorhythm of blood pressure and increasing variability of SBP.

Keywords: ambulatory blood pressure monitoring, neurocirculatory dystonia

Comparative evaluation of clinical data in patients with myocardial bridge and atherosclerotic stenosis of coronary arteries

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Concealed undiagnosed anomalies of coronary arteries – myocardial bridge (MB) can cause an acute myocardial infarction of young (and athletes) and middle-aged people.

The aim: to identify the characteristics of disease caused by the presence of MB over the coronary artery or the presence MB and atherosclerotic stenosis of coronary arteries (CAAS).

Materials, findings: 10298 patients were examined with the help of coronary angiography (during the 7-year period). It was found that 364 (3,5%) pts had MB: 1st group – pts with an isolated MB (114 pts); 2nd group – pts with MB and Arterial Hypertension (AH) (59 pts); 3rd group – MB and atherosclerotic stenosis of coronary arteries (CAAS) (105 pts); 4rd group – MB, CAAS and AH (75 pts). 82/114 pts with MB have atypical angina (72%). 45/59 pts 2nd group with MB and AH have atypical angina (76%) ($p_{1-2}=0,539$). 80/105 pts with MB mixed with CAAS have effort angina of the 2nd or the 3rd class (76%). 60/75 pts of 4th group have effort angina (80%). It was proved that cases of acute myocardial infarction (MI) met more frequently in the group of pts with mixed MB and CAAS 16/105 pts (15,2%) ($p_{1-3}=0,001$), as well as in the group with MB, CAAS and AH – 9/75 pts (12%) ($p_{1-4}=0,014$). The highest frequency of occurrence of MI in anamnesis cases was revealed in the group of pts with MB mixed with CAAS and AH 35/75 pts (47%) ($p_{1-4}=0,00$; $p_{2-4}=0,05$; $p_{3-4}=0,04$).

Conclusions: 1) Most of the patients with myocardial bridge have atypical angina (72%), and patients with combined coronary artery disease have effort angina of the 2nd or the 3rd class (76%). 2) The presence of congenital MB may lead to the occurrence of acute coronary syndrome with the development of MI significantly more frequently in patients with atherosclerosis of the coronary arteries.

Keywords: acute coronary syndrome, atypical angina, myocardial bridge over coronary artery, ischemic heart disease, coronary angiography

The influence of biosynthesis of interleukin-6 on the change of the production of interleukin -1 β in blood serum at patients with q-wave myocardial infarction complicated by acute heart failure

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Important factors of pathogenesis of coronary heart disease are immunological mechanisms of inflammation to which increasing value is given in formation of atherosclerosis, sharp coronary syndrome, and myocardial infarction. The nature of cytokines change at patients with myocardial infarction attracts special attention.

Purpose of research: Study of dynamics of cytokines concentration in blood serum at patients with Q-wave myocardial infarction complicated by acute heart failure of III-IV class by Killip.

Research methods: Cytokines were examined in blood serum at 97 patients (middle age of $58,5 \pm 1,06$) with Q-wave myocardial infarction. Blood serum was received on the 1st, 7th and 14th days of the disease. Control group included 16 healthy male patients. The concentration of interleukins was defined by solid-phase immunoassay analysis, using sets by CJSC «Vektor-Best» (Russia).

Received results. IL-1 β level in the 1st day of myocardial infarction didn't change at patients with complicated and uncomplicated myocardial infarction in comparison with control group ($0,91 \pm 0,50$ pg/l and $0,73 \pm 0,34$ pg/l against $0,71 \pm 0,27$ pg/l). Subgroup of patients with cardiogenic shock had significant decrease in comparison with control group ($0,13 \pm 0,10$ pg/l against $0,71 \pm 0,27$ pg/l, $p < 0,01$) and group of patients with uncomplicated myocardial infarction ($0,13 \pm 0,10$ pg/l against $0,73 \pm 0,34$ pg/l, $p < 0,01$). Subgroup of patients with pulmonary edema had significant increase of IL-1 β in comparison with control group and group of patients with uncomplicated myocardial infarction ($1,26 \pm 0,71$ pg/l against $0,71 \pm 0,27$ pg/l and $0,73 \pm 0,34$ pg/l respectively, $p < 0,01$).

Patients with cardiogenic shock had the increase of IL-1 β level on the 7th day ($0,31 \pm 0,2$ pg/l and $0,39 \pm 0,2$ pg/l), on the 14th day the indicators of myocardial infarction were increased in comparison with control group ($2,97 \pm 1,78$ pg/l against $0,71 \pm 0,27$ pg/l, $p < 0,01$). Patients with pulmonary edema had significant increase of indicators on the 7th day in comparison with control group ($2,20 \pm 0,88$ pg/l against $0,71 \pm 0,27$ pg/l, $p < 0,01$); on the 14th day there was a decrease in the level of concentration of IL-1 β ($1,75 \pm 0,88$ pg/l). There was increase of IL-6 in the 1st day at patients with uncomplicated myocardial infarction in comparison with control group ($12,4 \pm 3,9$ pg/l against $1,98 \pm 0,7$ pg/l, $p < 0,01$). In the process of scarring of myocardial infarction the concentration of IL-6 was decreasing by the 7th day ($5,8 \pm 1,7$ pg/l) and by the 14th day ($4,4 \pm 0,84$ pg/l), but didn't reach reference values. In case of myocardial infarction complicated by acute heart failure IL-6 indicators were twice higher, than at patients with uncomplicated myocardial infarction ($25,4 \pm 5,8$ pg/l against $12,4 \pm 3,9$ pg/l). In process of scarring of myocardial infarction there was a gradual decrease of indicators, but exceeding by the 14th day ($6,6 \pm 0,8$ pg/l against $4,4 \pm 0,8$ pg/l). IL-6 values on the 1st day of myocardial infarction were significantly increased in subgroup of patients with cardiogenic shock ($18,15 \pm 7,07$ pg/l) and in subgroup of patients with pulmonary edema ($15,67 \pm 3,46$ pg/l).

Conclusions: One of the reasons for intensive biosynthesis of IL-6 is the absence of the changes of the level of IL-1 β blocking IL-6 gene.

Increased level of IL-6 follows macrofocal myocardial infarction and is observed on the 1st day of myocardial infarction at cardiogenic shock.

Keywords: myocardial infarction, cardiogenic shock, acute heart failure, cytokine

Coronary artery disease in women in Morocco

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Objectives: Although men have a higher incidence of cardiovascular disease than women in Morocco, coronary artery disease remains one of the leading cause of death in women in our country. Our study in the department of cardiovascular surgery in the Ibn Sina hospital in rabat has pointed out different clinical, angiographic and surgical characteristics in men and women surgical patients.

Methods: Subjects included in this retrospective analysis were 1950 men and 145 women who were candidate for coronary artery by-pass graft surgery between May 1995 and August 2011 in our institution. Medical history, physical and laboratory information were collected from each patient and men and women were compared for differences in base line characteristics.

Results: In this study, women undergoing CABG surgery were found to be older and to have a smaller body size. They were more likely to have hypertension and diabetes compared to men, however a smaller percentage of women are smoker. In our study women were more likely than men to have more severe angina, a previous myocardial infarction and abnormal left ventricular function. In addition, results of this study showed that male surgical patients have more multivessel disease than women, but there were equal proportions of men and women with left main coronary disease. Our results indicate that the hospital mortality rate for women who underwent bypass surgery was higher than the rate for men. The mortality rates for CABG for men and women are respectively 2.4 % and 4.1 %.

Conclusion: In our study we found that among predictive information of operative mortality rates in women provided by two basic risk factors, that is to say emergency operation and left ventricular impairment, we can add the number of operable vessels and the average vessels diameter. Such risk in women may well be due to smaller body size and diameters of their coronary vessels rather than gender per SE. But it may also result in women being treated at later stage in the progression of the coronary artery disease.

Keywords: ischaemia, coronary artery disease, cardiovascular surgery

Arterial stiffness in patients with ischemic stroke and arterial hypertension

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Arterial stiffness exhibits independent prognostic value in regard to fatal and non-fatal cardio-vascular events, including ischemic stroke in patients suffering from arterial hypertension. Measurement of indices during a day is of special interest, because these parameters are susceptible to diurnal fluctuations related to patient's activities of daily living.

Aim: to examine arterial stiffness indices in patients with complicated course of arterial hypertension and possibilities of correction of these parameters.

Materials and methods: 60 patients suffering from arterial hypertension complicated by non-cardioembolic ischemic stroke who were admitted to the hospital during first 48 hours after the development of acute neurological symptomatology has been included in the research. Indices of arterial stiffness (PWV, cBP) were evaluated with the help of application program Vasotens (BPlab, "Peter Telegin") on the basis of statistical analysis of pressure traces. Fixed combination of perindopril and amlodipine was used as antihypertensive medicine. All patients suffered from arterial hypertension at an average 7.3 ± 3.2 years and didn't receive regular antihypertensive therapy before development of ischemic stroke.

Results: there were numerous modifiable risk factors of cardiovascular diseases development, such as smoking – in 62.5%, overweight – in 34.5%, dyslipidemia – in 87.4%. PWV on the 10th–14th day after development of was 11.4 ± 1.6 m/sec, cSBP – 140.8 ± 12.5 mm Hg, cPBP – 56.1 ± 7.9 mm Hg. To the 3rd month of treatment PWV was decreased up to 10.8 ± 1.2 m/sec, cSBP – up to 132.6 ± 11.9 mm Hg, and cPBP – up to 52.7 ± 5.1 mm Hg. To the 6th month of treatment PWV was 10.6 ± 1.6 m/sec, cSBP – up to 129.9 ± 12.1 mm Hg, and cPBP – up to 50.6 ± 3.1 mm Hg. Degree of neurologic deficit to the 10th – 14th day markedly decreased in all patients practically by 61.5% on the NIHSS scale, and by 60.0% on Rankine scale. To the 6th month of therapy decrease up to $1.6 \pm 1/0$ points on the NIHSS scale, and up to 1.0 ± 0.1 points on Rankine scale was fixed. Correlation dependence between degree of neurological deficit on the NIHSS scale, PWV ($r=0.63$, $p<0.05$) and cPBP ($r=0.58$, $p<0.05$) was revealed.

Summary: as can be seen from the above, we were getting the impression that increased arterial stiffness is one of the pathogenetic mechanisms of ischemic stroke development on the background of long-standing uncorrected arterial hypertension, which can directly influence cerebral blood flow and lead to increase of neurological deficit's degree. PWV and cBP can be used as prognostic indices of functional outcome of acute ischemic stroke.

Keywords: arterial stiffness, ischemic stroke, arterial hypertension

The prevalence of asymptomatic organ damage in patients with hypertension

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Objective: To analyze the prevalence of asymptomatic myocardial damage and brachiocephalic arteries [BCA] in patients with hypertension to identify individuals at high risk.

Materials and methods: The study was conducted in 162 patients (62 men and 100 women) surveyed in the Rostov regional hospital from May to December 2015. Patients addressed the difficulties of correction of blood pressure in clinics in the community, because of the deterioration and lack of efficacy of the therapy. The average age of women was 55.98 ± 8.28 years, of men was 48.22 ± 11.33 years. All patients performed the calculation of body mass index, echocardiography by standard methods, ultrasound of the BCA, treadmill tests, electrocardiography. Patients with any of the cardiovascular events in history (acute myocardial infarction, acute ischemic stroke, verified angina, coronary artery bypass grafting, percutaneous coronary intervention, coronary artery stenting, etc.) were excluded. The mean index of left ventricular mass [ILVM] in men was 141.24 ± 13.11 g / m². According to the recommendations of the ESH / ESC 2013, ILVM more than 115g / m² is the criterion for asymptomatic myocardial damage. Asymptomatic myocardial damage detected in 83.87 % of men. In 40.32 % of the thickness of the intima-media complex [CIM] of the internal carotid artery [CA] with 2 sides greater than 0.9 mm. This feature is classified as asymptomatic damage CA, and can be attributed to the patient at high risk for recommendations ESH / ESC 2013. The combination of thickening of the CIM and atherosclerotic plaques [AP] were detected in 17 men (27.42 %). AP without thickening of the CIM found in 3 patients (4.8 %). Asymptomatic CA damage was found in 45.16 %. Thus, asymptomatic myocardial damage in men occurred 1.89 times more likely than asymptomatic CA. Isolated thickening of the CIM without an increase ILVM found in 1 case (1.6%). Consequently, in 85.48 % found asymptomatic myocardial damage and CA, which can be attributed to these patients at high risk. Average ILVM in women was 132.84 ± 29.7 g/m². According to the recommendations of the ESH / ESC 2013 high risk include women with ILVM more than 95g / m². Asymptomatic myocardial damage in women found in 89.4 %. In 28 % of cases in women thickness of the CIM exceeded 0.9 mm. AP were detected in 19 women (19%). AP without thickening of the CIM were detected in 8 women (8 %). Thus, asymptomatic lesion of BCA detected in 27 % of cases. Thickening of the CIM more than 0.9 mm (or AP) without an increase in ILVM was found in 2.5% of cases. It is possible to increase the group of women, which we attributed to the group of high cardiovascular risk to 91.9%.

Conclusions: The left ventricular hypertrophy in men and women met with the same frequency by more than 80% of cases. Asymptomatic lesion BCA in men occurred 1.67 times more frequently than women ($p < 0.05$).

Keywords: brachiocephalic arteries, index of left ventricular mass, thickness of the intima-media complex, atherosclerotic plaques, high cardiovascular risk

Diagnosis of decompression intravascular gas formation in divers, the method of radionuclide scintigraphy of the myocardium

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Modern requirements for the treatment and prevention of cardiovascular diseases dictate the need for early detection and prognosis of myocardial damage. Traditional imaging methods used in modern cardiology (echocardiography, coronary angiography, magnetic resonance imaging, computed tomography in vascular mode), do not reveal the development of early (subclinical) disorders of myocardial perfusion. Therefore, a special place in the preclinical diagnosis of ischemia is owned by radionuclide methods of investigation. The principle consists in the accumulation in the myocardium of the radiopharmaceutical is proportional to the volume of coronary blood flow.

The study included 31 people, male, military service under contract, ranging in age from 21 to 44 years. Patients were divided into 3 groups. The first group included 20 people whose professional activity is connected with intermittent exposure to hyperbaric gaseous medium. The second group consisted of 7 people with proven diagnosis of myocarditis moved, and the third group consisted of 4 healthy men. All subjects belonged to the white race, and lived in the North-West region of Russia.

Radioisotope studies were conducted on a two-detector gamma camera E. Cam (Siemens). For the assessment of myocardial perfusion performed single photon emission computed tomography with ^{99m}Tc-methoxyisobutylisonitrile (MIBI) at rest and during exercise. Computer processing of data allowed us to obtain two dimensional pictures of slices of the myocardium of the left ventricle (LV) short axis, arranged concentrically from the apex to the base of the heart. The LV was divided into 16 standard myocardial segments with an additional allocation of tops. Estimated size of the zones and the degree of impairment of the accumulation of MIBI by which to assess regional changes in myocardial perfusion of left ventricle. To increase the resolution methods for image processing and the fastest receipt of reliable information regarding the extent of diffuse lesions of the myocardium, we developed an integral index – the index of the uneven perfusion of the LV. As such characteristics were selected analogue numerical average differential is the average of the absolute values of the differences of levels of perfusion in the LV segment and all neighboring. Adjacent segments were considered, at least on this one point. Clinico-radiological diagnosis, obviously, allows with 100% accuracy to identify cases of diffuse lesions of the myocardium with normal perfusion in healthy persons.

Conclusions:

- Perfusion scintigraphy of myocardium allows to obtain a qualitative assessment of diffuse myocardial lesions of myocarditis and the effects of occupational factors in the form of decompression intravascular gas formation.
- Poignantly analysis of polar maps of perfusion scintigraphy of the myocardium with the help of modern methods of multivariate statistics allows to differentiate the genesis of inflammatory disorders of perfusion of the left ventricle from decompression intravascular gas formation.
- The use of the estimated index of uneven perfusion of the left ventricle allows to increase the resolution of the standard protocol diagnosis of diffuse small-focal myocardial lesions and to determine the severity of these changes due to repeated hyperbaric conditions influences the gaseous medium.

Keywords: perfusion scintigraphy of the myocardium, divers, professional cardiovascular risk factors, single-photon emission computed tomography, prevention of cardiovascular diseases

Importance of evaluation and quantification of left atrial function using strain imaging

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Introduction: In the contraction-relaxation cycle of the myocardium the left atrium play an important but often forgotten and neglected role. The atria contribute up to 30% of left ventricular filling and cardiac output and are particularly important in the setting of impaired left ventricular function.

Objectives: Ischemic heart disease may lead to an increase in fibrosis, causing remodeling of the myocardium, resulting in a deterioration of myocardial function. For an adequate cardiac pump function, the contractile function of left atrium is of crucial importance. Left atrial function can be evaluated by strain measurements of the left atrial wall.

Methods: The study group consisted of 681 ambulant and asymptomatic male patients with a normal systolic left ventricular ejection fraction, divided in six groups: 3 groups healthy subjects (HS): 40–59years; 60–79y; 80–99y and 3 groups coronary patients (CP) treated with stent implantation or surgical revascularization: 40–59years; 60–79y; 80–99y. For the contractile function of the left atrium we assessed by strain measurements the reservoir function (RF), the conduit function (CF) and the booster pump function. The more positive the strain value the better the elasticity and elongation capacity of the left atrium.

Results: Statistically significant decrease of left atrium RF in CP compared with HS ($p=0,000$). Also subdivided in age groups left atrium RF decreases significantly with age as well in HS as in CP ($p=0,000$). The same findings for the left atrial passive emptying fraction or CF; statistically important decrease of left atrium CF in CP compared with HS ($p=0,000$) and when subdivided in age groups progressive decrease with age.

Conclusion: Strain imaging permits us to quantify the contractile function of left atrium, resulting in early detection of left atrial dysfunction. The characteristics of left atrial dysfunction namely a significantly reduced elasticity and elongation capacity of the left atrium are more pronounced in CP and occur earlier at a younger age in patients with ischemic heart disease, compared with normal controls. Age and ischemic heart disease are both independent factors in the development of atrial dysfunction. Until age 80 the atrial strain curve in CP is situated on a lower level but with a similar course as in normal controls. A further deterioration of the left atrial function but without statistically significant differences between HS and CP is established above 80 years. It seems that in older age groups and in patients with ischemic heart disease the adapted and possible compensatory mechanisms as the left atrial booster pump function fail, resulting in a decreased cardiac output with a higher risk for complications as arrhythmias and thrombo-embolic events. Atrial measurements expressed earlier than left ventricular function the myocardial contractile reserve.

Keywords: Left Atrium, Strain Imaging, Cardiac Function, Ischemic Heart Disease

Non-invasive contribution to the diagnosis of ischemic heart disease using Speckle-Tracking Echocardiography of the left ventricle

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Introduction: Ischemic heart disease is the most important cause of cardiac morbidity and death. Early detection of cardiac deterioration is imperative. To reach a large population safe, easy accessible and reliable non-invasive investigation methods are required.

Objectives: Speckle-tracking echocardiography is a new technique founded on pure 2D gray scale ultrasound acquisition and provides non-doppler, angle-independent and objective quantification of myocardial deformation and of left ventricular systolic and diastolic dynamics. Left ventricular dysfunction is a sensitive predictor of cardiovascular atherosclerotic diseases.

Methods: We investigated 969 male self-supporting and ambulant patients with thoracic pain but with a can-do attitude, divided in 496 healthy subjects (HS) with documented normal coronary arteries and in 477 coronary patients (CP), treated with multiple stent implantation or bypass surgery. Both groups were divided in three age groups: 40-59y, 60-79y and 80-99y. We measured by speckle-tracking echocardiography the “global longitudinal peak systolic strain average” (GLPSSavg) of the left ventricle, divided in 24 segments, and also the “average peak longitudinal strain of the 5 myocardial segments with the lowest strain values”(Avg5LSS). The more negative the strain value, the better the myocardial contractile reserve. Measurements of maximal left ventricle diameter plus maximal atrial diameter (LVLA) were obtained during end-expiration to eliminate respiratory variation and an average of five beats was measured. Measurement of E/E' completed our investigation.

Results: GLPSSavg is statistically significantly decreased in CP (-14,5), compared with HS (-19,4) (p=0.000). No statistically significant differences of GLPSSavg between the age groups in HS nor in CP. For all age groups significant decrease(p=0,000) of GLPSSavg in CP compared with HS. The same findings for Avg5LSS: no statistically significant differences between the age groups in HS nor in CP but again statistically significant decrease of Avg5LSS for all age groups in CP (-8.5) compared with HS (-14,9) (p=0,000). LVLA is in all age groups higher in the CP (9,51cm) compared with HS (8,27cm) (p=0,000). E/E' is for all groups significantly higher (p=0,000) in patients with ischemic heart disease (12,66) compared with healthy subjects (8,61).

Conclusion: Speckle-tracking echocardiography is an opportunity for early detection of left ventricular dysfunction before other non-invasive investigation methods could detect cardiac deterioration. Notwithstanding all patients were ambulant we documented a statistically significant difference between HS and CP in the deformation capacity of the left ventricular myocardial wall, resulting in dilated left heart cavities in CP with a higher risk for heart failure, arrhythmias and thrombo-embolic events. There exists a high probability for a correct diagnosis of an underlying ischemic heart disease when we establish in the same patient a GLPSSavg lower than -17% with an avg5LSS lower than -11%, with LVLA higher than 9,5cm and E/E' higher than 11,0.

Keywords: Speckle-tracking echocardiography, longitudinal peak systolic strain, ischemic heart disease

Risk of resistant hypertension: role of arterial stiffness and baroreflex dysfunction

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Poor control of blood pressure (BP) in patients with hypertension (HTN) associated with cardiovascular complications and worsening of patients prognosis. Search of predictive markers is important clinical problem of resistant HTN (RHTN) management.

The present study has been aimed on assessment the risk of ambulant patients with true RHTN without prior cardiovascular events during 5 years follow-up in association with baseline arterial baroreflex sensitivity (BRS) and arterial stiffness.

Patients and methods: We examined 336 ambulatory patients with uncontrolled HTN (94 males and 242 females) 39 – 69 (54±3) years old on a combined antihypertensive therapy in 2008 – 2009 years. The repeat “office” BP measurements, ambulatory BP monitoring (ABPM) were performed in all patients. Patients were screened for secondary HTN exclusion. Carotid-femoral pulse wave velocity (PWV) was estimated by SphygmoCor (Atcor). Beat-to-beat BP at resting was registered using Finometer Pro device (Amsterdam). Spontaneous BRS was calculated by sequence method Follow up provided every 6 months visit to specialized antihypertensive centre.

Results: Thus, “true” RHTN was found in 46 patients (13,7%). PWV was higher compared with age-matched patients with uncontrolled HTN who achieved goal BP during treatment modification period: 8,2±1,7 m/s vs 7,0±1,4 m/s, P = 0.01. The PWV closely correlated with age (r=0.49, P=0.042), “office” systolic BP (r=0,53, P=0.09), mean systolic BP during ABPM (r=0,61, P=0.009). Baseline BRS was less in RHTN compared with uncontrolled HTN (5,6 ±2,0 ms/mm Hg vs 6,3±1,3 ms/mm Hg P=0,039). We found negative correlation between baseline spontaneous BRS and baseline PWV values (r=-0.37, P=0.046) in “true” resistant group (n=46).

During follow up 10 patients (21,8%) had cardiovascular events: 1 patient with RHTN died due to intracerebral hemorrhage, 1 patient had a stroke, 2 – transient ischemic attack, 2 – permanent atrial fibrillation, 1 case of successful coronary revascularization, 1 transcatheter coronary angioplasty with stenting due to acute coronary syndrome and 2 cases of newly diagnosed diabetes mellitus during the study period. The patients with complicated RHTN characterized of profound BRS decrease (3,9±1,2 ms/mm Hg, P=0,09) and simultaneous increase of baseline PWV (10,2±1,4, P=0,044).

Conclusion: True” resistance to treatment is rather infrequent cause of insufficient BP control. In the most cases resistance to treatment can be overcome by treatment intensification. Insufficient control of BP in RHTN associates with cardiovascular complications. High risk of RHTN associated with increase of PWV values and depression of spontaneous BRS.

Keywords: arterial stiffness, baroreflex, hypertension, pulse wave velocity, risk of hypertension

Relationship of the heart rate in the heart prenosological changes in young adults

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72 students of the Voronezh State Medical Academy named after N. N. Burdenko among them 18 boys and 54 girls, (mean age $21.9 \pm 0,1$ years), were involved in the one-stage study. The integral indicator (II) of the dispersion mapping were determined in the students on the device "Cardiovisor-: 6 C". Two groups of students: the "office" heart rate at rest below 80 beats per minute (group 1) and the "office" heart rate at rest more than 80 beats per minute (group 2) were formed taking into account the "office" heart rate at rest. "Myocardium" I I immediately after exercise, in 2 and 4 min after exercise in the second group was higher and amounted to: $16.9 \pm 1.23\%$, $17.3 \pm 1.66\%$ and $17.0 \pm 0.92\%$ respectively, statistically significantly differing from similar parameters of the first group of students immediately after the exercise and 4 minutes after the test. "Myocardium" I I in the first group of students reached: $13.3 \pm 0.42\%$, $14.2 \pm 0.46\%$, $14.4 \pm 0.43\%$ and $14. \pm 0.39\%$ at rest, immediately after the load in 2 and 4 minutes after the test, respectively, not deviating from the initial value by more than 1% and not exceeding 15% at the height of the test and at the end of the recovery period. In the second group "Myocardium" I I did not reach the initial value ($14.1 \pm 1.17\%$) in 4 minutes after the exercise test differing from it by 3%. Hence, the state of the cardiovascular system can be assessed as "borderline" in the students of the second group having the "office" heart rate at rest more than 80 beats per minute. The values of G6 I I at the height of the load in 2 and 4 minutes were statistically different in the second group and were interpreted as significant changes of the left ventricular repolarization process, as a result of metabolism at the height of the load. Also, myocardial hypoxia was not excluded. Changes in repolarization of individual sections of the left ventricular myocardium with probable signs of myocardial hypoxia were recorded in 2 and 4 minutes after the exercise. We do not have significant differences concerning the level of anxiety and depression in the groups studied, but the students of the second group reached the level of anxiety 9.0 ± 1.4 points, occupying the position of boundary between the subclinical and clinically significant anxiety and depression level was 5.3 ± 0.95 points. In the first group of the students the values of anxiety and depression were within the normal range – 5.7 ± 0.66 and 3.7 ± 0.56 points, respectively, not reaching the sub-clinical manifestations. In the first group of students, both male and female, stress level was average and amounted to 2.7 ± 0.14 and 2.5 ± 0.09 points, respectively. In the young men of the second group stress level was high, reaching 1.35 ± 0.22 points, and the girls in this group reached an average level of stress magnitude.

Keywords: heart rate, test with physical exercise, young adults

Effect of lipid-lowering therapy on coronary plaque composition in diabetic patients assessed by virtual histology intravascular ultrasound

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Introduction: Although lipid-lowering therapy is recommend for ischemic heart disease, there are little data about the effect of lipid-lowering therapy on coronary plaque composition in diabetic patients. **Purpose:** The purpose of this study was to evaluate the effect of achieved low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) goal on plaque composition of intermediate coronary lesion in diabetic patients assessed by virtual histology intravascular ultrasound (VH-IVUS).

Methods: In this prospective, observational study, 71 diabetic patients who underwent percutaneous coronary intervention (PCI) for culprit lesion were enrolled and treated with moderate intensity of atorvastatin (12.3 ± 8.8 mg) for 9 months. The each plaque compositions of non-culprit lesions was investigated at baseline and at 9-month follow-up according to the achieved LDL-C and TG level at 9 months after PCI.

Results: The LDL-C ≤ 70 mg/dL was achieved in 38 patients (53.5%) and the TG ≤ 100 mg was achieved 34 patients (47.9%) at 9-month follow-up. Beneficial changes of attainment of LDL-C ≤ 70 mg/dL were the absolute necrotic core volume regression (-1.2 ± 8.6 mm³ vs. 2.7 ± 7.2 mm³ in LDL-C > 70 mg/dL, $p=0.046$) and the percentage fibrous volume expansion ($1.9 \pm 7.3\%$ vs. $-5.4 \pm 12.9\%$ in uncontrolled LDL-C, $p=0.004$). On the other hand, beneficial effect of attainment of TG ≤ 100 mg was observed only in the percentage of necrotic core volume reduction ($-2.1 \pm 7.2\%$ vs. $1.8 \pm 7.4\%$ in TG > 100 mg, $p=0.025$).

Conclusions: In diabetic patients, optimal lipid-lowering therapy for achieving target levels of TG as well as LDL-C in diabetic patients with coronary artery disease might lead the favorable coronary plaque composition, which can contribute the plaque stabilization.

Keywords: Diabetes, Triglyceride, Coronary plaque, Intravascular ultrasound

The role of adipokines in obesity-related hypertension

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Background: Obesity is known to be a risk factor for hypertension (HTN), while underlying pathways still need to be investigated. Adipokines may play a role being implicated in the regulation of vascular endothelial and smooth muscle cells functions, facilitation of organ damage.

Purpose: The aim of the present study was to compare the profile of serum adipokines and their associations with blood pressure levels (BP), endothelial function and arterial stiffness in obese and normal body weight hypertensive patients and healthy controls.

Methods: We examined 30 hypertensive obese patients (BMI more than 30 kg/m²), age and sex-matched 18 normal-weight hypertensive patients and 15 healthy controls. Ambulatory blood pressure monitoring (ABPM, SpaceLabs 90207), applanation tonometry (SphygmoCor, Arter Medical) with calculation of central aortic pressure, pulse wave velocity (PWV) and augmentation index (AI) were performed in all subjects. Reactive hyperemia index (RHI) was assessed by EndoPAT (Itamar Medicals) device. Adipokine levels (adiponectin, leptin, resistin, visfatin, adiponin) were determined by using Bio Plex Pro Human assays.

Results: Adiponectin level was significantly higher in healthy controls and normal-weight hypertensive patients compared to obese subjects (4.3 +/- 1.7, 4.0 +/- 2.3 and 3.3 +/- 1.9 pg/ml, respectively; ANOVA, p=0.049), there were no differences in other adipokines levels between the groups. Vascular stiffness and endothelial function were within normal values, though PWV was higher and RHI was lower in hypertensive groups compared to healthy controls (8.7 +/- 0.3 versus 6.8 +/- 1.6 m/s; p=0.02 and 1.8 +/- 0.08 versus 2.6 +/- 0.9; p=0.02, respectively). However, only in obese subgroup some adipokines were associated with diastolic BP levels – adiponin with “office” diastolic BP (r=0.427, p=0.048), resistin grades with “office” (r=0.488, p=0.025) and central (r=0.456, p=0.038) diastolic BP and also visfatin levels with central diastolic BP (r=0.451, p=0.03), as well as RHI was associated with leptin levels (r=-0.5, p=0.001), PVW with leptin (r=0.5, p=0.001) and resistin (r=0.5, p=0.001) levels.

Conclusions: Obese hypertensive patients are characterized by decreased adiponectin levels and both peripheral and central diastolic BP and vascular damage appear to be associated with adipokines levels.

Keywords: hypertension, obesity, adipokines, arterial stiffness

Sex differences in the effects of high-fat diet feeding on rat heart Na⁺/K⁺-ATPase activity

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Background: In heart, sodium-potassium adenosine triphosphatase (Na⁺/K⁺-ATPase) has a critical role in the regulation of contraction of cardiomyocytes. The existence of a relationship between obesity, insulin resistance (IR) and cardiovascular disease is well known and all these pathophysiological conditions are linked to reduction in cardiac Na⁺/K⁺-ATPase activity.

Aim: Considering the sex differences previously found for the insulin sensitivity profile in different tissues, the aim of this study was to investigate whether a sex-dependent effect of a long-term high-fat diet (HFD) feeding exists on Na⁺/K⁺-ATPase function and expression. We used HFD to determine the effects of obesity on the key components of the insulin signaling pathways: PI3K and protein kinase B (Akt) and the consequences of these effects on the regulation of Na⁺/K⁺-ATPase, in heart of male and female rats.

Methods: Wistar rats (160–240g) of both sexes were fed a standard diet or an HFD (10 weeks fed with balanced diet for laboratory rats enriched with 42 % fat). Serum insulin levels were determined by the RIA method, and serum glucose levels were measured by using a GLUC-PAP kit. To validate the level of IR and function of β cells we calculated: index of insulin resistance (HOMA-IR) and index of insulin secretion (HOMA- β). Na⁺/K⁺-ATPase activity were assessed spectrophotometrically by measuring the consumption of ATP. Western blot method was used for measuring the phosphorylation of Akt, protein expression of p85 and p110 subunits of PI3K as well as α_1 and α_2 subunits of Na⁺/K⁺-ATPase.

Results: No significant changes in the levels of insulin and glucose as well as in the values for HOMA-IR and HOMA- β indexes were observed in obese females compared with control females. However, all of these parameters were significantly higher in obese males compared with control males. Na⁺/K⁺-ATPase activity was not changed in obese females compared with control females, while it was significantly reduced in obese males compared with control males. Phosphorylation of Akt was significantly increased in obese females and significantly reduced in obese males compared with corresponding controls. There were no changes in the levels p110 subunit of PI3K in both sexes, while the level of p85 subunit was reduced in obese males compared with control males. The level of α_1 subunit of Na⁺/K⁺-ATPase was not changed, while α_2 subunit protein level was significantly increased in obese females compared with control females. In obese males compared with their controls protein level of both, α_1 and α_2 subunits of Na⁺/K⁺-ATPase were significantly decreased.

Conclusion: These results suggest an existence of gender dimorphism in the cardiac Na⁺/K⁺-ATPase regulation. Development of IR has led to a reduction in phosphorylation of Akt, and levels p85 subunit of PI3K, α_1 and α_2 subunit of Na⁺/K⁺-ATPase, which caused a reduced activity of the Na⁺/K⁺-ATPase in heart of obese male rats, while obese female rats are protected.

Keywords: sodium potassium adenosine-triphosphatase, obesity, insulin resistance, cardiovascular disease

Impact of losartan on indicators of exercise tolerance and quality of life in patients with chronic heart failure

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Aim of the study. To study the effect of losartan on indicators of exercise tolerance and quality of life parameters in patients with coronary heart disease (CHD) complicated with chronic heart failure (CHF).

Research methods. The study involved 60 patients with coronary heart disease complicated with CHF FC I-III. The study included patients aged 45-60 years. From 60 patients 18 were with FC I, 22 were with FC II and 20 patients were with FC III of CHF. All the patients took losartan over 6 months with standard therapy (spironolakton, beta-blockers, antiplatelet agents); dose of losartan titrated 50-100 mg per day (average dose was $66,3 \pm 25,6$). All the patients underwent a six-minute walk test (6MWT) and evaluation of quality of life (QOL) using the “Minnesota questionnaire.”

Results. Initial results of 6MWT in patients with CHF FC I were $454,4 \pm 21,95$ meters, with FC II were $384,17 \pm 25,3$ meters, with FC III were $237,3 \pm 33,5$ meters. Initial QOL parameters in patients with CHF on the “Minnesota questionnaire” total index of quality of life (QOL TI) showed a significant increase in the sum of points with increasing of CHF FC and points amounted $24,3 \pm 1,32$ points in patients with FC I, $36,8 \pm 2,36$ points in patients with FC II, $44,67 \pm 2,28$ points in patients with FC III.

Against the background of 6 months losartan therapy in addition to standard therapy it was observed a significant advance of tolerance to physical activity with increasing of six-minute walk distance in patients with I, II and III FC of CHF by 13.1%, 14.5% and 16.6% ($p < 0.001$). Increased exercise capacity of patients was associated with improvement of quality of life in patients with chronic heart failure, which was reflected in a decrease in QOL TI: in patients with I, II, III FC of CHF to 32.4%, 23.8%, 13.9% ($p < 0.001$) respectively, compared with initial results. It was noted that significant inverse correlation between QOL TI and 6MWT results with a correlation coefficient $r = -0,809$ respectively.

Conclusions. Against the background of 6 months therapy with the inclusion of losartan it was observed increase in exercise tolerance and significant improvement in quality of life in patients with CHF.

Keywords: exercise tolerance, quality of life, chronic heart failure, coronary heart disease

Matching rate of rank the between the pulse wave velocity and wearable wristwatch-type sphygmomanometer in 24 hours of hemiplegia in the maintenance phase for health care

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This study is part of a study aimed at to be used in the management of arteriosclerosis of hemiplegics of the maintenance phase using the pulse wave velocity.

Purpose: The aim is to clarify the match rate of rank the between the pulse wave velocity and wearable wristwatch-type sphygmomanometer in 24 hours of hemiplegia in the maintenance phase.

Participations: Hemiplegia after cerebral vascular disorders, for people (n = 44), which uses the elapsed welfare facilities from the onset of more than two years. Enrolment is to walk alone. They agreed to the described.

Methods: We measured the blood pressure of 24 hours every 15 minutes in the paralysis measurement of the wrist of the participants by a wristwatch-type sphygmomanometer. It used BPro (Healthstat, Singapore) of data of ambulatory blood pressure monitoring (ABPM). The affected brachial-ankle pulse wave velocities were measured by BP-203(Nihon Corin) every 6 hours. Evaluation was order matching rate the between the order of PWV value of 24 hours indicating the good of the vessel hardness (slow speed) and the order of value of ABPM of the same point in time. Statistical analysis, descriptive statistics and from the data in this period, ABPM, to determine the degree of matching of the time zone in which the peak value of the time zone and baPWV which showed a peak value of the acceleration is present, was verified by Goodness fitness test. Using by the IBM-SPSS v20.

Results: Successive values of baPWV every 6 hours and charts concordance rate ABPM at each time was 60%. Linearity of one group is 80%, non-linearity group was 55%. The average value and standard deviation of the time distribution ratio of the activity-rest, sleep time (2SD), 1SD, 2SD, were divided into 2SD above three groups, to determine the time zone coincidence of the peak value in each group. Those who showed the ABPM that matches the baPWV variation of every 6 hours in the 24 hours is 60% and the remaining 40% showed a peak value independent of the ABPM. Time zone for each of ABPM, matching degree of acceleration peak value time zone and PWV peak value time zone is ABPM60%, acceleration peak was 55%. Concordance rate of 68% within 1SD of each classification by the degree away from the mean value of the time distribution ratio of the activity-rest, sleep, 1~ 2SD within is 9%, 2SD or more was 22%.

Conclusion: The baPWV and cross-order match rate of ABPM showed 60% of the match. The application of the analysis of biological information, can be expected to monitor the inhibiting the deterioration vascular function of hemiplegics of maintenance phase using a wristwatch-type sphygmomanometer for health care.

Keywords: ABPM, hemiplegics, pulse wave velocity, wristwatch-type sphygmomanometer

Associations of psycho-social risk factors and the severity of coronary bed lesion with lipid parameters in patients with acute coronary syndrome who live in the North

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Goal: To assess the contribution of non-conventional (psycho-social) risk factors and the severity of coronary bed lesion to the change of levels of lipid spectrum in patients with acute coronary syndrome who live in the North.

Materials and methods: A research study of 108 patients (women-22,2%, male-77,8%) with acute coronary syndrome at the age of 45 to 64 years ($55,6 \pm 5,9$), treated at “District cardiology centre of diagnostic and cardiovascular surgery” in 2015 was conducted. The research study included an analysis of the severity of coronary bed lesion on the scale of the SYNTAX, assessment of the probable hospital mortality on the scales of TIMI and Grace, analysis of lipid spectrum rate (total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglyceride (TG)); a survey among patients on a specially designed questionnaire consisting of general questions (age, sex, duration of residence in the North, marital status, education, occupation, income level) was carried out, assessment of the psychological state of the person (validated questionnaire of social support F-SOZU-22, anxiety scale of Spielberger-Hanin, inversion test of emotional reflection), «Audit» test (checking the alcohol consumption). Statistical processing has been done with the use of parametric and nonparametric statistical methods in Microsoft Excel and SPSS version 13.

Results: In the general group of patients a direct association of the level of TC, LDL-C levels and the probable hospital mortality by Grace scale ($r=0,26$, $p=0,006$, $r=0,23$, $p=0,018$, respectively) has been revealed; direct link of LDL-C from the length of residence in the North ($r=0,19$, $r<0,05$) and the level of social integration ($r=0,22$, $r<0,05$), and inverse association of this indicator from the patient's body weight ($r=-0,19$, $r<0,05$). In the analysis of indicators in the group of women a correlation of indicators of TC, LDL-C and income levels ($r=0,59$, $p=0,01$, $r=0,67$, $p=0,003$, respectively) has been found out; association of the increase of levels of LDL-C in patients without permanent employment ($r=0,49$, $p=0,03$) has been revealed. In a subgroup of men significant correlation in body weight and marital status with HDL-C ($r=-0,29$, $p=0,03$, $r=0,31$, $p=0,005$, respectively) has been found out; the direct association of TG level increase in patients with overweight and obesity ($r=0,32$, $r<0,05$) has been revealed. The identification of correlations of indicators of trait anxiety with TC level ($r=-0,22$, $r<0,05$) has been noted.

Conclusion: In the general group of patients with acute coronary syndrome direct associations of indicators of total cholesterol and LDL-C levels with the indicators of possible hospital mortality on the scale of Grace have been found out. Correlations of the length of residence in the North and the reduction of the level of social integration with LDL-C have been revealed. In the group of women the connection of income and lack of permanent employment with the LDL-C level has been defined. Increase of body weight in men has been associated with the decreased level of HDL-C and increase in TG, and the single status in the group of patients – with the decreased level of HDL-C.

Keywords: acute coronary syndrome, psycho-social risk factors, lipid spectrum

Coronary atherosclerosis and red blood cell dysfunction: systematic approach for real clinical practice implementation

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Recent studies have shown that higher red blood cell distribution width (RDW) is associated with increased mortality risk in patients with clinically significant cardiovascular disease (CVD). Never the less up to present there is still certain gap in understanding of possible mechanisms and clinical implementation of that fact.

The purpose of the study was to investigate whether there is association between morphological and biochemical parameters of coronary atherosclerosis and red blood cell dysfunction markers, and to assess possible clinical implementation of RBC dysfunction markers into real clinical practice.

Materials and methods. 2 740 patients with high pretest probability of coronary atherosclerosis in age range of 26 ... 79 years old were involved in the study. Involved patients were stratified according to the results of angiography into: I – no signs of coronary atherosclerosis, II – hemodynamically non-significant and III – hemodynamically significant coronary artery stenosis (CAS). In 56 men glucose loading test was performed to study erythrocytes system “behavior”.

Results. In direct compare within patients with different degrees of CAS were revealed significant differences in leukocytes (6.3 ± 1.5 ; 6.9 ± 2.3 ; 7.4 ± 2.0 , $p = 0.000$), lymphocytes (34.8 ± 6.9 ; 33.2 ± 8.8 ; 32.3 ± 6.7 , $p = 0.003$) and granulocytes (60.2 ± 7.4 ; 61.6 ± 8.6 ; 32.6 ± 7.1 , $p = 0.006$) counts, hemoglobin concentration (137.8 ± 14.1 ; 138.6 ± 16.6 ; 141.9 ± 13.6 , $p = 0.011$) and hematocrit (39.9 ± 3.9 ; 40.2 ± 41.2 ; 41.2 ± 3.8 , $p = 0.003$). No significant differences in MCV, MCH, RDW, MPV or PDV in these subgroups were detected (p levels 0.353, 0.446, 0.386, 0.880, 0.746 and 0.997, respectively). Comparison within age subgroups elucidated progressive decrease in RBC ($p = 0.000$), hemoglobin level (p level = 0.000) and hematocrit ($p = 0.000$) with aging, hence all values were within reference range. RDW presented negative association with total cholesterol level: $RDW = -1.015 * TC^2 + 29.689 * TC + 17.225$, $R^2 = 0,945$. Erythrocyte system disturbing by glucose concentration increase show to be resistant in patients with isolated hypercholesterolemia. Usage of classification trees reveals increase of haemodynamically significant coronary atherosclerosis in elderly male patients with typical clinical presentation of angina, ubnormal BMI, leukocytosis $> 6,0 * 10^6/L$, RDW $> 14\%$, MPV $> 8,5$ mkm, fasting glucose – $6,0$ mmol/L, total cholesterol > 185 mg/dL, triglycerides > 104 mg/dL, and diastolic blood pressure > 100 Hg.

Conclusion. Received data suggest RBC involvement in coronary atherosclerosis pathogenesis due to energy balance and membrane rigidity. RBC dysfunction markers may be easily implemented into clinical practice as a component of decision making tool patients in high pretest probability of coronary atherosclerosis

Keywords: coronary artery stenosis, RDW, risk stratification, coronary atherosclerosis

Features of left ventricular remodeling in patients with arterial hypertension and multifocal coronary arteries defeat

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The remodeling of the left ventricle at hypertension (AH) increases risk of cardiovascular complications which depends on type of remodeling of LV. Hypertrophy of a myocardium at arterial hypertension is connected with high end systolic pressure in LV, also increase of the total peripheral vascular resistance. Dysfunction of endothelia at multifocal atherosclerotic conducts to violation of humoral mechanisms of an auto regulation of a vascular tone and promotes violation of coronary haemodynamics. It is important that the combined action of these factors conducts to progressing and increase of need of a myocardium for oxygen and in the conditions of decrease in a coronary reserve to ischemia of subendocardial layers.

The aim of research was to study the features of remodeling of LV and coronary hemodynamic at patients in conditions of long current of AH and hemodynamically not expressed multifocal defeat of coronary vessels.

The group of 20 patients of Republican Clinical Hospital (RCH) of Kazan was examined. Criteria of inclusion in group were AH degree III with more than 15 years of disease lasting, a hypercholesterolaemia with increase of the general cholesterol more than 5,5 mmol/l and LDL cholesterol more than 2,5 mmol/l against therapy. Clinically patients group had no typical and nontypical complaints of angina, but treated in group with high apriory probability of CHD. To all patients besides an ESG and echocardiography (EchoCG) for an assessment of coronary haemodynamics and stratification of risk the ESG-*synchronized single-photon emission computer tomography (SPECT)* of a myocardium on the *Philips Bright View Tc99M* gamma chamber was carried out. For studying of features of defeat of proximal coronary course multislice computed tomography (MSCT) of heart and coronary vessels was carried out: *Siemens Somatom Sensation 64 tomograph*.

Results of researches showed concentric model of a hypertrophy with increase in mass of a myocardium to 300.5 ± 15.4 g and index of LV mass to 146.4 ± 7.8 . SPECT: the unevenly thickened myocardium with asymmetric accumulation in hypertrophied apex and anteroseptal segments with diffusion decrease of contractility during loading was visualized. By results of MSCT an asymmetric thickening (interventricular septum of basal part thickness up to 2.5 ± 0.3 cm, apex segments to 1.3 ± 0.1 cm, forward wall 1.7 ± 0.2 cm) was noted. The expressed calcification of coronary arteries (calcium index up to 900 ± 150.8 on a scale of Equivalent Agatston Score) was noted. At all patients multiple plaques of eccentric type in the right coronary artery, circumflex branch (Cm), anterior interventricular branch (LAD) without stenoses of lumen were visualized. Only at 30% of patients in the pool of Cm and LAD the prolonged calcinated concentric plaques in a proximal and medium third with stenoses of lumen up to 30-40% was noted.

The research showed possibility of asymmetric hypertrophy at the combined multifocal atherosclerosis of coronary arteries and AH in a type of their multifactorial influence. Due to the lack of significant defeat of the proximal coronary course and existence of signs of diffuse decrease of contractility, the clinic of angina is caused by diffuse ischemia of the subendocardial layers of unevenly thickened myocardium.

Keywords: multifocal atherosclerosis, coronary haemodynamics, asymmetric hypertrophy

An elevation serum level of endothelial monocyte activating polypeptide-II in hypertensive patients with type 2 diabetes and obesity.

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Endothelial dysfunction – is common features of arterial hypertension, diabetes, obesity. Endothelial monocyte activating polypeptide-II – proinflammatory cytokine with anti-angiogenic activity. However, the role of this cytokines in arterial hypertension is not understood. The aim of this study was to investigate serum levels of endothelial monocyte activating peptide-II (EMAP-II) in hypertensive patients. Serum levels of EMAP-II were determined by immunoenzyme assay. Statistical analysis was performed by use Student's test and Person's. The data were presented as means±SD. Were examined 41 hypertensive patient with type 2 diabetes, 18 obese hypertensive patients, 9 – non-obese hypertensive patients, 18 – control. Were found an increased serum level of EMAP-II in hypertensive patients with type 2 diabetes compared to control ($4,86\pm 2,3$ and $1,03\pm 0,5$ ng/ml respectively, $p<0,05$), in hypertensive patients with obesity compared to control ($2,62\pm 1,24$ and $1,03\pm 0,5$ ng/ml respectively, $p<0,05$), and in non-obese hypertensive patients compared to control ($2,03\pm 0,33$ and $1,03\pm 0,5$ ng/ml respectively, $p<0,05$). Also, the level of EMAP-II correlated with the serum levels of HbA1c, blood glucose in hypertensive patients with type 2 diabetes ($r=0,57$, $r=0,51$, respectively, $p<0,05$), insulin, HOMA in hypertensive patients with type 2 diabetes ($r=0,57$, $r=0,64$, respectively, $p<0,05$) and in obese hypertensive patients ($r=0,72$, $r=0,36$, respectively, $p<0,05$), body mass index in obese hypertensive patients ($r=0,85$), total cholesterol, HDL, LDL, triglycerides in hypertensive patients with type 2 diabetes ($r=0,43$, $r=-0,45$, $r=0,46$, $r=0,66$ respectively, $p<0,05$) and in obese hypertensive patients ($r=0,73$, $r=-0,5$, $r=0,85$, $r=0,57$ respectively, $p<0,05$). The revealed change could reflect an endothelial dysfunction in this pathological state. Hyperglycemia, dyslipidemia, insulin resistance, obesity appears to be significant factor to contributing elevation of EMAP-II.

Keywords: Endothelial monocyte activating polypeptide II, endothelial dysfunction, arterial hypertension, type 2 diabetes, obesity

Changes in the Structure and Function of Myocardium in Geriatric Patients with Coronary Atherosclerosis Who were Referred for Percutaneous Coronary Intervention

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Introduction: The leading cause of death among persons older than 65 years, both men and women is coronary heart disease (CHD). A number of studies have proven the clinical efficacy of the technique of coronary angioplasty and stenting. Especially important are prevention and treatment of coronary artery disease in patients of elderly and senile age. For risk stratification of perioperative cardiac complications is necessary to study structural-functional changes of the myocardium in geriatric patients.

Purpose: We aimed to study structural-functional changes of the heart in patients of elderly and senile age who were referred for percutaneous coronary intervention.

Materials and methods: We included 82 patients with coronary heart disease were referred for percutaneous coronary intervention. 66% of the examined patients whose average age was 74 years suffered from angina pectoris of the III functional class, 51% suffered a myocardial infarction. Echocardiography with tissue Doppler imaging of the myocardium and Wall Motion Tracking was performed using the ultrasound device «Artida Toshiba» (Japan).

Results: In patients without myocardial infarction in the anamnesis, prevailed single-vessel lesion of coronary vessels (71%), while in individuals after myocardial infarction, more than half (54%) had multivessel lesion. In both groups there was a dystrophic lesions of the valve apparatus. 60% of individuals after myocardial infarction showed a combined damage of valves from small to moderate. In the group of patients without myocardial infarction in the anamnesis there was isolated lesions of the valves, without combined lesions of the valves. Concentric hypertrophy of the left ventricle (LV) in both groups was 84%. Concentric LV remodeling occurred in 7% of patients without myocardial infarction in anamnesis, eccentric hypertrophy was not identified in this group of patients. All the examined patients had diastolic dysfunction and decrease of left ventricular global longitudinal strain, more severe in persons after myocardial infarction. In addition, in this group of patients compared with patients without myocardial infarction in anamnesis, were significantly more dimensions of the left atrium and LV, lower values of LVEF and segmental indices of longitudinal systolic and diastolic function.

Conclusions: The data obtained indicate a more pronounced structural and functional changes of the heart in CHD patients of elderly and senile age who were referred for surgical intervention after myocardial infarction compared with patients without myocardial infarction in the anamnesis. The decrease in left ventricular global strain may be a marker of reduced systolic function. Further research is needed to identify the most informative indicators of successful revascularization and risk of complications in these patients.

Keywords: dysfunction of the myocardium, infarction, coronary stenting, elderly, strain

Genetic determinism of family forms of thrombophilia in patients with coronary heart disease

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Goal: Determination of the frequency of family forms of thrombophilia in patients with CHD.

Materials and methods: Using the method of random sampling, the main group included n=130 men with coronary heart disease, (average age of $50,8 \pm 10,4$) was formed. The control group included n=39 healthy men, average age $47,5 \pm 3,8$ (p 0,06). Exclusion criteria for both groups: acute coronary syndrome, cancer, concomitant diseases in the stage of decompensation, inflammatory diseases, surgery. 17 parameters of the hemostasis system and 3 parameters of endothelial dysfunction, genetic mutations in 12 parameters were evaluated. Next, the main group was divided into two subgroups and compared with each other: I (n=101) – CHD with a history of thrombotic (HT), II (n 29) – CHD without HT. These subgroups were ranked on the family HT and made: I –n=41, II – n=17. Statistical analysis of the material was performed using Statistica 6.0 software.

Results and discussion: The patients with CHD are characterized by a moderate thrombinemia (p <0,01), pent anticoagulant link (increased fibrinogen and fibrinogen pool of components, increase in the activity of factor VIII and Willebrand factor). In addition, there was endothelial dysfunction (elevated homocysteine content and endothelin-1, p <0,01). Differences in the genetic mutations were obtained in two parameters: MTRR (p 0,03) in the main group and FGB (p 0,02) in the control group. The frequency of thrombotic events among CHD patients was 77,7% (p <0,01): myocardial infarction – MI (95%), stroke and other arterial thrombosis (5%). In subgroup I (n=101) with HT – thrombinemia was expressed greater due to significant excess SFMC level (p=0,04). No significant differences in genetic mutations between subgroups I and II were found. Studing these subgroups on genetic mutations based on a family HT number of MTHFR C677 and MTRR genes in group I was significantly greater ($\leq 0,05$) than in group II, and the elevated homocysteine levels was over 13 $\mu\text{mol} / \text{l}$ in both groups. In contrast to the detected breaches in the hemostatic system in both groups, a significant prevalence of factor VII gene heterozit (p=0,05) in group II was revealed.

Conclusions: The patients with CHD showed signs of moderate thrombinemia and endothelial dysfunction, which were more evaluated in patients with HT. The frequency of thrombotic events among CHD patients was 77,7%. Family HT was accompanied by the increase in the number of homozygous MTHFR C677 and MTRR gene. Family thrombophilia was 31,5%. Abnormal gene factor VII was found in patients without HT. The presence of which leads to a decrease in the activity of factor VII in the blood by 30%, and a 2-fold reduction in the risk of thrombosis, in particular myocardial infarction, even in the presence of significant coronary atherosclerosis.

Angiotensin II -induced rat VSMC proliferation involves ADAM12 and PKC δ via EGFR –dependent and –independent signaling pathways

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Aim: Angiotensin II (Ang) is involved in abnormal proliferation of vascular smooth muscle cells (VSMCs) associated with pathogenic vascular remodeling. Ang stimulation results in extracellular signal-regulated kinase (ERK1/2) activation through transactivation of the epidermal growth factor receptor (EGFR). In addition, Heparin-binding EGF-like growth factor (HB-EGF) and metalloproteinases have also been detected in VSMCs and shown to be regulated by Ang. In this study, we investigated the role of EGFR, ERK1/2, HB-EGF, ADAM12 and PKC δ in mediating the mitogenic action of Ang in rat VSMCs.

Methods: Western blot and SDS-PAGE were used to monitor phosphorylation of EGFR and ERK1/2. BrdU test was used to measure proliferation of rat aortic VSMC primary culture.

Results: Incubation of primary cultured VSMCs with Ang (100 nM) for 5 minutes resulted in significant increase of ERK1/2 phosphorylation by 4.3-fold ($p < 0.001$), EGFR phosphorylation by 7.8-fold ($p < 0.001$) and VSMC's proliferation by 5.6-fold ($p < 0.001$). Pretreatment with EGFR tyrosine kinase inhibitors, 10mM PD169540 an irreversible inhibitor, or 10mM AG1478 (reversible inhibitor), significantly reduced Ang-induced VSMC's proliferation by 50% and 37%. Separate pretreatments for 30 minutes with 500 mM phenylephrine (general metalloproteinase inhibitor) or 10mM KB-R7785, (specific ADAM12 inhibitor) or 10mM anti-HB-EGF antibody, significantly reduced Ang-stimulated EGFR phosphorylation by 60%, 72% and 80%, also reduced ERK 1/2 phosphorylation by 58%, 42% and 38%. Furthermore, same pretreatments reduced Ang-induced VSMC's proliferation by 23%, 23% and 20%, respectively. Pretreatment of VSMCs with 5mM rottlerin, a specific inhibitor of PKC δ , significantly reduced EGFR and ERK1/2 phosphorylation by 80% and 55% and by 34% reduced Ang-stimulated VSMC proliferation.

Conclusions: The results showed that Ang-induced VSMC's proliferation correlates more with ERK1/2 activation than EGFR activation. Further, these results indicate that Ang acts through: EGFR-dependent and –independent, and ERK1/2 signaling pathways, at least in part *via* PKC δ and ADAM12 to up-regulate proliferation of VSMCs.

Keywords: ADAM 12, Ang, ERK1/2, EGFR, VSMC proliferation

Carotid plaque instability in patients with acute coronary syndrome estimated with high resolution ultrasound

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The aim of our study was to assess carotid plaque structure characteristics and its echogenicity in patients with acute coronary syndrome with ultrasound duplex scanning.

Materials and methods. The study included 95 pts (89% male) with acute coronary syndrome (ACS) aged $58,4 \pm 10,4$ years and 23 pts (76% male) with documented coronary heart disease (CHD) aged $62,5 \pm 8,4$ years. The inclusion criteria in ACS group was occurrence of acute myocardial infarction ($n=94$) and/or unstable angina ($n=1$) not later than 3-5 days before ultrasound examination. Duplex scanning of carotid arteries was held with Philips IU22 ultrasound system and L9-3 linear array transducer by two experience operators in block of intensive therapy. Atherosclerotic plaques in CCA, in bifurcation of CCA, in ICA from right and left side were investigated (according to Mannheim carotid IMT and plaque consensus 2011 and recommendations of American Society of Echocardiography 2008). We assessed traditional criteria of plaque instability: heterogenous structure, hypoechogenic component, irregular plaque surface and additional criteria: «layered» structure of plaque, local calcification and positive remodeling. Off-line analysis of B-mode images and plaque gray scale median (GSM) was performed with computer semi-automated workstation MultiVox.

Results: 235 plaques of ACS pts and 53 plaques of CHD pts were studied. In ACS group in comparison with CHD group there were more plaques with such parameters as heterogenous structure (77,4% and 58,4%, $p=0,0172$), irregular surface (23,8% and 9,4%, $p=0,0114$), «layered» structure (58,3% and 36,2%, $p=0,004$) and positive remodeling (19,6% and 9,4%, $p=0,047$) We found insignificant difference of hypoechogenic plaque component (44,3% and 31,9%, $p=0,08$) and GSM value (50 and 57,7, $p=0,06$) between ACS and CHD pts. There were no differences in local calcification in ACS and CHD pts (23% and 23%, $p=NS$).

Conclusion: Our study demonstrates more frequent plaque instability in carotid arteries in patients with acute coronary syndrome than in coronary heart disease. The newly introduced parameter «layered» structure of atherosclerotic plaque is found most significant.

Keywords: carotid artery, plaque, instability, ultrasound, acute coronary syndrome

Is genesis ventricular arrhythmias in patients with stable coronary artery disease always obvious?

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The purpose: to estimate antiarrhythmic (AA) effect of myocardial revascularization (MR) in patients with coronary artery disease (CAD) and ventricular arrhythmia (VA) depending on its different genesis.

Materials and Methods: 80 patients ($49,5 \pm 11,5$ years, 64% men) with stable CAD, normal ejection fraction ($52 \pm 5\%$ by Simpson) and high grade VA (Lown class III to V). All patients have passed the coronary angiography (CA). All patients had significant stenosis, and MR was performed.

Algorithm for management of the patients: 1. Before and after MR: Holter monitoring (HM), treadmill tests (TT), echocardiogram were performed. 2. If AAE still remained after RM noninvasive electrophysiological mapping of VA and psychodiagnostic were done.

Results: The patients were divided into the 3 groups. Groups were comparable on a sex, age. In the I-st group there were 37 (46,3%) patients with transitory myocardial ischemia (TMI) during which VA appeared/progressed. The II-nd group – 33 (41,3%) patients with TMI and VA, which weren't connected on time with TMI and were registered only at HM. The III-d group – 10 (12,5%) patients with post-infarction cardiosclerosis had no TIM during TT, VA were registered only at rest. The results in 6 months after RM: in I-st group AA effect was observed in 22 patients (68%), in II-nd group – in 21 (64%). All patients in the III group had no AA effect. It was established that the localization of ectopic pacemaker center in this group didn't coincide neither with a scar, nor with the area of artery revascularization. The psychodiagnostics revealed the high level of trait anxiety and 100% of AAE of the psychotherapy in these patients.

Conclusions: Genesis of VA in patients with stable CAD may be different – it can be connected or not connected with TIM. In patients with TIM AA effect after MR makes more than 60% regardless of a direct or indirect connection of VA with TIM. In the I-st group AA effect is caused by removal of the main cause of VA – ischemia. In the II-nd group where VA had no direct connection with TIM, AA effect assume could be explained with improvement of blood supply of a myocardium in general. If there are no TIM signs during a TT the probability of AA effect after RM is very small. If there is no AA effect after RM it is necessary to continue to search an actual cause of VA. It is established that the high level of trait anxiety in these patients can be the reason of VA.

Keywords: ventricular arrhythmia, coronary artery disease, myocardial revascularization, genesis, antiarrhythmic effect

Coronary vessels atherosclerosis in hypertension patients

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141 patients with arterial hypertension (AH) of I – III degree, middle and high vascular risk (basic group) and 163 patients with normal blood pressure (comparison group) were surveyed. There were 35 women (11,51 %) and 269 men (88,49 %), middle age $48,7 \pm 5,2$ year. Inclusion criteria were AH and normal blood pressure. Exclusion criteria's were coronary heart disease and chronic heart failure III and IV functional class of NYHA. The basic demographic indicators (sex and age) distinctions between groups it has not been revealed.

We examined coronary arteries (total 10 segments at patient) with determination of coronary calcification scoring with method of computer angiography (CT) and serum lipid spectrum. Atherosclerotic changes as soft and calcified atherosclerotic plaques have been revealed at 96 basic group patients (68,08%) and at 75 comparison group patients (46,01%), $p < 0,05$, OR 2,54; 95% SD 1,56-4,00, $p = 0,015$. Single-vessel disease had 42 basic group patients (29,78 %) and 30 comparison group patients (18,40%), $p < 0,05$. Multivessel disease was found significantly more often at AH patients 54 (38,29 %) and 45 (27,60%) patients accordingly, $p < 0,05$. OR 1,63; 95% SD 1,00-2,64, $p = 0,048$. Most frequently abnormalities were detected in left anterior descending artery (84 basic group patients, 59,57% and 64 comparison group patients, 39,26%, $p < 0,01$. OR 2,27; 95% SD 1,43-3,61, $p < 0,001$).

Blood pressure is associated with the atherosclerosis progression in coronary vessels. Ca revealed significantly more in hypertensive patient's coronary arteries (64,53%) then at patients with normal blood pressure (42,33%, $p < 0,001$). AH leads to the formation of calcified plaques (OR 2,24; 95% SD 1,39-3,63, $p < 0,001$) without stenosis (OR 2,41; 95% SD 1,14-4,12, $p < 0,001$). Average content of Ca at coronary arteries patients with AH was $123,7 \pm 151,8$ Agatston's units, it is significantly more, then at patients with normal blood pressure, $77,2 \pm 191,3$ Agatston's units, $p < 0,05$. The number of patients with AH of III degree and Ca content of more than 75 percentiles of sex-age norm in coronary arteries was significantly greater than in the comparison group (OR 3,75; 95% SD 1,15-12,29, $p = 0,021$).

Ca level directly correlated with patients' age ($r = 0,43$, $p < 0,05$), systolic blood pressure ($r = 0,58$, $p < 0,05$) and multivessel disease at patients with AH of III degree ($r = 0,849$, $p < 0,001$).

Serum lipoproteins spectrum changes were detected at 74 basic group patients (52,48 %) and at 78 comparison group patients (47,85%), $p > 0,1$. Significant distinctions between groups of patients with normal and atherosclerosis change vessels were not revealed. It is not established authentic interrelation between contents of the serum total cholesterol and LDL cholesterol and number of the changed segments of coronary arteries and Ca level at vascular wall in both groups of patients.

Hypertension is an independent and significant risk factor for development of coronary artery atherosclerosis. Initial atherosclerosis displays of coronary arteries at hypertension patients without CHD more often detected, than serum lipoproteins changes.

Keywords: arterial hypertension, atherosclerosis, coronary arteries

Proinflammatory cytokines serum levels and clinical course of acute myocardial infarction

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Introduction: Inflammatory process is implicated in atherosclerotic plaque destabilization leading to the development of acute coronary syndrome. Acute myocardial infarction (MI) is characterized by local aseptic inflammation associated with systemic inflammatory response. Increased production of proinflammatory cytokines such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) typically seen in the early phases of AMI can facilitate heart muscle damage with further maladaptive remodeling in case of above named cytokines redundant activity.

Purpose: to analyze interrelationships of IL-1 β , IL-6 and TNF- α serum levels with clinical course and outcomes of AMI.

Methods and Results: In a prospective observational short term study IL-1 β , IL-6, TNF- α serum concentration were measured in 82 MI patients (mean age 65.4 ± 13.8 years). Risk stratification was estimated on admission according to the GRACE score. Blood samples had been drawn on admission to the hospital within 24 hours from the onset of symptoms. Control group included 20 age and gender matched healthy persons. Duration of the observation period was 14 days. All patients were divided into 2 groups: uncomplicated MI (group 1, n=47) and MI complicated by acute left ventricular failure such as cardiogenic shock and pulmonary edema (group 2, n=35).

All cytokine levels were significantly elevated in AMI patients in comparison to controls. Median concentrations of IL-6 were higher in group 2 compared to group 1 (27.45 vs 16.04 pg/mL; $P < 0.001$). The same difference was reveal for mean concentrations of TNF- α (24.74 vs 19.58 pg/mL; $P < 0.01$). While mean levels of IL-1 β did not significantly differ between studied MI groups.

Conclusions: Patients with acute MI complicated by acute left ventricular failure are characterized by higher serum levels of TNF- α , IL-6 then patient with uncomplicated course of MI. Determination of proinflammatory cytokines levels on admission in patients with acute MI may have additional predictive value to the GRACE score.

Keywords: myocardial infarction, inflammation, cytokines

Pre-hypertension and arterial hypertension in women with the early stage of rheumatoid arthritis

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Objective is to study the characteristics of pre-hypertension (Pre-HTN) and arterial hypertension (HTN) in women depending on the prescription of rheumatoid arthritis (RA).

Materials and methods: 53 women with early RA lasting less than a year were included into the study. RA was diagnosed by the criteria ACR/EULAR 2010. The average age was 52 years (30; 75). Salt taste sensitivity threshold (STST) was determined with R.J. Henkin's modified method. The bioimpedance analysis (body fat and fat-free masses, water), the monitoring of daily natriuresis, the evaluation of glomerular filtration rate (GFR) and risk factors were made. Statistical data were obtained with «Statistica» v 6.1.

Results: Pre-HTN occurred in 21% cases in patients with early RA. It was 1.2 times more frequently because of the increased diastolic blood pressure (DBP). The primary Pre-HTN was diagnosed at the same time with RA in 100% of cases. HTN was diagnosed in 70% (primary HTN – 13 %). The blood pressure in Pre-HTN was SBP 130(135)139/DBP – 80(84)89 mm Hg. Chronic kidney disease (CKD) in Pre-HTN was in 29% (HTN – 32%). The average GFR was 1.2 times lower in Pre-HTN (72 and 86 ml/min/1.73m²) respectively. CKD was 1.1 times more frequent in HTN. STST in Pre-HTN was high 0.88 (0.08; 1.28) – 56%, middle -30 %, low -14%, in HTN it was high – 2.21 (0.64; 5.12) – 89%, middle – 0%, low -11%. According to natriuresis the patients with Pre-HTN were divided into three groups: the first – less than 100 mmol/day (37%), the second – 100-200 mmol/day (63%), the third – more than 200 mmol/day (0%). The average natriuresis in Pre-HTN was 101 (81; 138), in HTN – 129 (79; 228) mmol/day. The excessive fluid in the body was 1.2 times higher in Pre-HTN (73, 61%). The number of risk factors was 6(8)12 in Pre-HTN and 7(9)12 in HTN. There is direct correlation between CKD, Pre-HTN, HTN and STST, excessive fluid, natriuresis ($p < 0.05$). There is correlation between Pre-HTN, CKD and risk factors (stress/ depression, abdominal obesity, family history for CVD, unbalanced diet) ($p < 0.05$), and also erythrocyte sedimentation rate, rheumatoid factor ($p < 0.05$) in 21% of patients.

Conclusion: Thus, pre-hypertension and hypertension have the following characteristics. The risk factors (salt sensitivity, natriuresis, abdominal obesity, unbalanced diet), the inflammatory markers determine the development of Pre-HTN and HTN and renal disease. The number of risk factors is equally high in Pre-HTN and HTN. 29% of patients with Pre-HTN and 32% with HTN have CKD in early stages of RA. It is the additional risk factor for cardiovascular complications, HTN development and stabilization.

Keywords: pre-hypertension, hypertension, rheumatoid arthritis, risk factors, cardiovascular complications

Risk factors and prognosis of acute myocardial infarction in patients of middle age

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Actuality: Coronary heart disease (CHD) and acute myocardial infarction (AMI) is one of the most common causes of morbidity and mortality in Russia. The ability to predict AMI patients is relevant for a differentiated approach to the treatment and prevention of disease.

Objective: Risk prediction of AMI in men and women and the average age with the help of modern statistical methods.

Methods: The study included 98 middle-aged patients with AMI, among whom there were 66 (67,3%) men and 32 (32,7%), women (their average age was $54,3 \pm 0,6$ years, and a group control (40 patients without proven CHD). Evaluated the clinical and medical history of patients, lipid, glucose metabolism with the calculation of HOMO-IR index, CRP. Using a multifactorial logistic regression method was developed by a calculator to calculate the risk AMI in Excel 2007 program. For creation of calculator us such parameters were selected as the patient's sex, age, presence of smoking fact, the parameters of lipid and glucose metabolism, the level of CRP. Smoke was detected in 54 (81,8%), middle-aged men and 7 (21,9%) women. The level of blood glucose levels in middle-aged men was $5,1 \pm 0,1$ mmol/l, women – $5,7 \pm 0,1$ mmol/l. Average insulin levels among middle-aged men was $13,9 \pm 1,9$ mIU/ml, in women of this age group – $8,7 \pm 1,2$ mIU/ml. HOMO-IR index (index of insulin resistance) in men with AMI mean age was $3,1 \pm 0,5$ meED/ml, in women – $2,3 \pm 0,3$ meED/ml. Dyslipidemia was diagnosed in 57 (86,4%), middle-aged men, mainly due to the increase in LDL level to $2,52 \pm 0,1$ mmol/l and HDL to reduce the level of $0,96 \pm 0,2$ mmol/l. In 31 (96,9%), middle-aged women diagnosed dyslipidemia, mainly due to the increase in LDL to $2,8 \pm 0,2$ mmol/l and increasing TG levels up to $2,56 \pm 0,1$ mmol/l. The level of CRP was elevated in all patients with AMI and was middle-aged men $25,3 \pm 3,3$ mg / l in women – $71,4 \pm 2,7$ mg / l.

Conclusions: Thus, using parameters such as gender, patient age, smoking, parameters of lipid and glucose metabolism (including insulin level and the index HOMO-IR), CRP, created calculator prediction of myocardial infarction for middle-aged patients, it is relevant and important for the development of individual programs of primary and secondary prevention for each patient, taking into account gender, age and its available risk factors.

Keywords: acute myocardial infarction, risk factors, prevention, risk calculator, dyslipidemia

The study on carotid atherosclerosis associated to certain biochemical blood parameters

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Aim: to study the intensity of carotid atherosclerosis in correlation to certain biochemical blood parameters.

Materials and methods: the current study was carried out upon 45 citizens of the Orenburg district – outpatients who had been diagnosed with stage 2 hypertension, CHD, exertional angina functional class 2-3 and had been treated by cardiologist. The patients were aged from 50 to 80 and selected by means of high cholesterol levels (over 7 mmol/L). The average age of the patients was $64,62 \pm 7,51$ years: 20 (44%) of them were male, the average age was $63,54 \pm 7,68$; 25 (56%) were female, the average age was $65,81 \pm 7,01$ years. Screening ultrasound of carotid arteries (CA) was carried out by the standard scanning methods of Vivid 3 Ultrasound System. Proximal and distal segments of the common CA, bifurcation and extracranial internal CA were examined for atherosclerotic plaques (ASP). The stenosis degree was measured by ultrasound cross-section as the degree of arterial diameter narrowing. The most severe stenosis underwent the analysis. In order to estimate the relationship of the intima-media thickness (TIM) and biochemical blood parameters the correlation coefficient was calculated as well.

Results: hemodynamically significant carotid artery stenoses failed to be revealed in the patients. The frequency of ASP among the examined patients resulted in 3 (6%): 2 male and 1 female. Average TIM thickness was $0,96 \pm 0,11$ mm: $1,03 \pm 0,13$ mm in male patients and $0,981 \pm 0,105$ mm in female ones. Total cholesterol (TH) level was $7,69 \pm 0,68$ mmol/L: $7,64 \pm 0,70$ mmol/L in male and $7,88 \pm 0,45$ mmol/L in female. CRP level – $38,37 \pm 8,96$ mg/L in male and $22,44 \pm 13,12$ in female. The patients with TIM over 1,0 revealed the lipid spectrum different from the average data, the CRP levels exceeded the average $29,83 \pm 15,96$ and $25,87 \pm 11,45$. The correlation between TIM and the parameters of TH and CRP showed the moderate correlation only between TIM and the CRP level ($r_{xy}=3,5$).

Conclusions: hemodynamically significant carotid artery stenoses in the patients with AH and CHD were not revealed despite the increased levels of TH and CRP. Atherosclerotic plaques revealed only in 6% of the cases. TIM was mainly dependent on C-reactive protein than on the total cholesterol level.

Keywords: carotid atherosclerosis, Total cholesterol, C-reactive protein, intima-media thickness, atherosclerotic plaques

Loading doses of statins before elective percutaneous coronary interventions

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Purpose of the study. Compare the effect of loading doses of atorvastatin and rosuvastatin on the value of the acute myocardial injury and acute inflammatory response to the intervention, determined by the dynamics of cardiac biomarkers (high-sensitivity troponin I (TnI) and MB fraction of creatine phosphokinase (CPK MB), as well as high-sensitivity C-reactive protein (hsCRP), for planning endovascular interventions on the coronary arteries.

Materials and methods. An open prospective comparative study, including 68 patients referred for elective percutaneous coronary intervention (PCI). At baseline, all patients taking statins for a long time in the standard lipid-lowering therapy. The first group included 33 patients who received a loading dose of 80 mg of atorvastatin 12 hours before the intervention and then save this dose for 2-6 days. The second group included 35 patients treated with rosuvastatin 40 mg / day in the same way. The level of cardiac biomarkers TnI and CK MB was determined at baseline, 12, 24, 48 and 72 hours after surgery. HsCRP levels were determined at baseline and at 5 days post-PCI.

Results. It is shown that on the background of a loading dose of rosuvastatin occurs significantly less increase in TnI and CK MB (26.7% and 27.1%, respectively) during the first 12 hours after the procedure, as well as a decrease of 24.3% with an increase in the number of patients more 1 x ULN TnI levels and a decrease of 12.1% in the number of patients with an increase in creatine kinase MB more than 3 x ULN after the procedure. Baseline hsCRP was 1.65 (0,9-4) and 2,8 (0,8-6,8) mg / l in groups load atorvastatin and rosuvastatin, respectively, $p = 0.59$. After 5 days after the intervention level of hsCRP was significantly increased in the first group to 4.55 (1,6-8,7) mg / l, $p = 0.001$. In the second group hsCRP not only increased but even decreased slightly to the 5th day of observation (2,75 (1,5-6,5) mg / L), $p = 0.16$.

Conclusion. Loading dose of rosuvastatin has a better preventive effect on the development of acute myocardial injury during PCI, and more significantly reduces the overall inflammatory response to intervention compared with a loading dose of atorvastatin.

Keywords: coronary artery disease, stable angina, percutaneous coronary intervention, statins

Predictors of attainment target lipid levels in high cardiovascular risk patients

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Objective: Dyslipidemia is recognized as a prominent risk factor for cardiovascular disease. The recent cholesterol guidelines recommend aggressive statin therapy in patients with high cardiovascular risk. However, high-intensity statin therapy may be insufficient to achieve LDL-C targets. The aim of the study was to investigate the efficacy and predictors of attainment of target LDL-C during short-term high-intensity statin therapy in patients with high cardiovascular risk.

Methods: In 187 patients with history of clinically evident cardiovascular disease and fasting low-density lipoprotein cholesterol (LDL-C) >1.8 mmol/l or non-high-density lipoprotein cholesterol (non-HDL-C) >2.6 mmol/l (64.2% male, 60.8±8.6 (M±SD) years, current smoking 41.7%, abdominal obesity 64.7%, arterial hypertension 89.8%, myocardial infarction 72.7%, percutaneous coronary intervention 58.3%, coronary artery bypass surgery 12.8%, non-hemorrhagic stroke 29.9%, diabetes mellitus 21.9%, symptomatic peripheral arterial disease 7.5%, chronic heart failure NYHA II 54.5%, chronic kidney disease 12.3%, total cholesterol (TC) 5.4±1.5 mmol/l, HDL-C 1.1±0.3 mmol/l, LDL-C 3.3±1.2 mmol/l, triglycerides (TG) 2.1±1.3 mmol/l, very LDL-C (VLDL-C) 0.9±0.4 mmol/l, non-HDL-C 4.3±1.4 mmol/l, previous statin therapy 74.3%) efficacy and safety of 1 month of high-intensity statin therapy (atorvastatin 80 mg/day) was assessed. Wilcoxon test and multivariate logistic were performed. P

Results: 76 patients (40.6%) achieved target LDL-C level

Conclusion: Short term high-intensity statin therapy is effective only in 40.6% of high cardiovascular risk patients. Baseline LDL-C may be a predictor of early response in this patient population. Lower baseline LDL-C is associated with attainment of target LDL-C.

Carbon monoxide releasing molecule induces endothelial nitric oxide synthase activation by calcium and PI3/Akt-dependent mechanism

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Aims: The aim of the present study was to elucidate the potential role of carbon monoxide (CO) in nitric oxide (NO) production and to explore the underlying mechanisms in endothelial cells (ECs).

Main methods: Bovine artery ECs were treated with CO releasing molecule (CORM-2) to observe its induced cytotoxicity, nitric oxide synthase (eNOS) activity. The investigation of eNOS activation mechanism is determined by intracellular Ca^{2+} level and eNOS phosphorylation, eNOS dimer/monomer and ROS level.

Key findings: CORM-2 could increase NO production and stimulates an increase in the intracellular Ca^{2+} concentration. The CORM-2-induced NO production persisted in the presence with EGTA, and abolished under BAPT-AM treatment indicating that intracellular Ca^{2+} release play a major role in eNOS activation. The inhibition of IP3 receptor diminished the CORM-2-induced intracellular Ca^{2+} increase and NO production. Furthermore, CORM-2 induced eNOS Ser¹¹⁷⁹ phosphorylation and eNOS coupling, but did not alter the eNOS gene expression. CORM-2 was further found to activate Akt over various time courses. Treatment with specific PI3-kinase inhibitors inhibited the increases in NO production and phosphorylation but no effect on eNOS coupling. CORM-2-induced eNOS Ser¹¹⁷⁹ phosphorylation is intracellular calcium-dependent, since pretreatment with intracellular Ca^{2+} chelator inhibits these processes. Although CORM-2 increases intracellular ROS, treatment with antioxidant enzyme catalase and antioxidant NAC could not abolish the CORM-2-induced eNOS activity and phosphorylation indicating ROS is not involved in CORM-2-induced eNOS activity.

Significance: In our study, we found CORM-2 enhances NO production and intracellular calcium level in ECs. Furthermore, CORM-2 induces Akt, eNOS phosphorylation, and eNOS dimerization.

Keywords: Carbon monoxide, endothelial nitric oxide synthase, nitric oxide, calcium, Akt

Elevated Lipoprotein(a) is associated with Worse Prognosis in Diabetic Patients with symptomatic Coronary Artery Disease

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Backgrounds: Along with type 2 diabetes, elevated Lipoprotein(a) [Lp(a)] is also known as a surrogate biomarker for cardiovascular disease. However, recent studies have demonstrated that Lp(a) level was lower in type 2 diabetic patients than in non-diabetic patients. We sought to evaluate if elevated Lp(a) is associated with worse prognosis in diabetic patients with coronary artery disease (CAD).

Methods: 1494 diabetic patients (62.3% male, mean age 63.5 ± 10.3 years) with CAD were enrolled from 2002 to 2012 at Gangnam Severance Hospital. CAD was diagnosed by invasive coronary angiography. Laboratory values for lipid parameters including Lp(a) were obtained at the day of coronary angiography and analyses were done shortly after sampling. Patients were divided into tertile groups according to their Lp(a) levels. Baseline risk factors, coronary angiographic findings, length of follow-up, and major adverse cardiovascular event (MACE) including cardiac death and non-fatal myocardial infarction (MI) were recorded.

Results: Over a mean follow-up period of 4.4 ± 2.6 years, there were 59 MACEs (35 cardiac death and 24 non-fatal MI) with an event rate of 3.9%. Elevated Lp(a) was a significant predictor of MACE on univariate and multivariate Cox proportional survival analysis [HR 3.869 (95% CI 1.855-8.067, $p < 0.0001$) and HR 2.890 (95% CI 1.373-6.084, $p = 0.005$)]. Kaplan-Meier survival analysis revealed that elevated Lp(a) was associated with worse prognosis ($p < 0.0001$). Furthermore, survival probability plot according to Lp(a) tertiles after adjustment of age, gender, hypertension, hyperlipidemia, smoking habitus, and extent of CAD revealed that elevated Lp(a) was associated with worse prognosis ($p < 0.0001$).

Conclusions: Elevated Lp(a) is associated with worse prognosis in diabetic patients with coronary artery disease.

Keywords: Lipoprotein(a), diabetic mellitus, coronary artery disease

Lipoprotein subclasses and activities of LCAT and CETP in hypertensive obese children

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Background: Childhood obesity strongly promotes development of primary hypertension. Both obesity and hypertension in children are associated with changes of lipid profile. Novel scientific approaches suggest that routine lipid measurements should be complemented with more in-depth analysis of lipoprotein particle characteristics and metabolic pathways included in development of dyslipidemia. However, distribution of lipoprotein subclasses and activities of lipid transfer proteins in hypertensive obese children are mainly unexplored.

Objectives: To determine low-density lipoprotein (LDL) and high-density lipoprotein (HDL) subclasses distribution and activities of lecithin:cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP) in hypertensive and non-hypertensive obese children.

Methods: Forty hypertensive and 25 non-hypertensive obese children were enrolled. Obesity was defined as a BMI \geq 95th percentile according to age and gender. Lipoprotein subclasses were assessed by polyacrylamide gradient gel electrophoresis. LCAT and CETP activities were determined as a rate of formation and a rate of transfer of cholesteryl esters (CE). Overall CETP activity of each sample, regardless of the direction of CE transfer was presented as absolute value and labeled as net CETP activity. CETP activity leading to depletion of HDL-CE was labeled as proatherogenic CETP activity.

Results: Despite of comparable values of serum lipid parameters, a shift toward smaller LDL and HDL subclasses was observed in hypertensive compared to normotensive obese children. Activities of LCAT were similar, but proatherogenic CETP activities were significantly higher in the hypertensive group ($P < 0.05$). Net CETP activity was in positive correlation with relative proportions of LDL III_B ($\rho = 0.336$; $P < 0.05$), LDL IV_B ($\rho = 0.353$; $P < 0.05$) and small, dense LDL particles ($\rho = 0.366$; $P < 0.05$). LCAT/net CETP correlated positively with relative proportion of LDL I ($\rho = 0.303$; $P < 0.05$), while negatively with proportions of LDL III_B ($\rho = -0.360$; $P < 0.05$), LDL IV_B ($\rho = -0.389$; $P < 0.01$) and small, dense LDL particles ($\rho = -0.350$; $P < 0.05$).

Conclusions: The results of our study demonstrated a tendency toward altered distribution of lipoprotein subclasses in favor of more proatherogenic particles in childhood hypertension. In addition, increased proatherogenic CETP activity was seen in hypertensive obese children when compared to their normotensive obese counterparts. Significant associations between CETP activity and prevalence of small, dense LDL particles suggest their contribution in the development of obesity-related hypertension in children.

Keywords: Lipoprotein subclasses, LCAT, CETP, Childhood hypertension

The features of the gene expression of the monocytes scavenger receptor in different clinical forms of atherosclerosis

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The aim of this study was to evaluate the level of expression of two genes belonging to the class of scavenger receptor – CD36 and CD 68 in atherosclerotic plaques and peripheral blood of patients with atherosclerosis of different severity.

Materials and methods: Analysis of gene expression CD 36 and CD 68 was conducted in 48 people. Of these 30 patients were free of clinical signs of atherosclerotic vascular lesions, but with the presence of risk factors for cardiovascular disease (group 1) and 18 people have been confirmed with clinical and diagnostic method for the diagnosis of multifocal atherosclerosis (group 2). The first group of patients, gene expression analysis was performed in peripheral blood and in the second group in the peripheral blood and in atherosclerotic plaques withdrawn during surgical interventions. The relative level of gene expression was assessed using the $2^{-\Delta\Delta CT}$ method according to the Livak and Schmittgen T. K. The significance of differences was determined using a non-parametric statistical test t-memory test ($p = 0.05$). Statistical analysis was performed with using of standard mathematical methods by means of the programs Microsoft Excel-2010.

Results: Analysis of expression of CD36 gene, the product of which triggers a cascade of inflammatory reactions and the formation of foam cells showed a significant increase in its activity in cells of the atherosclerotic plaque and peripheral blood 2 nd group ($p = 0.0495$) and in the peripheral blood of the 1st group of patients ($p = 0.0024$). There is evidence that oxidized LDL increase expression of the gene by activating gamma receptor stimulates of peroxisome proliferation – PPAR γ , as well as by increased expression of CD36 as monocytes into macrophages proliferate. Expression of the CD68 gene was significantly increased in cells of the atherosclerotic plaques in comparison with cells of the peripheral blood of patients in both groups ($p = 0.00027$ $p = 0.0054$ and respectively). Moreover, the relative level of expression of this gene is significantly decreased in the cells of peripheral blood in patients with multifocal atherosclerosis compared to another group ($p = 0.00023$).

Conclusion: Thus, the study represents a significant contribution to the development of scavenger receptor of atherosclerotic vascular lesions. When this difference in the expression level of these genes in patients with varying severity of disease (in particular, reduced CD68 expression in peripheral blood) can be both diagnostic and prognostic factor. The experimental data in combination with additional instrumental studies of the functional state of cardio – vascular system, can improve the accuracy of diagnosis of atherosclerosis and possible complications of the last in the early stages, thereby reducing morbidity and mortality.

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Case Report

Contrast enhanced ultrasound in carotid atherosclerosis.

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Aim of the study: determination of possibilities of application contrast enhanced ultrasound (CEUS) in diagnosis of atherosclerosis.

Materials and methods: From October, 2014, till May, 2015, in our institute was made 21 CEUS examination of 18 patients with different cardiovascular pathology. CEUS were performed on ultrasound system iU 22 (Phillips) with linear L9-3 transducer, according to the recommendations of EFSUMB (2011). In 3 time CEUS was performed in the 3D mode ultrasound (with the linear volume transducer VL13-5, at min MI). Intravenously injection 1,2/2,4 ml of contrast agent of Sonovue (Bracco), depending on the studied artery, was made. The maximum total dose for one patient was 3,6 ml. Degree of a vascularization of structures was estimated qualitatively (Shah F., 2007).

Results: 17 plaques were investigated: 9 heterogeneous plaques, 6 homogeneous hypoechoic plaques, 2 echolucency plaques. The percent of a stenosis were from 50 to 90 %. The more calcified plaque didn't include in the investigate. Researches of the 17 carotid plaques find in 3 cases considerable accumulation of contrast agent in plaques (intraplaque neovascularization) with a maximum accumulation on 30-40 sec, in 8 cases – moderate, in 6 cases – to indicate no appearance of neovascularization within the plaque (at the same time, in 2 cases was considerable contrasting of vasa vasorum of an adventita). At an assessment of surgical interventions (3 stents of ICA and SFA, 1 carotid endarterectomy) clear visualization of a lumen and wall allowed to find 2 cases of a restenosis with moderate accumulation of contrast agent.

Conclusion: Contrast enhanced duplex ultrasound – the high-informative, fast, safety method allowing determining a new parameter – degree of a intraplaques neovascularization, which characterizing instability of atheroma.

Keywords: atherosclerotic plaque, duplex ultrasound, contrast-enhanced ultrasound, Sonovue, neovascularization

Experience in the use of statins in patients with chronic myocarditis and heart failure with preserved ejection fraction

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To date in the use of statins in chronic heart failure a large number of contradictory data. In specially designed trials (CORONA and GISSI-HF) is devoted to the influence of rosuvastatin on the prognosis of patients with CHF, were obtained negative data. At the same time, a meta-analysis of 17 randomized clinical trials showed that atorvastatin, unlike rosuvastatin, has a beneficial effect on LVEF and levels of brain natriuretic peptide. These data raise the question about the possible impact of molecular differences in their pharmacological statins and pleiotropic effects. In particular, atorvastatin, possessing lipophilic properties, able to penetrate into cardiomyocytes in contrast to hydrophilic rosuvastatin. Perhaps this explains the cardiac effects of atorvastatin. However, in a recent study of PEARL with a lipophilic pitavastatin in patients with HF treated with this drug, there were no differences in the frequency of primary end-point (hospitalization due to worsening HF and cardiac death) compared with placebo. In the same study in patients with EF \geq 30% was observed somewhat lower incidence of the primary end point during treatment with pitavastatin compared with placebo, whereas in patients with EF $<$ 30%, taking the drug, on the contrary, there was a trend toward more frequent.

It was considered that in the overall picture of the effect of 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors on the immune system after 24 weeks of treatment with statins in 52 patients with chronic myocarditis. For this purpose serum concentration of antibodies has been studied to the myocardium and immunoglobulin G and A to cardiac myosin during therapy with atorvastatin 5–20 mg/day in patients with chronic myocarditis. For the detection of antibodies to the myocardium and specific classes of immunoglobulins A and G to cardiolipin used enzyme-linked immunosorbent assay in the modification of ELISA. Each patient included in the study, were conducted twice instrumental examination including echocardiography with measurement of the size of the chambers of the heart in systole and diastole, the assessment of systolic and diastolic function and echocardiography monitoring for the purpose of registration of arrhythmias events. To evaluate the clinical manifestations of heart failure we used a scale for assessing the clinical condition and estimate the 6-minute walk distance. The data is registered twice – before and after treatment. The results were compared with a control group of 25 healthy people. It was found that statins improved the clinical course of symptoms and signs of heart failure in patients with myocarditis in the stage of chronic inflammation: reduced functional class of heart failure, improved systolic function of the heart and arrhythmogenic potential.

Keywords: inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A- reductase inhibitors, chronic myocarditis, saved ejection fraction, antibodies to the myocardium, asymptomatic heart failure

Epidemiology

State carotid arteries and lipid metabolism in healthy women in different periods of life

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Objective: to study the state of the carotid arteries and lipid metabolism in healthy women in different periods of life.

Materials and methods: the study included 80 healthy women: 30 women – in the reproductive age (Me 35,5 years (25%;75%:32,0;43,0 years) – group 1, 30 perimenopausal women (Me 49,0 years (25%;75%:48,0;51,0 years) – group 2, and 20 – postmenopausal women (Me 54,5 years (25%;75%:53,0;58,0 years) – group 3. Body mass index (BMI) was determined by the formula Quetelet. Examinations were performed by doppler ultrasound of brachiocephalic arteries on «Logiq 5 Expert». To evaluate the thickness of the intima-media complex (IMT) and the presence of signs of subclinical atherosclerosis. Levels of total cholesterol (TC), LDL cholesterol (LDL), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) were investigated. Statistical processing of the data was performed using the package «Statistica 6.0» application software (StatSoft Inc., USA).

Results: body mass index (BMI) in women of reproductive age was significantly lower (Me 23,4 kg/cm² (25%;75%:22,7;24,8 kg/cm²) compared to group 2 (Me 26,7 kg/cm² (25%;75%:23,9;30,1 kg/cm²) and group 3 (Me 25,4 kg/cm² (25%;75%:23,3;27,6 kg/cm², $p_{1-2}=0,001$, $p_{1-3}=0,043$, $p_{2-3}=0,087$). A similar trend was observed in relation to lipid metabolism parameters-women in group 1 level of total cholesterol did not go beyond reference values (Me 5,15 mmol/l (25%;75%:4,50;5,50 mmol/l), whereas in group 2 (Me 5,59 mmol/l (25%;75%:4,99;6,66 mmol/l) and group 3 (Me 6,15 mmol/l (25%;75%:5,30;6,59 mmol/l) was significantly elevated ($p_{1-2}=0,003$, $p_{1-3}=0,014$, $p_{2-3}=0,109$). No significant differences in the level of atherogenic and anti-atherogenic fractions of lipoproteins, although 23% of women in perimenopause had hypertriglyceridemia (Me TG 1,57 mmol/l (25%;75%:1,17;2,01 mmol/l)). Ageing showed a trend toward structural changes in carotid arteries. Thus, only 2(7%) women in group 1 showed an increase in IMT, in the group 2 – 3(13%) and in the group 3 – in 4(24%) women. Symptoms subclinical atherosclerosis of the carotid arteries were determined only in peri- and postmenopausal women, while in 2 women (4%) in group 2 had unilateral stenosis common carotid arteries bifurcation to 20-30% and 30-40%. Over expressed stenotic changes were observed in group 3: stenosis of both carotid bifurcations up to 20% – in 2 (11%) women, up to 20-30% – in 1 women (6%), and up to 30-40% – in 4 women (24%).

Conclusions: With age in healthy women BMI was increased, and there was increasing lipid metabolism alterations and related structural changes in the carotid arteries which were more pronounced in postmenopausal women.

Keywords: healthy women, lipid metabolism, subclinical atherosclerosis

Prehypertension prevalence in population-based sample of Saint-Petersburg inhabitants

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Introduction: Prehypertension (PHT) is a predictor of hypertension (HT), associated with an increased risk of major cardiovascular-disease events. The study estimates prevalence of PHT in population-based sample of Saint-Petersburg inhabitants.

Methods: A novel epidemiological survey of cardiovascular risk was performed in a multi-step stratified random sample of approximately 1600 participants. 1600 participants aged 25-65 years were recruited. All subjects signed informed consent and filled validated questionnaires regarding lifestyle, concomitant disease and medication. Anthropometry, fasting blood sampling, blood pressure (BP) measurement were performed. Office BP was registered by OMRON (Japan) twice on right hand in sitting position with calculation of mean BP. Optimal BP was detected as BP<120/80 mm Hg, PHT as BP=120-139/80-89 mm Hg, HT as BP≥140/90 mm Hg or antihypertensive treatment. Statistical analysis was performed using SPSS Statistics 20.

Results: Data analysis was possible in 1592 participants (567 males (35,6%) and 1025 females (64,4%)). The optimal BP (BP<120/80 mm Hg) had 453 patients (28,5%), the PHT (BP=120-139/80-89 mm Hg) had 475 patients (29,9%), the HT (BP≥140/90 mm Hg or antihypertensive treatment) had 662 patients (41,6%). The optimal BP was registered in 150 persons 25-34 years old (49,3%), in 139 persons 35-44 years old (44,1%), in 102 persons 45-54 years old (22,3%) and in 62 persons 55-64 years old (12,1%). The PHT was detected in 114 persons 25-34 years old (37,5%), in 101 persons 35-44 years old (32,1%), in 145 persons 45-54 years old (31,7%) and in 115 persons 55-64 years old (22,4%). The HT was diagnosed in 40 persons 25-34 years old (13,2%), in 75 persons 35-44 years old (23,8%), in 210 persons 45-54 years old (46,0%) and in 337 persons 55-64 years old (65,6%). The optimal BP was registered in 92 males (16,3%) and 361 females (35,3%). The PHT had 216 males (38,2%) and 259 females (25,3%). The HT was diagnosed in 258 males (45,6%) and 404 females (39,5%). p<0,0001 between age groups and genders.

Conclusions: Prehypertension was detected in near 1/3 of participants in the selected age group. Males have prehypertension significantly more often than females. While prevalence of prehypertension and optimal BP decreases with age, prevalence of hypertension increases.

Keywords: prehypertension, prevalence, epidemiology

Peculiarities of Coronary Arteries Lesion in CHD patients in Donetsk region (Ukraine)

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Objective: to examine the level and structure of coronary arteries lesion (CA) in patients with CHD in Donetsk region and their connection with the major risk factors according to the data of scheduled coronary angiography (CAG).

Material and methods: There were analysed CAG results in 299 CHD patients, exertional angina of III-IV FC, among them there were male pts – 245 (82 %), females – 54 (18 %). 186 pts had myocardial infarction (MI) in anamnesis (62,2 %), diabetes mellitus (DM) – 25 pts (8,4 %), arterial hypertension (AH) – 237 pts (79,3 %).

Findings: out of 299 CAG, 225 pts (75,3 %) had stenotically significant CA lesion. Isolated lesion of the left coronary artery (LCA) – in 61 (27,1 %), right coronary artery (RCA) – in 22 (9,8 %), LCA+RCA – in 142 (63,1 %) cases. LCA lesion happened 2,8 times more often than RCA, and multivascular CA lesion – by 71,1 % more often than monovascular. CA lesion in males was by 19,2 % higher than in females, and CA multivascular lesion prevailed – by 62,1 % more often in males than in females. Females had prevailing monovascular CA lesion – by 14,3 % more often than in males. Both males and females had isolated lesion of RCA considerably more seldom than LCA. There is a marked high level of CA lesion in males of all age groups. This difference is levelled by the age of 70 y.o. Analysing dynamics of CA lesion frequency depending on sex and age, it should be noted that they have a sharp rise of their lesion in males since 45 y.o., in females – since 55 y.o. Since 50 y.o. in males and 55 y.o. in females the CA lesion rate remains high and does not change significantly with the age.

Conclusions: In Donetsk region a sharp rise in CA lesion in females is marked too early: since 50 y.o., and in males – since 45 y.o.

At heavy angina pectoris 26 % of those examined did not reveal stenotically significant CA lesion. In males CA lesion is higher than in females with prevailing multivascular lesion.

Females have more often monovascular CA lesion (LCA), a sharp rise in multivascular CA lesion is marked since 60 y.o. Out of risk factors it should be noted that there is a high frequency of combination of CA lesion with arterial hypertension (79,3 %) and smoking (46,4 %).

Keywords: coronary arteries lesion, coronary angiography, coronary heart disease, angina pectoris

Risk factors of CVD and the necessity for population-based prevention in Tomsk

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Tomsk is a typical urbanized city of Western Siberia where solving population health problems is a relevant task. The study was performed as a part of the international investigation titled “Epidemiological study of the causes of the dramatic fall in life expectancy in Russia” in a framework of the project called “Epihealth Russia”. A total of 67,316 persons (37,832 of males and 29,484 of females; compliance rate of 98.9%) aged 30 to 74 years underwent screening in practical medicine. Screening was performed by 45 medical practitioners from 15 health care centers of Tomsk. The study of risk factors showed that the prevalence rates of smoking were as high as 69.1% in men and 20.6% women; every fifth man and half of women were passive smokers; 23.5% of men and 5.1% of women consumed more than 10 cigarettes a day; 55.9% of men and 10.5% of women consumed more than 20 cigarettes a day. The prevalence rates for high blood pressure were 47.6% in males and 40.3% in females; the prevalence rates for overweight were 49.8% and 39.2% in men and women, respectively. Taking into account various degrees of obesity, risk factors associated with excess body weight were found in 60% of men and in 66.9% of women. Obtained data demonstrated the presence of unfavorable risk factor profile and the necessity for an integrative program for CVD prevention at the population level in practical medicine.

Keywords: population, risk factors, cardiovascular diseases

12-year dynamics of blood lipid parameters in ageing population in Russia

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Objective: to analyze age-related dynamics in blood lipid profile in ageing population of Novosibirsk, Russia.

Materials and methods: The study was conducted within the frame of the international epidemiological HAPIEE Project. A random sample of male and female population of Novosibirsk was examined in 2003-2005 (baseline survey of participants aged 45-69 years), 2006-2008 and 2014-2015 (participants were aged 55-79 years); the third ongoing survey is conducted in the frame of RSF supported project. Serum concentrations of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C) were measured by enzymatic methods; concentrations of low density lipoprotein cholesterol (LDL-C) and non-HDL cholesterol were estimated by Friedewald method. The analysis included data on 168 men and 253 women, who had serial lipid measurements at each survey. The average age of participants in the first wave was 56,9±6,8 years, the second – 60,9±6,9 years, on the third – 68,9±7,0 years.

Results: There was a significant decrease in TC concentrations over time; the overall means (in men and women combined) were 6,41 (±0,06); 5,75 (±0,06) and 5,56 (±0,06) mmol/l in the first, second and third survey, respectively ($p < 0,001$). In men, the respective mean concentrations were 6,11 (±0,09), 5,45 (±0,09) and 5,39 (±0,09) mmol/l; in women, the mean values were 6.61 (±0.08), 5,95 (±0,08) and 5.72 (±0,07), respectively (p -values in men and women < 0.05). The gender- and age-related dynamics in the levels of non-HDL and LDL cholesterol were similar. We found no clear age-related dynamics in TG levels. The levels of HDL cholesterol were also decrease.

Conclusion: In this population sample of Novosibirsk residents, the concentrations of atherogenic blood lipid fractions (TC, non-HDL, and LDL cholesterol), as well as of HDL-cholesterol, decreased with age in both sexes.

Keywords: blood lipids, age, population

Metabolic profile of female survivors of Siege of Leningrad

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Objective. The impairment of perinatal nutrition could promote to development of cardiometabolic disorders in the adult life. The aim of our study was to assess special features which contribute longevity in women who survived early life starvation during Second World War (1941-1944).

Design and methods. 222 female survivors of Leningrad Siege and 36 participants of control group were examined. Controls of the same age were born in other regions of the Soviet Union (Russia), but not in Leningrad, and after war were constantly living in Leningrad (St. Petersburg). All participants were interviewed by special questionnaire regarding lifestyle, socioeconomic risk factors, cardiovascular disease, comorbidities and medication. Blood pressure was measured twice on right arm in the sitting position after 5 minute of rest. Anthropometry were performed according to standard procedures. Fasting serum lipids and plasma glucose were measured on Hitachi-902. Informed consent was obtained from all participants.

Results The groups were comparable by age, fasting glucose and blood pressure. In spite of comparable anthropometric characteristics (weight, height, body mass index, waist and hip circumference) females survivors had significantly lower waist/hip ratio compared to the control group (0,85 vs 1,01, $p < 0,05$). Survivors had also significantly lower prevalence of hypertriglyceridemia (40 (17,9%) vs 12 (34,3%), $p < 0,05$) and higher level HDL compared to the survivors (63 (28,5%) vs 16 (45,7%), $p < 0,05$).

Conclusions. Females survivors despite negative remote influence of perinatal starvation are alive might be due to favorable metabolic profile and fat distribution.

Keywords: the Siege of Leningrad, metabolic profile, starvation, cardiometabolic disorders, waist/hip ratio

Lipid ratios and ambulatory blood pressure: implication of HDL-C, expectations, and concerns

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Introduction: Unwittingly, rough contest of lipids for supremacy in atherosclerosis consumes most attention of researchers over the last time, underlining important anti-atherogenic properties of HDL-C which is additionally a favorite alongside all lipids. So, attenuated HDL-C adversely boosts risk of coronary artery disease/myocardial infarction. Moreover, deleterious HDL-C independently aggressively influences on central arterial stiffness. These facts may be eye-catching, but findings arranged on far distance from what we briefly countenanced in our trial, frustrating development of intracranial atherosclerotic stenosis at detrimental HDL-C, link between HDL-C and risk of its appearance have been ensnared by ambiguous circumstances.

Methods: We estimated ambulatory blood pressure (BP) and lipid ratios between HDL-C, LDL-C, TC, TG (EPOGH, n=324).

Results: Our huge worry is that among all testimonies crucial suggestion acceding to HDL-C/LDL-C ratio has great value in assessment of cardiovascular risk, especially when absolute values of individual lipoproteins perceive as normal (Nigeria), is likely to provide resort for allies and foes alike. Intriguingly, embarked proof that level of high-sensitivity C-reactive protein correlated with HDL-C/TC and HDL-C/TG endorsed blizzard of reasonings (CALLISTO). If to glance at chronic kidney disease (CKD) term, careful designation, without dissenting impressions, that study of renal function appraisement in elderly hypertension highlighting ratios suffered from plentiful resources as follows: HDL-C/TC enhanced from 1tertile to 3tertile; GFR(MDRD) increased and uric acid decreased; but 2tertile had highest GFR(CKD-EPI) and lowest serum creatinine. According elicited regards, we supposed that no one even bothered to make a case as to how expressive ratios integrated with BP in comparative appreciation, therefore in partial analysis with gender inclusion we scrutinized association of HDL-C/TC with 24-h SBP (r=-0.404), 24-h DBP (r=-0.390), day SBP (r=-0.380), day DBP (r=-0.337), night SBP (r=-0.352), night DBP (r=-0.360); HDL-C/TG with 24-h SBP (r=-0.345), 24-h DBP (r=-0.310), day SBP (r=-0.320), day DBP (r=-0.262), night SBP (r=-0.324), night DBP (r=-0.307); HDL-C/LDL-C with 24-h SBP (r=-0.367), 24-h DBP (r=-0.360), day SBP (r=-0.350), day DBP (r=-0.314), night SBP (r=-0.308), night DBP (r=-0.321), P<0.001 for all, however it is not high-rise enough to be truly desolate concerning cardiovascular disease events. It was daring to share willingness to affirm plausibility of theoretically substantiated solution towards gender disparities in heart disease risk with exhilarating questions of postmenopausal period and to draw depletion of HDL-C/TC and HDL-C/LDL-C in women with syndrome. What was most exciting was the utility to which predictive role of HDL-C/TC aspires in set of factors for metabolic syndrome; for instance, amidst Ghanaian postmenopausal women the anticipation of TG/HDL-C, HDL-C/TC was squeezed out from facts in possible respectability. It put out costing effect for atherosclerosis and hurtful complications not lagging behind that vehement opposition of low HDL-C adversely toughens endothelial dysfunction/oxidative stress. From magic point, in cohort study smokers before training provided exceedingly irritating lipid profile in comparison with non-smokers (HDL-C, TG, HDL-C/TG, TC/HDL-C).

Conclusions: Eventually, serious stepped-up rhetoric from amicably profitable proposals will be yet judged in further discussions – and in years ahead – as much on the way we conducted our decisions as on the inferences we reached.

Keywords: blood pressure, lipid ratios, cardiovascular disease

Left ventricular diastolic dysfunction, the traditional risk factors in women with systemic lupus erythematosus

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Objectives. To determine the frequency of left ventricular diastolic dysfunction (LVDD) in women with systemic lupus erythematosus (SLE) in prospective 10-years supervision, to study its association with the disease activity, the inflammatory markers, and the traditional risk factors.

Methods. The study included 40 female patients with a confirmed diagnosis of SLE. The assessment of the SLE (SLEDAI 2K) activity, the damage index (SLICC DI), the cardiovascular risk factors (RF) and echocardiography were performed in all patients at the time of their inclusion into the study and after 10 years of supervision. The diastolic function of the left ventricular was assessed in compliance with the recommendations of the Russian Society of Cardiology.

Results. At the moment of inclusion into the study the average age of the patients was 33 ± 10 , the disease duration was 7 ± 3.5 years, the disease activity SLEDAI 2K was 9 ± 7 grades, the damage index SLICC DI was 1.5 ± 1 grades, the average glucocorticoids dose (GC) was 16 ± 12 mg per day. In 10 years, the average age of the patients was 43 ± 10 , the disease duration was 17.5 ± 4.8 years, the disease activity was 2 ± 1.5 grades, the damage index was 4 ± 1.9 grades, the average GC dose was 6 ± 2 mg per day. The patients with SLE in the initial point had higher indices of the disease activity, the average GC doses, and concentration of C-reactive protein ($p<0.05$). The duration of the disease, the duration of GC therapy, and the damage index were significantly higher in 10 years ($p<0.05$). At the time of inclusion into the study, 76% of the patients had at least one RF. 14% of the patients did not have any of the RF. The frequency of the RF at the beginning of supervision was as follows: arterial hypertension (24%), dyslipidemia (24%), diabetes mellitus (5%), overweight (25%), hypodynamia (25%), smoking (22%), aggravated family history in respect of cardiovascular diseases (39%). In 10 years of supervision, in 97% of the patients at least one of the RF was detected, most frequently that of arterial hypertension (42%), and 45% had a combination of the RF. Over the 10-year disease period, there was revealed a 20% increase of the frequency of arterial hypertension and dyslipidemia (44vs24%) ($p<0.05$), a 6% increase in the number of patients with overweight and hypodynamia (31vs25%), a 3% increase in the number of smokers (25vs22%). Differences in frequency of detection was not revealed LVDD (22.5 vs25%) ($p>0.05$). Among the LVDD patients type I prevailed. At the time of the study there was traced a correlation between LVDD and high disease activity ($r=+0.207$), high levels of C-reactive protein ($r=+0.203$), dyslipidemia ($r=+0.19$), and administration of high doses of GC ($r=+0.201$). In 10 years of supervision, the development of LVDD correlated with the development of arterial hypertension ($r=+0.19$), high damage index ($r=+0.19$), and concomitant ischemic heart disease ($r=+0.3$).

Conclusions. LVDD is a significant predictor of chronic heart failure and can have long-term subclinical duration. The predictors of the development of the LVDD are the traditional risk factors, as well as autoimmune inflammation, which is the basis of SLE.

Keywords: left ventricular diastolic dysfunction, cardiovascular risk factors, systemic lupus erythematosus

Concordance of Glucose Based and of HbA1c Based Diagnoses of Diabetes in Patients with Established Coronary Atherosclerosis: A Comparison Between Men and Women

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Concordance between glucose based and HbA1c based diagnoses of diabetes differ between populations. Here, we aimed at investigating their concordance in men and in women with stable coronary artery disease (CAD).

We measured fasting glucose as well as HbA1c and performed standard 75g oral glucose tolerance tests in a consecutive series of 711 patients, 513 men and 198 women, who had angiographically proven coronary artery disease (CAD) but not previously diagnosed diabetes. Based on glucose values, diabetes was diagnosed with a fasting plasma glucose (FPG) ≥ 126 mg/dl or a postchallenge glucose ≥ 200 mg/dl 2 hours after the oral glucose load; based on HbA1c values diabetes was diagnosed with an HbA1c $\geq 6.5\%$.

Among men, 33 had diabetes based on fasting or postchallenge glucose values, of whom 26 also had diabetes according to the HbA1c criterion. Of the 480 men who did not have diabetes based on glucose values, 446 also did not have diabetes according to HbA1c criteria; among women, 3 had diabetes based on glucose values, of whom 2 also had diabetes according to the HbA1c criterion. Of the 195 women who did not have diabetes based on glucose values, 185 also did not have diabetes according to HbA1c criteria. Concordance of Glucose and HbA1c criteria was similar in men and women (92% and 94%; $p=0.335$). Applying glucose criteria as a standard, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the HbA1c criterion for men were 78.8%, 92.9%, 43.3%, and 98.5%, respectively. For women, sensitivity, specificity, PPV and NPV of the HbA1c criterion were 66.7%, 94.9%, 16.7%, and 99.5%, respectively.

We conclude that concordance of glucose and HbA1c criteria among patients with stable CAD is high and is similar in men and women with CAD. However, for both sexes the sensitivity of the HbA1c criterion is poor in this patient Population.

Keywords: gender, coronary artery disease, methodology, diabetes diagnosis

Prevalence of hidden diabetes in our population with risk factors by ambulatory glycated hemoglobin determination

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Introduction: It's known the interest in detecting hidden diabetes, therefore early intervention is a great trick to avoid complications. In this way, Interventions have been proposed both in overall general population and in population with risk factors or with glucose determination and with oral glucose overload. Recently the determination of glycated hemoglobin (A1c) has been also used. The ADA established a few years ago a diagnosis ranges: A1c to 5.6% non-diabetic population, A1c from 5.7% to 6.4% pre-diabetes and with A1c > 6.5% diabetes, as well as a few risk factors for the development of diabetes mellitus that we have taken into account in this work.

Objectives: To detect the prevalence of hidden diabetes in our population with risk factors, by ambulatory A1c determination.

Methods: A study was conducted on a semi-urban health center of our health area that serves a small population, close to 5,500 people, by capturing and opportunistically A1c determination with an automatic analyzer terminal (Siemens DCA Vantage.) for the period of two months, with the following criteria: BMI > 30 and at least one other risk factor or a BMI between 25 and 30 and at least two risk factors, which are: gestational diabetes, polycystic ovary syndrome, hypertension, HDL < 35 and / or hypertriglyceridemia, A1c between 5.7-6.4% or carbohydrate intolerance in pre-test and first-degree relatives with type 2 diabetes mellitus.

Results: 41 subjects were captured, of which 4 (9.75%) had an A1c > 6.4% and 23 (56.09%) had values between 5.7 and 6.4%.

Conclusions: Patients with risk factors in our population, showed, by determining A1c, a prevalence of hidden diabetes close to 10% and an outstanding pre-diabetes prevalence higher than 50%.

Familial hypercholesterolemia

Mutational analysis of PCSK9 gene in a group of patients with familial hypercholesterolemia – the Polish National Centre of Diagnostics and Treatment of Familial Hypercholesterolemia report

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Aim: To date, mutational analysis of LDLR and APOB genes was performed in 1427 probands with familial hypercholesterolemia (FH) and their family members registered at the Polish National Centre of Diagnostics and Treatment of Familial Hypercholesterolemia. LDLR or APOB pathogenic alterations were not found in 889 individuals. Within this group, PCSK9 molecular analysis was performed in 453 probands.

Methods: All probands were clinically diagnosed with FH according to a Dutch Lipid Clinic Network criteria. Genomic DNA was extracted from peripheral blood. Mutational analysis of LDLR, APOB and PCSK9 was performed by Sanger sequencing and MLPA technique or ADH MASTR v2 assay followed by MiSeq targeted re-sequencing. The presence of the LDLR or APOB mutation was confirmed by independent PCR followed by Sanger sequencing or MLPA reaction.

Results: In a studied group of 453 probands, 99 (21.8%) PCSK9-InsLEU carriers were found. 95 patients were heterozygotes and 3 were homozygotes for p.L22dup. In one individual heterozygous p.L21_L22dup was detected. In addition, the following heterozygous PCSK9 variants were found: LRG_275t1:c.-309C>T, p.T3T, p.R46L, p.R96C, p.R237Q, c.1181-115T>A, c.1681+65C>T and c.*39G>A. In contrast to p.R46L substitution which was detected in four probands, other PCSK9 alterations were identified in a single patients. To our knowledge, LRG_275t1:c.-309C>T, p.T3T, p.R237Q, c.1181-115T>A, c.1681+65C>T and c.*39G>A variants were not previously described. Four variants (LRG_275t1:c.-309C>T, p.R96C, p.R237Q and c.*39G>A) were assumed as probably pathogenic.

Conclusion: As expected, PCSK9 alterations are relatively rare in a population of Polish individuals with familial hypercholesterolemia and accounts for approximately 0.9% of patients. However, molecular analysis of the entire coding sequence of LDLR and PCSK9 and fragment of exon 26 of APOB should be performed in Polish patients with familial hypercholesterolemia. Additional studies are required to confirm the pathogenic nature of detected PCSK9 genetic variants.

Disclosures: No relevant conflicts of interest to declare.

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Keywords: familial hypercholesterolemia, PCSK9, mutational analysis

Targeted next-generation sequencing of the APOB gene in patients with familial hypercholesterolemia

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Aim: Mutations in the apolipoprotein B (APOB) gene cause inherited hypercholesterolemia. The aim of this study was identification of a spectrum of SNVs in the APOB gene in Russian patients with familial hypercholesterolemia (FH).

Methods: A total of 12 Caucasian patients with a clinical diagnosis and family history of FH were screened for the APOB gene. Next generation sequencing was performed using the NimbleGen, Roche technology and NimbleGen Sequence Capture arrays (exons, introns, and flanking splicing regions of the gene) in all patients.

Results: Among 12 patients, we identified SNPs rs693 (T2515T), rs568413 (Y1422C), rs584542 (I2313V), rs1041968 (D2312D), rs1042031 (E4181K), rs1042034 (S4338N), rs1367117 (T98I), rs1799812 (L3377L), rs1801700 (N902N), rs1801701 (R3638Q), and rs1801703 (V4128M) with benign prediction and effect. Four SNVs are predicted to damage the structure of the APOB100 polypeptide by PolyPhen-2 rs679899 (A618V) (score of 1.000) and rs676210 (P2739L) (score of 1.000), rs12713844 (D1113H) (score of 0.960), and rs1801699 (N1914S) (score of 0.873).

Conclusions: We found no novel nucleotide substitutions in the APOB gene exons in our patients. The SNVs predicted to be damaging should be considered for further studies in order to verify the involvement of these variants in the FH.

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Keywords: familial hypercholesterolemia, APOB gene, polymorphism, gene

Lipid profile influence on epicardial fat thickness in familial hypercholesterolemia patients

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Disturbance of lipid profile is one of the main risk factors of cardiovascular diseases in familial hypercholesterolemia (FH). Other risk markers are discussed in literature. In some groups of patients the association between epicardial fat thickness (EFT) and the frequency of fatal and non-fatal cardiovascular events was revealed. EFT may be earlier predictor of cardiovascular disease. Epicardial fat (EF), or epicardial adipose tissue, is a visceral fat deposit around the heart.

Aim: to evaluate the influence of dislipidaemia on EFT in patients with FH.

Materials and methods: 88 patients were examined, 37 male, average age $37,8 \pm 1,3$, they were subdivided into two groups: 1) 47 normotensive FH patients (according to the Dutch Lipid Clinic Network criteria) without ischemic heart disease and without lipid-lowering therapy, average age $41,95 \pm 1,43$ years, 2) 41 normotensive patients with normal lipid profile, average age $41,95 \pm 1,43$. We performed for all patients lipid profile and calculated atherogenic ratio (AR) by formula $AR = TC - HDL / HDL$, where is TC – total cholesterol, HDL – high density lipoproteins. EFT was assessed by echocardiography. We considered normal body mass index (BMI) from 20 to $24,9 \text{ kg/m}^2$. Statistic was performed by «Biostat» and lineal regression analyze.

Results: In patients with FH the TC level and low density lipid (LDL) level were more higher than in second group ($8,72 \pm 0,17 \text{ mmol/l}$ and $6,04 \pm 0,15 \text{ mmol/l}$ comparable with $4,57 \pm 0,09 \text{ mmol/l}$ and $2,64 \pm 0,10 \text{ mmol/l}$), $p < 0,05$. The triglyceride (TG) level in first group was $1,78 \pm 0,13 \text{ mmol/l}$ and $1,15 \pm 0,10$ in the second ($p < 0,05$). The HDL level was the same in both groups. Regardless of BMI in FH patients EFT was higher ($4,4 \pm 0,24 \text{ mm}$) than in patients with normal lipid spectrum ($3,7 \pm 0,23 \text{ mm}$), $p = 0,03$. In people with excessive BMI EFT was higher in FH patients, than in individuals from the control group ($4,6 \pm 0,22 \text{ mm}$ and $3,69 \pm 0,27 \text{ mm}$ respectively, $p = 0,009$). The maximum difference between FH patients and persons with normal lipid profile was in women, accounting for respectively $4,31 \pm 0,22 \text{ mm}$ and $3,52 \pm 0,19 \text{ mm}$ ($p = 0,004$). We also estimate strength of influence of lipid factors to EFT by lineal regression analyze. EFT (in patients with normal lipid profile): $= 4,5 + 0,79 * TC + 0,87 * HDL - 0,80 * AR$. EFT (in patients with FH): $= 5,92 + 0,46 * TC + 1,86 * HDL - 0,95 * AR$

In patients with FH decrease the role of TC in EFT comparable with patients with normal lipid profile (correlation parameters is 0,46 and 0,79 accordingly) but increase the role of HDL (correlation parameters is 1,86 and 0,87 accordingly), it shows that degree of HDL influence in EFT in FH stronger in several fold than in patients with normal lipid spectrum). In both groups the role of correlation LDL and HDL (AR) was important.

Conclusions: In FH patients we had revealed a significantly higher EFT level, regardless of the presence of overweight ($4,4 \pm 0,24 \text{ mm}$ and $3,7 \pm 0,23 \text{ mm}$ comparable, $p = 0,03$). In patients with FH decreased the role of TC in EFT, but increased the role of HDL, comparable with patients with normal lipid profile.

Keywords: Familial hypercholesterolemia, Epicardial fat, dyslipidemia, atherosclerosis

Problem Statement and Perspectives in Early Identification of Patients with Familial Hypercholesterolemia in the Kyrgyz Republic

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According to the State Medical Information Center of Kyrgyzstan (2014 year) cardiovascular diseases (CVD) occupy the first place in the structure of total mortality (50.8%) in the Kyrgyz Republic, while in European countries this index is about 45%. Coronary heart disease (CHD) (63.9%) and cerebrovascular diseases (26.9%) contribute to the main cause of mortality (60%) from CVD. Attention is drawn to the fact that Kyrgyzstan has a considerable number of deaths from heart diseases in the working age population (32.0%). High rates of CVD morbidity and mortality in Kyrgyzstan are partly due to the underestimation of the importance of familial hypercholesterolemia (FH) including by possibly higher prevalence of FH which requires need to develop National Programs on early diagnosis and treatment of patients with FH.

Aim: To assess the prevalence of FH and implement FH diagnostic algorithms, assess and optimize treatment of FH patients in the Kyrgyz Republic.

The registration card of FH patients will be developed on **the first stage of the program**. Further training of doctors on the issue of FH and patients awareness will be carried out with the help of educational materials. Health professionals involved in the treatment of FH patients will be accredited in the field of CVD prevention. **On the second stage of the program** the database will be formed from a random sample of adult population of Bishkek and Chui region centers of family medicine, city clinical hospitals No. 1, No. 6, Railway clinical hospital, with total cholesterol (TC) levels $\geq 7,5$ mmol/l and/or low density lipoprotein (LDL-C) $\geq 4,9$ mmol/l, particularly with a history of premature CHD, stroke, clinically significant peripheral atherosclerosis. Random test results of patients with TC $\geq 7,5$ mmol/l and/or LDL-C $\geq 4,9$ mmol/L will be analyzed from biochemical laboratory of the National Center of Cardiology and Internal Medicine (NCCIM) and private laboratories (“Bonetskiy”, “Yurfa”, “Human”). Potential participants for the study will be invited by phone or e-mail. Potential participants for the study will be invited by phone or e-mail. Those who have given prior consent to the monitoring and examination will be invited to the NCCIM. Because many family medicine centers and city hospitals determine only TC level in order to confirm the presence of high levels LDL-C all patients will be defined lipid profile. All participants voluntarily will sign informed consent. All patients' data (contact information, risk factors, CVD, therapy, particularly details of the lipid-lowering therapy) will be registered into cards.

Clinical diagnosis of FH will be verified using Dutch and/or British criteria. After verification the FH diagnosis family members will be tested by cascade screening. All FH patients will be prescribed treatment, side effects and adherence to the treatment will be monitored. Subsequent outpatient observation of all patients will be monitored.

The third stage involves a preliminary statistical data analysis; monitoring of cardiovascular events in FH patients after 1, 3, 5 and 10 years. Assessment of therapy effectiveness: surrogate endpoints – reduction of LDL-C to the target level, or to 50% from baseline. Soft endpoints – the time before the first cardiovascular events, nonfatal myocardial infarction, and stroke. Hard endpoints – total mortality, cardiovascular mortality, fatal myocardial infarction or stroke.

The fourth stage – implementation of approaches to screening, diagnosis and treatment of patients with FH in the Kyrgyz Republic, optimization of treatment with the inclusion of FH patients to the preferential category of patients for drug supply in the Program of the state guarantees, as well as development of LDL apheresis centers for drug-resistant patients.

Conclusion: Based on the diagnostic approaches to the early detection of FH in Kyrgyz population recommendations on using the most optimal diagnostic algorithm and treatment of FH will be created.

The First Experience in Monitoring Patients with Familial Hypercholesterolemia in the Kyrgyz Republic

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According to the State Medical Information Center of Kyrgyzstan (2014 year) cardiovascular diseases (CVD) occupy the first place in the structure of total mortality (50.8%) in the Kyrgyz Republic, while in European countries this index is about 45%. Coronary heart disease (CHD) (63.9%) and cerebrovascular diseases (26.9%) contribute to the main cause of mortality (60%) from CVD. Attention is drawn to the fact that Kyrgyzstan has a considerable number of deaths from heart diseases in the working age population (32.0%). Thus, there is a reason to believe that the high rates of CVD morbidity and mortality in Kyrgyzstan are partly due to the lack of understanding familial hypercholesterolemia (FH) consequences and high prevalence of FH.

Material and methods: There are 17 FH probands having 18 children included in the study (total number of examined – 35 people). Mean age of male probands is 46.3 ± 5.6 years, female probands 60.3 ± 8.5 years. Mean age of sons with FH is 28.6 ± 13.8 years, daughters is 35.3 ± 14.2 years. According to the Dutch diagnostic criteria (without DNA analysis) 7 patients (41.2%) (4 male and 3 female) have a definite diagnosis (>8 points) and 10 male probands (58.8%) have probable diagnosis (6-8 points) of heterozygous FH from 17 probands. 16 probands (94.1%) have premature CHD. All patients with FH take lipid-lowering therapy.

Results: There are 10 descendants (55.5%) inherited FH (4 boys and 6 girls) and 8 healthy descendants (44.5%) (4 boys and 4 girls) from total 18 descendants of the probands. There are no significant differences in the level of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) among male and female probands (TC 8.6 ± 1.6 mmol/l vs. 9.2 ± 0.2 mmol/l; LDL-C 6.4 ± 1.1 mmol/l vs. 7.3 ± 0.1 mmol/l), but significant differences in high density lipoprotein cholesterol (HDL-C), triglycerides (TG) (HDL-C 0.9 ± 0.2 mmol/l vs. 1.4 ± 0.1 mmol/l, $p < 0.01$; TG 2.6 ± 0.9 mmol/l vs. 0.9 ± 0.4 mmol/l, $p < 0.001$), and atherogenic index of plasma (AIP) (0.461 vs. -0.192 , $p < 0.005$). A comparison of lipid parameters in fathers probands and their sons with FH revealed significant differences for TG (2.6 ± 0.9 mmol/l vs. 1.3 ± 0.3 , $p < 0.01$), AIP (0.461 vs. -0.110 , $p < 0.01$) and HDL-C (0.9 ± 0.1 mmol/l vs. 1.7 ± 0.3 , $p < 0.001$). There are no statistically differences in lipid profile in mothers probands and their daughters with FH (TC 9.3 ± 0.2 mmol/l vs. 9.1 ± 1.5 mmol/l, LDL-C 7.3 ± 0.1 mmol/l vs. 7.1 ± 1.4 mmol/l). Significant differences in lipid profile have not been identified comparing sons and daughters of the probands with FH (TC 8.6 ± 1.3 mmol/l vs. 9.1 ± 1.5 mmol/l, LDL-C 6.3 ± 1.2 mmol/l vs. 7.1 ± 1.5 mmol/l).

Conclusion: Thus, FH is highly heritable disease. The most unfavorable indices of lipid profile observed in the group of male probands. Children probands have no significant differences by gender in the lipid spectrum.

FH homozygote without cardiovascular disease at the age of 40

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Objective: Familial hypercholesterolemia (FH) is an autosomal disease of lipid metabolism, caused mostly by the mutations within the LDL receptor. Recently, the prevalence of this disorder has been estimated to be even 1:200.

Methods: 135 Czech Caucasian hypercholesterolemic patients were screened by PCR-RFLP for the most common LDL receptor mutation c.1775G>A (Gly592Glu). In the case of the restriction site presence, this result was confirmed by direct sequencing of exon 12.

Results: Female patient (born in 1973) was detected to be homozygous for c.1775G>A mutation within the LDL-receptor gene. Her plasma lipid levels in 2004 were – TC 10.4, LDL-C 8.3, HDL-C 1.8 and TG 0.6, all in mmol/l. The on treatment lipid levels have been as follows: TC 4.45±0.7 and LDL-c 2.7±0.6 mmol/l. She carried apoE3/3 genotype. The carotid intima-media thickness (cIMT) measurement in 2007 showed no plaque with cIMT of 0.77mm. The patient is free of symptomatic cardiovascular or cerebrovascular disease.

Conclusions: We have detected an FH homozygote with well controlled dyslipidemia and no overt CVD at the age of 40. This case contradicts general belief the homozygous FH patients respond poorly to lipid lowering therapy. It documents *LDLR* mutation itself does not cause accelerated atherosclerosis when plasma LDL cholesterol levels can be controlled. Thus, it is a prove of the need of early detection and treatment of FH patients.

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Keywords: Familial hypercholesterolemia, homozygote, LDL receptor, cholesterol

Frequency of familial hypercholesterolaemia among adults with severe hypercholesterolaemia

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Familial hypercholesterolaemia (FH) is a genetic disorder leading to decreased cellular uptake of LDL and increased plasma LDL cholesterol concentrations. Lifelong elevated plasma LDL cholesterol levels in these patients lead to premature coronary heart disease (CHD). Recently, direct screening in a Northern European general population diagnosed approximately 1/200 with heterozygous FH. According to the Consensus Statement of the European Atherosclerosis Society (2013), FH is underdiagnosed and undertreated.

The aim of the study was to detect the frequency of FH among adults with severe hypercholesterolaemia.

Methods. 106 patients with severe primary hypercholesterolemia (LDL cholesterol level above 4,9 mmol/l) of age between 18 and 76 years were involved into survey. Familial history and clinical history, including information about CHD risk factors, were obtained and physical examination was conducted. Biochemical results of LDL levels were analyzed in all patients. Screening of FH was performed using the Dutch Lipid Clinic Network criteria.

Results. In 55 patients definite FH were diagnosed. All patients had very high basal LDL cholesterol levels (from 6,05 to 12,9 mmol/l), that was significantly higher than in patients with probable, possible or unlikely FH. Clinical history of premature CHD was detected in 25 patients with definite FH under the age of 50 years and in 20 other patients. Physical examination revealed tendon xanthomas in 52 patients with definite FH. In one patient the corneal arcus was also identified.

Conclusion. The frequency of FH among adults with severe hypercholesterolaemia is more than 50 percent. The most important criterion to reveal FH in this category of patients is the presence of tendon xanthomas.

Keywords: familial hypercholesterolemia, tendon xanthomas

Genetics

Polymorphism Arg389Gly gene ADRB1 in patients with chronic heart failure of Uzbek nationality

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Purpose: To study the features of polymorphism Arg389Gly gene ADRB1 in patients with chronic heart failure (CHF) of Uzbek nationality.

Material and methods: In patients with CHF 154 Uzbeks have been studied the genetic determinants of alleles and genotypes Arg389Gly gene ADRB1. The control group consisted of 150 healthy individuals – men of Uzbek nationality. Study polymorphism Arg389Gly gene ADRB1 was conducted using polymerase chain reaction.

Results: Analysis of the distribution of genotypes Arg389Gly gene ADRB1 in patients with CHF showed: Arg/ Arg – was 62.3%; Arg/ Glu – 33.1 %, Glu/Glu – was 4.5%. In the group of healthy individuals Arg/ Arg genotype occurred in 47.3%, Arg/ Glu at 52%. Patients in the control group allele Arg was –73.3%, and allele Glu – 26.7%. Patients with CHF frequency in Arg allele –was distributed as follows: 78.9% and Glu – 21.1%.

Conclusion: In patients with CHF of Uzbek nationality dominated Arg/ Arg polymorphism gene ADRB1.

Keywords: chronic heart failure, Polymorphism, gene ADRB1

The role of composite of platelet receptors genes and cytochrome P450 genes polymorphisms in developing of adverse cardiovascular events in patients with atherosclerosis and coronary heart disease

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Background: The identification of cardiovascular events (CVE) predictors in patients with evidence of atherosclerosis remains up-to-date.

Purpose: To investigate the association of single nucleotide polymorphisms (SNPs): rs2046934, rs1126643, rs5918, rs6065, rs4244285; rs4986893 with CVE in patients with atherosclerosis.

Methods: 130 patients with stable angina grades II-IV who underwent coronary artery bypass grafting were enrolled. At baseline total cholesterol level was equal 5.02 ± 1.5 mmol/l; low density lipoproteins – 3.43 ± 1.5 mmol/l. All patients were on statin and antiplatelet therapy. After CABG 69 patients were receiving ASA (100 mg of enteric form), 61 patients were receiving dual antiplatelet therapy (enteric form ASA 100 mg + clopidogrel 75 mg). Mean follow up period was equal $10,9 \pm 5,2$ months. The primary end point included the composite of all-cause mortality, myocardial infarction (MI), ischemic stroke. The control group included 185 healthy volunteers. Platelet function was evaluated using light transmission aggregometry (Chronolog 490, USA) with ADP ($5 \mu\text{M}$) and arachidonic acid (1 mM). The following single nucleotide polymorphisms (SNPs) were identified by real-time PCR or PCI with electrophoretic detection: rs2046934 (H1/H2) on P2RY12 [encoding platelet ADP receptor] (n=100); rs1126643 (C807T, Phe224Phe) on ITGA2 [encoding collagen receptor] (n=87); rs5918 (176 T→C, Leu33Pro) on ITGB3 [encoding fibrinogen receptor] (n=91); rs6065 (Thr145Met) on GP1BA [encoding platelet receptor for Von Willebrand factor] (n=114); rs4244285 (*2) (n=84) and rs4986893 (*3) (n=83) on CYP2C19 [encoding cytochrome P450 activity].

Results: The prevalence of SNPs: rs5918, rs6065, rs4244285, rs4986893, rs2046934 did not differ significantly between patients and healthy volunteers. The mutant allele (T) of ITGA2 was detected more often in healthy volunteers: 67,2% vs 51,7% ($p=0,021$). Before and after CABG there was no significant difference in the platelet aggregation between carries of the mutant ITGA2 allele and non-carries. During follow-up period 12 CVE were registered: 3 strokes, 6 MI, 3 deaths. Patients with composite mutant alleles of ITGB3+CYP2C19*2 or CYP2C19*2+ITGA2, and with the mutant allele (*2) of CYP2C19 met end points more often than patients with other gene combinations (wild type homozygotes, presence of one mutant allele of ITGB3 or ITGA2, the composite of mutant alleles of ITGB3+ITGA2 or ITGB3+ITGA2+ CYP2C19*2) (HR=4, 95% CI: 2,19-7,29, $p=0,008$). Carriers of ITGB3 mutant allele showed higher AA-induced platelet reactivity values on the 1st-3rd day after CABG (27,5% in mutant allele carriers vs 12,7% in wild type carriers, $p=0,016$). No differences in platelet activity between carriers and non-carriers of other listed mutant alleles were observed.

Conclusion(s): Carriage of the combination of mutant alleles ITGB3+CYP2C19*2, CYP2C19*2+ITGA2 and CYP2C19*2 is the possible predictor of CVE in patients with atherosclerosis and coronary heart disease

Keywords: atherothrombosis, predictors, single nucleotide polymorphisms, cardiovascular events

HDL prevent apoptosis of human primary macrophages and THP-1 macrophages through stimulation of FOXO1 phosphorylation

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Background: Atherothrombotic vascular diseases are the leading causes of death in the industrialized world. Macrophage apoptosis is a major contributor to the instability of atherosclerotic lesions. Tumor necrosis factor (TNF)- α , released by the macrophages results in cell death of lesion-resident cells. Antiatherogenic effects of plasma high-density lipoproteins (HDL) include the ability to inhibit apoptosis of macrophage foam cells via stimulation of PI3K/AKT signaling pathway. In the present study, we investigated the role of HDL in protecting macrophages from apoptosis induced by TNF-alpha. Also, we investigated the ability of HDL to activate AKT and to cause phosphorylation transcriptional factor FOXO1 and participation of protein kinase A (PKA) and soluble adenylyl cyclase in this process.

Methods: HDL were isolated from human plasma of healthy donors. Peripheral blood mononuclear cells (PBMC) were isolated by standard Ficoll gradient centrifugation from citrate-treated blood of healthy donors. THP-1 macrophages were a generous gift from Immunology Department of Institute of Experimental Medicine. Primary macrophages were analyzed for phosphatidylserine exposure by an annexin-V FITC/7AAD double-staining method using flow cytometry. THP-1 macrophages cytoplasmic and nuclear lysates were examined by Western blotting for FOXO1 protein. Selective inhibitors of PI3K (LY294002), PKA (H89) and soluble adenylyl cyclase (KH7) were used. Primary macrophages were examined by confocal microscopy for FOXO1 cytoplasmic and nuclear localization.

Results: We showed that TNF-alpha caused apoptosis of macrophages after 24 hours of incubation. Reduction of FOXO1 in macrophage cytoplasm had occurred already after 40 minutes of incubation with TNF alpha. We further showed that HDL (100 and 200 $\mu\text{g/ml}$) protected macrophages from TNF-alpha induced apoptosis after 24h combined incubation ($p=0,05$) and led to accumulation of FOXO1 in cell cytoplasm after short period of time.

Inhibition of PI3K/AKT signal pathway, PKA and soluble adenylyl cyclase decreased cytoplasmic FOXO1 ($p=0,03$, $p=0,05$, $p=0,08$, correspondingly) and increase FOXO1 with nuclear localization ($p=0,04$, $p=0,04$, $p=0,04$, correspondingly) in THP-1 and primary macrophages after combined incubation with TNF-alpha and HDL.

Conclusion: HDL prevented apoptosis of human primary and THP-1 macrophages induced by TNF-alpha through phosphorylation of FOXO1 by mechanisms involving PI3K/AKT, PKA and soluble adenylyl cyclase.

Keywords: HDL, TNF-alpha, PI3K/AKT, FOXO, macrophage

Quercetin Counteracts Hypoxia-Mediated Modulation of Gene Expression in SGBS Adipocytes

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Adipose tissue of obese subjects is characterized by a hypoxic environment which affects gene expression and appears to play a central role in the development of type 2 diabetes. The phytochemical quercetin like hypoxia acts at the mitochondrial membrane. We therefore aimed at investigating quercetin-triggered effects on hypoxic adipocytes.

To elucidate the impact of hypoxia on adipose tissue, we used mature adipocytes derived from a Simpson-Golabi-Behmel syndrome patient and applied microarray analysis and advanced computational methods for data analysis.

We found a striking association between the genome-wide gene expression pattern of hypoxia-treated adipocytes and diabetes-related biomarkers. Specifically we could demonstrate that hypoxic cultivation significantly increases transcription of genes involved in energy metabolism (Enolase, PFKP, and PFKFB4) and the development of diabetes (Adipsin, ANGPTL4, and PAI). However, supplementation with quercetin significantly decreased gene expression of these genes despite the hypoxic environment.

We conclude that quercetin is a natural opponent of the deleterious effects on gene expression induced by obesity and mediated by hypoxia.

Keywords: quercetin, adipose tissue, gene expression, hypoxia

Association TRPA1, TRPV1 genes with myocardial infarction in Siberia Caucasians

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The purpose: to investigate the association of single nucleotide polymorphisms in thermoreceptors genes, namely rs222747 of TRPV1 gene and rs13268757 of TRPA1 gene, with myocardial infarction in the Siberian Caucasian population, living in continental climate.

Materials and Methods: The study included two groups: 200 people (129 men, 71 women) with myocardial infarction (MI) and population control (420 people, comparable in sex and age with MI patients), representing subsample of population cohort examined in frame of international project HAPIEE (Health, Alcohol and Psychosocial factors In Eastern Europe). Genomic DNA was isolated from venous blood by phenol-chloroform extraction. Gene polymorphism was tested by real-time PCR using commercial kits according to the protocol of the manufacturer (probes TaqMan, Applied Biosystems, USA) on the instrument StepOnePlus. Statistical analysis was performed using SPSS 11.5 software. At first we determined the frequency of genotypes and alleles of SNPs in the studied group of patients with myocardial infarction and control group. Further, in both groups we evaluated the compliance of genotype frequencies with Hardy-Weinberg equilibrium. Odds ratio(OR) for a particular genotype is calculated as the ratio of chances. We used Fisher's exact two-way test for four-cell tables for comparison of samples by genotype frequencies.

Summary of the results: rs222747 genotypes frequencies were in Hardy-Weinberg equilibrium in both studied groups. No statistically significant association with myocardial infarction was found for this SNP. In case of rs13268757 Hardy-Weinberg equilibrium was observed only in the control group ($\chi^2 = 5.05$ for the group of myocardial infarction). The rs13268757 genotype AA frequency was significantly higher in MI patients than in control group – OR = 2.621 (95% CI 1,112-6,175), $p = 0,034$.

Conclusions: rs13268757 of TRPA1 gene is associated with myocardial infarction implicating potential involvement of thermosensing pathways in predisposition to atherosclerotic cardiovascular diseases.

Keywords: TRPA1, TRPV1, myocardial infarction, rs13268757, rs222747

Genetic markers of cardiovascular disease determined by seven SNPs identified in genome-wide association studies in Arctic Circle (Yakutia study)

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We studied the association of seven SNPs identified in GWAS with metabolic syndrome (MetS), arterial hypertension (AH), coronary atherosclerosis (CA) and myocardial infarction (MI) in Yakutian population depending on ethnicity and gender. The study population was composed of 456 patients with coronary heart disease (396 men, 60 women) and 483 controls (212 men, 271 women). The following 7 SNPs were studied: rs619203 (ROS1 gene), rs10757278 and rs1333049 (9p21.3), rs1376251 (TAS2R50 gene), rs2549513 (16q23.1), rs4804611 (ZNF627 gene) and rs17465637 (MIAF3 gene). For the first time in Yakutian population the following associations of SNPs are received: with MetS – in native: rs2549513 (in both gender $p=0.016$), rs4804611 (in both gender $p=0.009$, in men $p=0.034$), rs17465637 (in both gender $p=0.008$, in men $p=0.029$), and in non-native: rs619203 (in both gender $p=0.000$, in men $p=0.016$, in women $p=0.005$). With AH – in native: rs1376251 (in both gender $p=0.023$, in men $p=0.004$), rs2549513 (in women $p=0.028$), rs4804611 (in women $p=0.033$), and in non native: rs619203 (in both gender $p=0.033$, in women $p=0.002$). With CA – in native: rs1376251 (in both gender $p=0.007$, in men $p=0.006$), rs2549513 (in both gender $p=0.027$), rs17465637 (in women $p=0.040$), and in non native: rs619203 (in both gender $p=0.000$, in men $p=0.020$, in women $p=0.012$), rs2549513 (in both gender $p=0.006$, in women $p=0.024$), rs4804611 (in both gender $p=0.002$, in women $p=0.008$), rs10757278 (in both gender $p=0.047$), rs1333049 (in women $p=0.030$), rs17465637 (in both gender $p=0.046$). With MI – in native: rs1376251 (in both gender $p=0.002$, in men $p=0.005$) and in non native: rs619203 (in both gender $p=0.000$, in men $p=0.009$), rs2549513 (in both gender $p=0.001$, in men $p=0.041$), rs17465637 (in men $p=0.047$). These genetic markers can be used for assessing the risk of cardiovascular disease in Yakutian population.

Keywords: Yakutian population, single-nucleotide polymorphisms, metabolic syndrome, coronary atherosclerosis, myocardial infarction

Sterol regulatory element binding transcription factor 2 gene rs2228314 single nucleotide polymorphism and lipid profile in Caucasian population of west Siberia

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Background and aims: we have analyzed the rs2228314 SNP of sterol regulatory element binding transcription factor 2 gene (SREBF2) and lipid profile in Caucasian population of West Siberia (Russia).

Methods: 277 randomly selected patients were included in the analyses in frame of HAPIEE project (9360 participants, aged 45-69, men 50%). Mean total serum cholesterol level (TC) was 236±43 mg/dl. The plasma lipid levels were determined by standard enzymatic assays. The rs2228314 (1784G/C) of SREBF2 gene was analyzed by RELF-PCR.

Results: frequencies of GG, GC and CC genotypes were 47%, 45% and 8% in population. The frequency of C allele was 0.3 in population. Mean total serum cholesterol levels in case of genotypes GG, GC and CC were 232±8 mg/dl, 239±8 mg/dl, 229±19 mg/dl in population. We have not found the association of the rs2228314 SNP with TC level in HAPIEE population ($p>0.05$). The differences of triglycerides and high density lipoproteins cholesterol levels between genotypes are not significant.

Conclusions: The Caucasian population of West Siberia is not significantly differs from populations of Europe by frequencies of alleles and genotypes. The SREBF2 rs2228314 SNP was not associated with serum lipid levels in Caucasian population of West Siberia.

Keywords: SREBF2 gene, rs2228314, total serum cholesterol level, population

Influence of distribution of lipidtransport system genes polymorphism on level of a coronary atherosclerosis at patients with unstable angina

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Background: Among the genes under consideration for involvement in the risk of CHD, most important are genes encoding apolipoproteins A, B, C, E, whose polymorphic variants have been studied in detail, including in our studies.

Objective: to study features of lipid metabolism and coronary arteries lesions according to the combined carrier «ε4» allele ε2ε3ε4 polymorphism of the apolipoprotein E and «S2» allele SstI polymorphism of the apolipoprotein CIII in patients with unstable angina (UA).

Material and methods: 141 patients with UA and coronary atherosclerosis and 50 healthy volunteers were observed. ε2/ε3/ε4 polymorphism of gene apolipoprotein E (APO E) and SstI polymorphism of gene apolipoprotein CIII (APOCIII) was performed by PCR-RFLP method.

Results: All patients have been divided into 2 groups: 37 patients (26,2%, I group) with a combination of “damaging” alleles «ε4» and «S2» against the others – 104 patients (73,8%, II group). In I group of patients Total cholesterol (TC) (238,0±54,3) and Low density cholesterol (LDL-C) levels (154,7±51,5) were above, than in the II group (220,6±39,8 and 154,7±51,5, P<0,05), accordingly. Simultaneously, at patients of I group was significantly lower value of High density cholesterol (HDL-C) level (34,1±6,3) in comparison with II group (36,8±6,8, P <0,05). ApolipoproteinB/ApolipoproteinA-I ratio at I group (0,9±0,3) was above (P <0,05), concerning II group (0,8±0,2).

Conclusions: Carriage «ε4» allele ε2ε3ε4 polymorphism of the apolipoprotein E and «S2» allele SstI polymorphism of the apolipoprotein CIII at unstable angina patients (UA) is the promoting factor in development of a coronary atherosclerosis and atherogenicdislipidemia among uzbek patients. According to results of coronary angiography this group of patients often are observed three and multi-vessel coronary disease (P<0,05).

Keywords: Lipidtransport genes polymorphism, coronary angiography

Pathogenetic role of Notch signaling in calcific aortic valve stenosis

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Purpose: Calcific aortic valve stenosis (CAVS) is the most common form of acquired valvular disease. A progressive mineralization of aortic valve leaflets is a major culprit in the development of CAVS. CAVS was believed to be a passive degenerative disease, but recent research has shown that it is actually an active, complex inflammatory-like process, reminding atherosclerosis. Cumulative evidence from recent studies shows that loss-of-function polymorphisms and mutations in *NOTCH1* are strongly associated with early calcification of aortic valves in humans, but the role of Notch signaling and the mechanisms that may contribute to CAVS remains unknown.

The aim of the study was to assess the expression level of Notch signaling components in human aortic valvular interstitial cells (VIC) derived from the CAVS patients.

Materials and methods: We included 68 patients with CAVS operated in Almazov centre: 32 of them had tricuspid aortic valve (TAV), 6 of which had moderate AS, and 26 had severe AS; 36 of them have bicuspid aortic valve (BAV), 2 of which had moderate AS and 34 had severe AS. The mean \pm SD age of patients was $62,09 \pm 5,64$ in the TAV group and $59,0 \pm 8,0$ in the BAV group. There were 10 healthy donors, whose cusps were used as controls. VICs were isolated from BAV and TAV cusps from patients with CAVS and from healthy donors. The baseline level of Notch receptors, ligands and target genes was estimated by qPCR.

Results: VICs from BAV group had significantly different levels of Notch signaling components comparing to TAV group, moreover both of the groups have significant difference comparing to healthy donors. We established a significant correlation between level of cholesterol and level of *NOTCH4* ($K=0,809$; $p<0,05$) and severity of aortic valve stenosis and *DLL4* level ($K=0,798$; $p<0,05$) in the TAV group and between diameter of the ascending aorta and *DLL4* level ($K=0,798$; $p<0,05$) and *NOTCH4* level ($K=0,732$; $p<0,05$) in the BAV group.

Conclusion: Our results show that Notch signaling is differently altered in VICs from BAV and TAV patients with CAVS. The observed correlations of CAVS clinical severity and down regulation of Notch components suggests that Notch signaling is directly involved in the pathogenesis of CAVS, however further research is needed to clarify the role of Notch in this process.

Keywords: Notch signalling, Calcific aortic valve stenosis

Metabolic Syndrome (Diabetes, Obesity)

Carotid arteries subclinical damage in patients with abdominal obesity

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Introduction: Abdominal obesity (AO) and arterial hypertension (AH) are atherosclerosis risk factors. One of the early signs of atherosclerosis is increase of intima-media thickness of the common carotid arteries (CCA IMT).

Study objective: To reveal subclinical damage of the CCA in hypertensive and normotensive subjects with AO.

Material and methods: We examined 216 patients with AO and 23 subjects with normal waist circumference without clinical signs of atherosclerosis. All of them underwent ultrasound duplex scan of CCA (ALOKA SSD-3500, Japan). CCA IMT above 0,9 mm was considered to be abnormal. Local CCA wall thickening exceeding by 50% and more thickness of the adjacent intima-media complex or CCA IMT above 1,3 mm were the criteria of atherosclerotic plaque.

Results: 60,9% of patients with AO were diagnosed with AH. In obese patients with CCA IMT below and equal to 0,9 mm systolic blood pressure (BP) was lower than in patients with CCA IMT above 0,9 mm ($132,2 \pm 1,5$ mm Hg vs $138,6 \pm 2,4$ mm Hg, $p < 0,01$). CCA IMT in obese normotensives was significantly higher than in control group ($0,72 \pm 0,03$ mm vs $0,55 \pm 0,02$ mm, $p < 0,01$). The rate of CCA IMT above 0,9 mm in obese hypertensives and normotensives did not vary (49,4% vs 69,8%, $p > 0,05$). CCA IMT in patients with AO and AH was higher than in obese normotensives ($0,90 \pm 0,02$ mm vs $0,82 \pm 0,02$ mm, $p < 0,01$). Atherosclerotic plaques of CCA were found in 39,8% of patients with AO.

Conclusion: In patients with abdominal obesity and normal blood pressure early signs of atherosclerosis were found in 49,4%. In obese hypertensive patients common carotid arteries intima-media thickness is higher than in normotensive obese patients.

Keywords: abdominal obesity, arterial hypertension, common carotid arteries intima-media thickness, atherosclerosis risk factors, subclinical damage

Chicken Hydrolysate Diets Reduce Inflammation and Atherosclerosis Progression in High-Fat Fed Mice

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Atherosclerosis is characterized by two fundamental hallmarks: lipid accumulation and inflammation. Recent studies have reported anti-inflammatory and anti-atherosclerotic effects of hydrolysed fish proteins. The present study investigated different chicken hydrolysates with regard to inflammation and hepatic lipid metabolism in a diet-induced obesity model in mice, and the most potent hydrolysates were further tested for effect on atherosclerotic lesions in apoE^{-/-} mice. 60 mice were divided into 5 groups (n = 12) and fed a high fat/high sucrose diet containing 20% casein (Control), or diets where casein was replaced with 10% of different enzymatic hydrolysates of chicken protein; Papain+ (PAP), Alcalase (ALC), Corolase PP (COR), or Protamex (PRO). Hepatic β -oxidation and plasma cytokine levels was measured after 12 weeks of dietary intervention. Two of the hydrolysates, ALC and COR, significantly increased hepatic β -oxidation, indicating an effect on lipid metabolism. The chicken hydrolysate diets had no influence on body weight or plasma lipid parameters, but they all reduced plasma cytokines IL-1 β , INF- γ , TNF α , and MCP-1 significantly compared to control. In addition, PRO and ALC reduced Rantes, while COR and PRO reduced GM-CSF and IL-1 α . Thus, ALC and COR was chosen for further analysis in an atherosclerosis model. 36 apoE^{-/-} mice were divided into 3 groups (n = 12) and fed a high-fat control diet or a high-fat diet containing 12.5% of either ALC or COR. After 12 weeks, the aorta was dissected from the aortic arch to the iliac bifurcation, and stained with oil-red-O for *en face* plaque analysis. A significant lower total plaque area was observed in the aortic arch region of COR-fed mice compared to control mice, while a strong tendency to reduced plaque area was observed in ALC-fed mice. Plasma lipid levels were not significantly affected, but cytokine levels indicated a lower level of systemic inflammation. These data indicate that ALC and COR reduced atherosclerotic plaque development in high-fat fed apoE-deficient mice by modulating the inflammatory response to a high-fat diet. This demonstrates that the dietary protein source has the potential to influence health parameters.

Keywords: atherosclerosis, inflammation, high-fat diet, chicken protein, beta-oxidation

The distribution of the metabolic disorders among obese patients, depending on the metabolic status

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Objective: There is a subgroup among obese people who have low risk of cardiovascular complications – this subjects can be considered “metabolically healthy” obese (MHO) individuals. The aim of the study was to evaluate the distribution of the metabolic components among MHO and metabolically unhealthy obese (MUHO) subjects.

Design and methods: As a part of all-Russian epidemiology survey ESSE-RF random sampling of 1600 Saint-Petersburg inhabitants stratified by age and sex was involved. Anthropometry (weight, height with body-mass index (BMI) calculation, waist circumference (WC)), blood pressure (BP) measurement and fasting blood-tests: glucose, lipids, CRP, insulin was performed according to standard protocols. Criterion for insulin resistance (IR) and elevated C-reactive protein (CRP) was taken the value of HOMA IR and CRP exceeding the 90th percentile in our sample of residents of St. Petersburg. Wildman criteria were applied for detection of metabolic health among obese (BMI \geq 30 kg/m²) people: presence of 0-1 factors (SBP \geq 130 or DBP \geq 85 mm Hg or antihypertensive therapy; triglycerides \geq 1.70 mmol/L; HDL $<$ 1.04 (males), $<$ 1.30 (females) mmol/L or lipid-lowering therapy; glucose \geq 5.55 mmol/L or hypoglycemic therapy; CRP $>$ 4.72 mg/L; HOMA $>$ 4.81).

Results: Obesity was detected in 428 (27.4%) participants. According to the Wildman criteria MHO were diagnosed in 85 (21.5%) people. Only 24 (28%) had ideal metabolic health, others had one component. It was revealed that 57.4% of patients with an MHO phenotype have elevated blood pressure, 19.7% – a decreased level of HDL, 9.8% – hyperglycemia and hypertriglyceridemia, 1.6% – elevated level of CRP and HOMA-IR. 85.2% MHO subjects had obesity according to waist circumference criteria.

Among patients with MUHO phenotype combination of 2 metabolic disorders was detected in 38.8% of patients, 3 – at 3.25%, 4 – at 20.2%, 5 – at 13.5%, 6 – at 2.2%. At 85.6% of MUHO patients revealed elevated blood pressure, 65.1% – decreased level of HDL, 55.4% – hyperglycemia, 49.7% – hypertriglyceridemia, 34.3% – increased level of HOMA-IR, 25.0% – elevated levels of CRP. Obesity at WC criteria was at 91.9% of the persons.

MHO and MUHO subjects did not differ significantly according to waist circumference criteria ($p = 0.13$).

Conclusion: Such metabolic disorders components as elevated blood pressure level and dyslipidemia are the most prevalent in MHO individuals as well as in MUHO.

Keywords: obesity, metabolic health

C-reactive protein and high molecular weight adiponectin in women with abdominal obesity: carotid intimal media thickness of common carotid arteries

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Objective: Abdominal obesity (AO) is generally held to be widely spread condition that affects populations of many countries. AO often results in severe cardio-vascular disorders. A diversity of structural and metabolic injuries can accompany AO, in particular, atherosclerosis of a carotid arteries, heart attack and failure, stroke, etc.

The aim of the present study was to find out probable associations, if any, between carotid intima media thickness (CIMT) of common carotid arteries (CCA) and C-reactive protein (CRP), high molecular weight adiponectin (HMW) and high density lipoproteins (HDL-C) in women with (AO) (IDF, 2005).

Methods: We had examined 55 women with AO aged from 30 to 55 years, as well as 15 women without AO (IDF, 2005). An ultrasound scan examination was performed on all patients. HMW was detected using ELISA method (DRG, Germany), HDL-C and CRP were detected using commonly accepted method (COBAS Integra).

Results: In women without AO, values of CIMT, CCA and CRP were lower than values received from women with AO [0,58 (0,48; 0,66); 0,78 (0,53; 1,19) mm, respectively, $p < 0,05$, for CIMT CCA] and [0,79 (0,08; 6,09); 4,26 (0,41; 10,03), respectively, $p < 0,05$, for CRP], but the values of HDL-C and HMW adiponectin were significantly higher [1,62 (0,92; 4,08); 1,32 (0,53; 3,27) mmol/L, respectively, $p < 0,05$, for HDL-C] and [4,19 (1,96; 8,12); 2,49 (0,50; 15,45) mcg/ml, respectively, $p < 0,01$, for HMW]. Significant correlations were defined among women with AO between: CIMT CCA with (a) AO ($r = 0,37$, $p = 0,03$); (b) HDL-C ($r = -0,25$; $p = 0,03$); (c) CRP ($r = -0,34$; $p = 0,01$); (d) HMW adiponectin ($r = 0,35$; $p = 0,01$). The multiple linear regression analyses had shown the association between CIMT CCA with (a) HMW adiponectin ($\beta = -0,31$; $p = 0,03$); (b) C-reactive protein ($\beta = 0,36$; $p = 0,01$). CIMT CCA $\geq 0,9$ mm had 19,2% AO patients. Logistic regression model was included in the analysis of (a) HMW adiponectin; (b) AO; (c) HDL-C; (d) CRP and (e) age; (f) CIMT CCA. Out of all the above parameters only (d) and (f) were significantly associated ($p = 0,02$).

Conclusions: The study had shown that there is a significant association between CIMT CCA, HDL-C and C-reactive protein on one hand, and high molecular adiponectin on the other, in women with abdominal obesity. But results of the logistic regression showed that CRP level has the greatest impact on CIMT.

Keywords: Abdominal obesity, High molecular weight adiponectin, Carotid intimal media thickness of common carotid arteries, C-reactive protein

Telmisartan attenuates hyperglycemia-aggravated VCAM-1 expression and monocytes adhesion in TNF α -stimulated endothelial cells by increasing GSK3 β -Ser⁹ phosphorylation

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Uncontrolled hyperglycemia accelerates endothelial damage and vascular inflammation caused by proinflammatory cytokines including tumor necrosis factor α (TNF α), which leads to arteriosclerotic cardiovascular diseases. Glycogen synthase kinase 3 β (GSK3 β) is reported to mediate TNF α -stimulated nuclear factor- κ B (NF- κ B) activation and expression of vascular adhesion molecules. Although a few clinical trials have suggested that telmisartan, an angiotensin II type 1 receptor blocker (ARB), decreases cardiovascular complications in diabetic patients, the underlying molecular mechanisms for the beneficial effects have not been fully elucidated. Here, we investigated a molecular mechanism mediating the telmisartan's beneficial effects on vascular inflammation in hyperglycemia-treated endothelial cells. Telmisartan dose-dependently attenuated the hyperglycemia-aggravated vascular cell adhesion molecule-1 (VCAM-1) expression and THP-1 monocytes adhesion, which accompanied an increased GSK3 β -Ser⁹ phosphorylation and a decreased NF- κ B p65-Ser⁵³⁶ phosphorylation. Among ARBs, including losartan and fimasartan, only telmisartan induced GSK3 β -Ser⁹ phosphorylation and showed the inhibitory effects on expression of VCAM-1 and phosphorylation of NF- κ B p65-Ser⁵³⁶. The telmisartan's beneficial effects were not changed by pretreatment with GW9662, a specific and irreversible peroxisome proliferator-activated receptor γ (PPAR γ) antagonist, although GW9662 clearly inhibited rosiglitazone-induced CD36 expression. Finally, ectopic expression of GSK3 β -S9A, a constitutively active mutant of GSK3 β , significantly restored the telmisartan-attenuated VCAM-1 expression, NF- κ B p65-Ser⁵³⁶ phosphorylation, and THP-1 monocytes adhesion. Taken together, our findings demonstrate that telmisartan ameliorates hyperglycemia-exacerbated vascular inflammation at least in part by increasing GSK3 β -Ser⁹ phosphorylation, which mediates a decreased VCAM-1 expression in a PPAR γ -independent manner. Telmisartan may be useful for the treatment of DM-associated vascular inflammation and cardiovascular diseases.

Keywords: Telmisartan, Vascular inflammation, Hyperglycemia, VCAM-1, GSK3 β

Some aspects of left ventricular remodeling in hypertensive patients with diabetic nephropathy

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Chronic overload of the left ventricle (LV) with arterial hypertension (AH) leads to structural and morphological reconstruction, namely hypertrophy, dilatation and changes in the geometry of the heart cavities and myocardium in general, that is remodeling. Today, special importance is given to the evaluation of the pathogenetic pathways of heart failure. Violation of LV systolic function, the primacy of which there is no doubt in focal destructive processes in the myocardium occurs in patients with hypertension, usually with long-standing pathological process. However, clinical signs of heart failure in hypertension observed in the early stages of its development. This is due process violation diastolic ventricular relaxation, the appearance of diastolic dysfunction. This requires a differentiated assessment of the contribution of the structural and morphological changes of the myocardium inherent remodeling in hypertension in the development of clinical manifestations of heart failure.

Methods: A total of 107 patients with AH in chronic kidney disease (CKD), diabetic nephropathy with 2 type diabetes mellitus. Preserved renal function was 42 patients, chronic renal failure (CRF) I degree in 20, CRF II degree – 27 and CRF III degree – in 18 patients. Echocardiography in M and B mode was conducted in the machine “Ultramark-9 ATL” (USA).

Results: Normal geometry (NG) was established in 8 (7.5%), concentric remodeling (CR) in 15 (14.0%), concentric hypertrophy (CH) in 52 (48.5%) and eccentric hypertrophy (EH) – in 32 (29.0%). Moreover, the NG was only observed in patients with CKD-0, where it reached 19.1% of the 42 patients. In the same group of patients with CR occurred in 9 (21.4%), CH 15 (35.7%) and EH – in 10 (26.8%) patients. In chronic renal failure I patients: CR have five (25%) patients and myocardial hypertrophy occurred in 15 patients (75.0%). The frequency of the concentric and eccentric LV hypertrophy was – at 56.0% and 25.0%.

Progression of CKD to II st. characterized by the increasing number of patients with CH to 62.9% ($p < 0.05$), while the frequency of EH remained almost the same as in the CRF-II, accounting for 33.8%. Significantly decreased the frequency of concentric remodeling to 3.7% ($p < 0.01$ compared to the CH and EH).

In patients with CRF III concentric hypertrophy occurred in 55.6%, which was not significantly lower than the frequency of CH in CRF II. The frequency of EH increased to 44.4%, which also did not differ significantly from both the CH group CKD III and EH in patients with CRF II.

Conclusion: The highest frequency of left ventricular remodeling in renal hypertensive patients with chronic renal failure have concentric and eccentric hypertrophy of the left ventricle, occurring 80.4% of all patients and emerging even before the development of renal failure. Concentric hypertrophy occurs most frequently in patients with chronic renal failure II-III. The frequency of eccentric hypertrophy increases with the progression of chronic renal failure.

Keywords: left ventricular remodeling, arterial hypertension, diabetic nephropathy, 2 type diabetes mellitus

Pathogenetic interrelationships of atherosclerosis and type 2 diabetes

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In the genesis of type 2 diabetes mellitus (DM2) is isolated circumstances inherent in the atherosclerotic process.

Purpose of the study: to identify risk factors for the association type 2 diabetes and atherosclerotic lesions of great vessels and also to clarify the features of the results of reconstructive interventions in patients with the mentioned nosological forms.

Materials and methods: The basis of the work was formed from observation of 65 patients with multifocal atherosclerosis, 42 of whose had type 2 diabetes (the main group). In the control group (23 patients) changes in carbohydrate metabolism haven't been recorded. Risk factors of atherosclerosis and hemodynamic changes in the perioperative period, biochemical parameters of blood, the amount of intraoperative blood loss, the results of surgical interventions, blood lipid profile were analyzed. A survey on the subject of hypertension were conducted and characteristics of its course were revealed. The results were separated on a scale of arithmetic values (mean) \pm standard deviation (SD). Comparing groups of arithmetic values was carried out by using the nonparametric Mann-Whitney test. The difference in categorical variables were analyzed by the Pearson χ^2 and Fisher test. Differences were considered statistically significant at $p < 0,05$. Mathematical processing was performed using STATISTICA software package 10.

Results: Arterial hypertension (including its uncontrolled version) was met three times more likely in patients with type 2 diabetes ($p < 0.05$). Lipid metabolism disorders with predominant increase in triglycerides also prevails in the group of patients with type 2 diabetes (93%; $p < 0.05$). Hemodynamic disturbances in patients with type 2 diabetes (under option hypotension) in 1 day after the operation marked twice as likely ($p < 0.05$). Among the postoperative complications peculiar to people with type 2 diabetes, is necessary to mark a greater frequency of adverse cardiovascular events (ischemic stroke, myocardial infarction, the thrombosis of operated segment). Postoperative infectious complications were also predominant in individuals with disturbances of carbohydrate metabolism.

Conclusions: DM-2 is similar to atherosclerosis pathogenetic basis and is characterized by higher probability of postoperative complications in reconstructive interventions on the main arteries.

Keywords: type 2 diabetes, atherosclerotic process, reconstructive interventions

TWEAK blockade decreases atherosclerotic lesion size and progression through suppression of STAT signaling in diabetic mice

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Introduction: Diabetes mellitus is associated with significantly increased rates of atherosclerosis. Complications affecting the vasculature are the major causes of morbidity and mortality among diabetic subjects. The biological mechanisms implicated in the development of diabetic vascular complications remain to be fully understood, but considerable attention has been paid to the role of endothelial dysfunction, inflammation and oxidative stress. One molecule implicated in all of these processes is the tumor necrosis factor-like weak inducer of apoptosis (TWEAK, *Tnfsf12*). However, the role of this cytokine under hyperglycemic conditions is currently unknown.

Approach and Results: Using two different approaches, genetic deletion of *Tnfsf12* and treatment with a TWEAK blocking mAb, we have analyzed the effect of TWEAK inhibition on atherosclerotic plaque progression and stability in streptozotocin-induced diabetic *ApoE* deficient mice. Diabetic *Tnfsf12^{+/+}ApoE^{-/-}* mice showed a 164% increase of lesion area compared with non-diabetic *Tnfsf12^{+/+}ApoE^{-/-}* mice ($p < 0.001$). Genetic inactivation of *Tnfsf12* reduced atherosclerosis extension (67% reduction; $p < 0.001$) and severity in diabetic *ApoE* deficient mice. Diabetic *Tnfsf12^{-/-}ApoE^{-/-}* mice display a more stable plaque phenotype characterized by lower lipid (40% reduction; $p < 0.001$) and macrophage content (32% reduction; $p < 0.05$) within atherosclerotic plaques compared with diabetic *Tnfsf12^{+/+}ApoE^{-/-}* mice. A similar phenotype was observed in diabetic mice treated with anti-TWEAK mAb. The proatherosclerotic effects of TWEAK were mediated, at least in part, by STAT1 activation and expression of proinflammatory target genes (CCL5, CXCL10 and ICAM-1), both in plaques of *ApoE* mice and in cultured VSMCs under hyperglycemic conditions.

Conclusions: Overall, TWEAK blockade delay plaque progression and alter plaque composition in diabetic atherosclerotic mice. These effects are related to the capacity of TWEAK to induce a proinflammatory response under hyperglycemic conditions. Therapies aimed to inhibit TWEAK expression and/or function could protect from diabetic vascular complications.

Keywords: Diabetes, Inflammation, Atherosclerosis, Mice, TWEAK

Effects of insulin resistance at lipid profile in hypertensive patients with normal and overweight

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Objective: To determine the nature and severity of the lipid profile in patients with arterial hypertension (AH) with normal and overweight, depending on the availability of insulin resistance (IR).

Materials and methods: we examined 120 patients with hypertension, of which 95 people (group 1) with normal body weight and 25 (group 2) – with overweight / obesity (BMI= $94,4 \pm 1,74$ kg). Patients in both groups were comparable in age, history and stage of hypertension (essential hypertension (EH) I-II stage, AH 1-2 degree), without significant comorbidities and randomly selected at the outpatient reception. All patients measured cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG) in blood. Research conducted glucose (G) fasting serum immunoreactive insulin (I) to determine the value of the coefficient QUICKI – index IR. Coefficient QUICKI = $1 / (\log (X)) + \log (18 * G)$. When QUICKI $< 0,32$ IR was diagnosed.

Results: in terms QUICKI IR was observed in 34 (36 %) patients of group 1 and 16 (64 %) in group 2. In these patients, there was a trend towards higher numbers of cholesterol, LDL, Tg compared with a group of hypertensive patients without IR. Thus, levels of cholesterol, LDL, Tg were 5.6 ± 0.11 mmol / l, 3.9 ± 0.10 mmol / l, 2.23 ± 0.07 mmol / l in patients of group 1 with IR, and 5.51 ± 0.07 mmol / l, 3.6 ± 0.07 mmol / l, 2.01 ± 0.07 mmol / l in patients of group 1 without IR. Such changes in blood lipid spectrum were determined in patients of group 2. Patients with IR have a cholesterol level – $6,15 \pm 0,03$ mmol / l, LDL – $4,01 \pm 1,23$ mmol / l, Tg – $2,5 \pm 0,03$ mmol / l. In the group of hypertensive patients without IR cholesterol level was $5,9 \pm 0,15$ mmol / l, LDL = $3,8 \pm 0,19$ mmol / l, Tg = $2,2 \pm 0,15$ mmol / l. The level of Tg in blood was significantly higher in patients with AH, IR and overweight than in patients with AH, IR and normal body weight: $2,5 \pm 0,03$ mmol / l and $2,23 \pm 0,07$ mmol / l ($p < 0,05$).

Conclusions: syndrome of IR was registered in 36% of examined hypertensive patients with normal body weight and 64 % of patients with overweight / obesity. In the group of patients with hypertension and overweight degree of hypertriglyceridemia was significantly higher than in hypertensive patients with IR and normal body weight.

Keywords: metabolic syndrome, arterial hypertension, insulin resistance, cardiovascular disease, obesity

Role of profibrogenic factors in increasing of arterial stiffness in patients with metabolic syndrome

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Aim: Carotid-femoral pulse wave velocity (PWV) and carotid intima-media thickness (cIMT) are surrogate methods of evaluating arterial stiffness and early atherosclerotic lesions, which associated with increased risk of cardiovascular complications. Galectin 3 and aldosterone – substances with profibrogenic and proinflammatory effects on cardiovascular system. The objective of this study was to compare the levels of galectin 3 and aldosterone in patients with metabolic syndrome (MetS) and healthy individuals and to identify the relationship between this substances, PWV and cIMT.

Methods: 190 persons (97 female and 93 male, 52,2±8,1 years old) were examined and divided into 2 groups: MetS (n=100) with 3 or more components (IDF, 2005) and healthy control (n=90) without metabolic disorders and cardiovascular diseases. Groups did not differ significantly by gender, age and eGFR ($p>0,05$). The examination included: medical history, anthropometry, galectin 3 and aldosterone levels in serum (Enzyme Immunoassay). The patients with hyperaldosteronism were excluded from the study. The assessment of cIMT was performed with ultrasound scanning. Carotid-femoral PWV was determined by Sphygmocor.

Results: Serum galectin 3 in patients with MetS was higher than in healthy individuals (480,2 [420,1;1240,4] and 270,1 [240,3;320,4] pg/ml, $p<0,001$) and aldosterone was significantly higher in patients with MetS (135,0 [83,5;203,8] and 69,8 [46,0;119,0] pg/ml, $p<0,001$). Carotid-femoral PWV in patients with MetS was higher than in healthy individuals (8,82±1,91 and 6,43±0,92 m/s, $p<0,001$), also as cIMT (0,93±0,21 and 0,61±0,12 mm, $p<0,001$). The galectin 3 was positive correlated with triglyceride ($r=0,543$, $p<0,001$), total cholesterol ($r=0,315$, $p=0,04$) and negative correlated with HDL-cholesterol ($r= - 0,474$, $p<0,001$). A positive correlation between galectin 3 and PWV ($r=0,624$, $p<0,001$) and cIMT ($r=0,761$, $p<0,001$) was revealed. The level of aldosterone was correlated with PWV ($r=0,463$, $p<0,001$). A positive correlation between galectin 3 and aldosterone in all patients was revealed ($r=0,524$, $p<0,001$). The multivariate regression analysis was demonstrated that the galectin 3 is an independent predictor of increasing the cIMT more than 0,9 mm in patients with MetS (OR=15,2, 95% CI 7,59-30,5, $p=0,001$).

Conclusions: Galectin 3 and aldosterone – markers of fibrosis were higher in patients with metabolic syndrome than in healthy individuals. “Gold standard” of arterial stiffness – carotid-femoral pulse wave velocity, carotid intima-media thickness were higher in metabolic syndrome patients than in healthy persons. We propose that the aldosterone can induce profibrogenic and proinflammatory effects of galectin 3 in processes of morphological changes in arterial wall.

Keywords: arterial stiffness, intima-media thickness, galectin 3, aldosterone, metabolic syndrome

Galvus the correction of dyslipidemia in patients with type 2 diabetes and metabolic syndrome

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The combination of diabetes mellitus type 2 and metabolic syndrome (MS) increases the risk of serious complications associated with disturbed as and lipide profil, which justifies a careful choice of antidiabetic drugs, deprived of the negative impact on the basic parameters of dyslipidemia.

Purpose: To evaluate the effectiveness of the correction drugs in patients with type 2 diabetes in combination with MS in the treatment of an inhibitor of dipeptidyl peptidase-4 (DPP-4) Galvus.

Material and methods: The study involved 80 patients with type 2 diabetes with MS at the age of 32-67 years. The blood was measured lipid profile: total cholesterol (TC), high and low-density cholesterol LDL-C and HDL-C, very low density lipoproteins cholesterol (VLDL-C), triglycerides (TG), atherogenic index (AI), as well as anthropometric data-height (m) weight (kg), with the index calculation Quetelet (kg/m^2). Laboratory tests were performed on the analyzer «Bio Screen MS 2000» (USA) with «Human» company reagents. 40 patients of the main group received the DPP-4 inhibitor vildagliptin (Galvus, of Novartis, Switzerland) -50 mg per day, and 40 patients of the control group received the combination of Metformin with sulfonylureas – Diabeton (Servie-France) – 2-4 mg. 1 time in the morning. The second study was carried out after 6 months of therapy.

Results: In the study group showed a significant reduction of high concentrations TC ($220,4 \pm 12,9$ and $178,9 \pm 8,1$ mg/dl), LDL-C ($137,1 \pm 11,4$ and $103,1 \pm 6,8$ mg/dl), VLDL-C ($42,2 \pm 3,2$ and $31,5 \pm 1,9$ mg/dl), TG ($210,8 \pm 16,2$ and $158,0 \pm 9,9$ mg/dl), AI ($4,7 \pm 0,4$ and $3,2 \pm 0,2$, $p < 0,05$) and statistically nonsignificant increase HDL-C ($41,1 \pm 1,7$ and $44,2 \pm 1,5$ mg/dl, $p > 0,05$), while the control group was observed misleading negative dynamics – increase TC ($202,6 \pm 9,2$ and $218,4 \pm 10,8$), LDL-C ($130,8 \pm 8,8$ and $145,6 \pm 10,1$ mg/dl), VLDL-C ($34,2 \pm 2,3$ and $38,9 \pm 2,9$ mg/dl), TG ($170,9 \pm 1,6$ and $14,9 \pm 194,5$ mg/dl) and AI ($4,5 \pm 0,36$ and $4,64 \pm 0,41$, $p > 0,05$), but HDL-C level has not changed. It was also observed a significant decrease Quetelet ($33,6 \pm 0,9$ and $32,2 \pm 0,8$ kg/m^2 , $p < 0,05$) in study and an increase in the control group ($33,1 \pm 0,9$ and $34,4 \pm 0,8$ kg/m^2 , $p < 0,05$).

Conclusion: The positive effect of Galvus on lipid spectrum indicated the predominant glucose-lowering effect compared to the combination of metformin with Diabeton in patients with type 2 diabetes with the MS.

Keywords: Diabetes mellitus, metabolic syndrome, lipide profil, antidiabetic drugs, inhibitor of dipeptidyl peptidase-4

The association between obesity, adipokines levels and inflammation in patients with early rheumatoid arthritis

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Actuality: The adipose tissue is an active endocrine organ that synthesizes adipokines (adiponectin, leptin, etc.). The relation between obesity, adipokines and inflammation are widely discussed. Rheumatoid arthritis (RA) may be considered as a model of chronic autoimmune inflammation, in which lean mass is reduced, but the fat mass (FM) is maintained or increased. Dual-energy X-ray absorptiometry (DXA) is able to clarify body composition.

Aim: To examine the correlation between obesity, adipokines synthesis and levels of inflammatory cytokines in patients with early RA.

Material-Methods: The study included 27 early RA patients (20 women, 7 men; 56 [46; 64] years old), never receiving anti-inflammatory therapy (glucocorticoids and disease-modifying antirheumatic drugs). The median disease duration was 8 [6,15] months. The majority of pts were seropositive for IgM RF (89%) and anti-CCP (96%). Medium or high RA activity was documented in all pts (DAS28 5,4 [5,0;6,5]). The control group consisted of 30 healthy subjects without rheumatic diseases, matched by age and sex with RA patients. Serum concentration of adipokines (adiponectin and leptin) was measured with ELISA, interleukins (IL) -1 β , 2, 4, 5, 6, 7, 8, 9, 10, 12, 13, 15, 17 – by multiplex technology X-MAP. DXA with densitometer HOLOGIC (USA) identify FM (g) in 19 RA patients.

Results: The abdominal obesity (WC \geq 80cm in women, \geq 94 in men) was observed in 22 (81,5%) RA patients, median BMI was 26,4 [23,2;30,8]. Anthropometric indicators (WC, BMI) were similar in RA patients and control group. Adiponectin level was higher in untreated RA patients than in the controls (23,0 [15,8; 67,0] vs 9,2 [5,6; 12,2]ng/ml), while leptin and visfatin concentration were lower than in the control group (25,0 [8,0; 32,0] vs 30,5 [19,0; 46,2]ng/ml, and 434 [336,533] vs 753[427;1000]ng/ml, respectively, $p < 0,05$ for all). Clear correlation was established between leptin and IL-4 ($r=0,4$, $p=0,04$), leptin and IL-17 ($r=0,4$, $p=0,03$). High visfatin concentration was associated with increased IL-5 ($r=0,4$, $p=0,03$), and IL-9 ($r=0,4$, $p=0,04$) levels. Adiponectin did not show correlation with any of these parameters. Serum concentration of leptin and IL-17 depends on the FM ($r=0,6$, $p=0,01$ and $r=0,5$, $p=0,05$, respectively), but no WC or BMI.

Conclusion: Statistically significant correlation was established between some adipokines (leptin, visfatin) and Th17, Th2 cytokine levels in early RA patients. Adipose tissue can be both a source of some adipokines and proinflammatory cytokines.

Keywords: obesity, rheumatoid arthritis, adipokines, fat mass, inflammation

Beneficial Effect of Sarpogrelate, a Serotonin Receptor Antagonist, on Coronary Artery Disease in Patients with Diabetes

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Objective: Sarpogrelate, a 5-hydroxytryptamine type 2 antagonist, is an antiplatelet agent. It may be a potential agent in treatment of macrovascular complication in diabetes. We performed a prospective interventional study to evaluate the effect of sarpogrelate compared with aspirin in Korean diabetic patients with subclinical coronary atherosclerosis.

Methods: Forty diabetic patients (25 men, ages 58.7 ± 6.8 years) who had mild to moderate atheroma evaluated with coronary multidetector-row CT (MDCT) were randomly assigned to either sarpogrelate 300 mg/day plus aspirin 100 mg/day (SPG+ASA group) or aspirin 100 mg/day only (ASA group) ($n = 20$ each) for 6 months. Coronary artery calcium score (CACS) and coronary artery stenosis and plaque volume were investigated. Primary outcome was change of coronary artery disease assessed by coronary MDCT. Secondary outcomes included change in risk factors of atherosclerosis such as glucose and lipid metabolism and subclinical atherosclerosis assessed by ankle-brachial index and pulse wave velocity.

Results: The CACS was decreased in SPG+ASA group (187.2 ± 229.5 to 179.2 ± 196.3) whereas it increased in ASA group (95.5 ± 152.6 to 98.9 ± 147.5), but differences were not statistically significant ($p = 0.780$ and $p = 0.602$, respectively). In SPG+ASA group, there was a small insignificant increase in maximal coronary stenosis (30.9 ± 20.7 to $32.4 \pm 16.7\%$, $p = 0.589$), however, it slightly decreased in ASA group (31.7 ± 15.7 to $29.7 \pm 18.2\%$, $p = 0.475$). The total plaque volume decreased from 69.8 ± 44.1 to 65.5 ± 46.3 mm³ in SPG+ASA group whereas it increased from 54.5 ± 52.4 to 56.8 ± 55.9 mm³ in ASA group, but both were not statistically significant ($p = 0.147$ and $p = 0.627$, respectively). There were no significant changes in glucose and lipid metabolism and subclinical atherosclerosis in both groups ($p > 0.005$ for all).

Conclusion: The present study demonstrates that sarpogrelate treatment seems to decrease in atheromatous plaque volume in diabetic patients. Longer studies with large scale are needed to validate these results.

Keywords: Sarpogrelate, Aspirin, Coronary artery disease, coronary multidetector computed tomography, type 2 diabetes

Simvastatin influence on left ventricle diastolic function and endothelial function at patients with metabolic syndrome features

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Aim: To investigate simvastatin influence on left ventricle diastolic function (LVDF) and endothelium function in patients with metabolic syndrome features.

Materials and methods: 32 male patients with essential hypertension (EH) and metabolic syndrome features, such as low-density lipoproteins (LDL) cholesterol more than 3.0 mmol/l, high-density lipoproteins (HDL) cholesterol less than 1.0 mmol/l, abdominal obesity and impaired fasting glycaemia before simvastatin 20 mg per day treatment and four month after were surveyed. Endothelium function by measuring a degree of the endothelium-dependent relaxation of a humeral artery with Doppler through a humeral artery diameter change at reactive hyperaemia, LVDF by isovolumic relaxation time (IVRT), E/A ratio, epicardial adipose tissue thickness (EATT), LDL, HDL cholesterol and serum fasting glucose concentration.

Results: After four month simvastatin treatment LDL cholesterol level has decreased from 3.43 ± 0.15 mmol/l to 2.68 ± 0.07 mmol/l, HDL cholesterol level has increased from 0.89 ± 0.06 mmol/l to 1.12 ± 0.05 mmol/l ($p < 0.05$). Thus, 29 patients (90.6%) had normal lipoproteins ratio. Endothelial function in all examined patients improved (a humeral artery diameter relaxation at reactive hyperemia has increased from 0.36 ± 0.03 mm (8.1%) to 0.57 ± 0.04 mm (13.4%) ($p < 0.05$). IVRT has improved from 82.7 ± 3.2 ms to 63.1 ± 2.9 ms, E/A ration has significantly increased from 0.61 ± 0.04 to 0.98 ± 0.04 . Thus, 28 patients (87.5%) had improved diastolic function. There was not significant change in fasting glucose level. Before simvastatin management its level was 6.4 ± 0.33 mmol/l and after four month – 6.21 ± 0.21 mmol/l ($p = 0.53$). In addition, 4-month simvastatin treatment did not affect EATT: 0.43 ± 0.02 cm and 0.39 ± 0.04 cm ($p = 0.66$).

Conclusion: Simvastatin inclusion in treatment of patients with metabolic syndrome features promotes lipid exchange improve, but does not influence glycemic exchange. Four-month simvastatin treatment improves endothelial function and increases diastolic function if it is impaired.

Keywords: simvastatin, metabolic syndrome, left ventricle diastolic function, endothelial function

Subclinical atherosclerosis in patients with psoriatic arthritis: its relationship with metabolic syndrome and disease activity

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Background: Psoriatic arthritis (PsA) patients (pts) have increased cardiovascular disease (CVD) risk due to combination of traditional risk factors (TRF) and autoimmune inflammation.

Objectives: to determine the frequency of metabolic syndrome (MetS) in pts with PsA, examine its relationship with subclinical atherosclerosis and disease activity.

Methods: 128 (F.- 61.7%, M. -38.3%) with PsA, according to the CASPAR criteria, mean age 43 [34; 49] years (yrs.), PsA duration -7 [3; 13] yrs., Psoriasis duration -15 [6; 26] yrs., DAS 3.86 [2.72; 5.14] without any signs of CVD were included. MetS was defined using by ESC criteria (2011). Carotid intima-media thickness (cIMT) was measured using a high-resolution B-mode ultrasound machine. Subclinical atherosclerosis was defined as mean cIMT > 0.9mm.

Results: MetS was found in 49 out of the 128 pts (38.3 %). Large waist circumference (abdominal obesity) was found in 72 out of the 128 pts (56.3%), low HDL – in 65 out the 128 pts (50.8%), elevated TGs – in 12 out the 128 pts (9.4%), high systolic BP – in 32 out of the 128 pts (25%). We divided pts into 3 groups: 1 – from 20 to 39 yrs, 2 – from 40 to 59 yrs, 3 – 60 yrs or more. MetS was found in the 1st group in 18,4%, in the 2nd group in 50%, 3rd group in 66,7%, $p=0,001$. We didn't find significant differences between DAS in three groups: 3,7 [2,6; 4,7] and 3,9 [3,1 5,2], 3,4 [2,7; 4,0] accordingly, $p=0,53$. Noted a significant increase of the cIMT from 1 up to 3 group: 0.68 [0.66; 0.75]mm, 0.76 [0.73; 0.83]mm, 0.86 [0.86; 0.93]mm ($p < 0,001$ for trend). The prevalence of subclinical carotid atherosclerosis (cIMT > 0.9mm) were in 26.5%, in 64.4% and in 100% accordingly, $p=0.01$. Significantly correlations were observed between cIMT and PsA duration ($R=0.18$, $p < 0.03$).

Conclusions: MetS was found in nearly 40% in pts with PsA. High frequency of a subclinical atherosclerosis and MetS were detected not only in pts with PsA of the senior age group, but also in pts young and middle age.

Keywords: Psoriatic arthritis, metabolic syndrome, subclinical atherosclerosis, autoimmune inflammation

N-acetyltransferase 2/NAT2 – regulator of lipid homeostasis: new/old player in metabolism of patients with ischaemic heart disease and metabolic syndrome

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Background and Aim: N-acetyltransferase 2, also known as NAT2, is an enzyme which in humans is encoded by the NAT2 gene. The aim of this study was to evaluate the relationships between NAT2/acetylator status (AS) polymorphism and lipid parameters (LP) of blood serum: total cholesterol (TC), triglycerides (TG), low density lipoproteins (LDL-C), high density (HDL-C), very low density (VLDL-C), atherogenic coefficient (AC), triglyceride coefficient (TGC), sum AC+TGC, product AC TGC in patients with ischaemic heart disease (IHD) and metabolic syndrome (MS).

Material and methods: One hundred-two men (mean age 47.83 ± 0.79 years) with stable IHD, MS were examined. The research program consisted general clinical examination, biochemical tests and instrumental methods. AS included markers: the degree of acetylation in the blood (DAB), the degree of total acetylation (DTA). For NAT2 phenotyping/AS (DAB, DTA) was used the “polymorphic” substrate – sulfadimezine. Sequential multivariate correlation analysis using the criteria Student-Fisher allowed to assess the associations of each individual parameter of AS: DAB, DTA and LP: TC, TG, LDL-C, HDL-C, VLDL-C, AC, TGC, sum of AC+TGC, product of AC TGC in tandem.

Results: Examination of the relationships between AS and LP could establish that the values of the variant, ≤ 10 th and > 90 th percentiles of DAB, DTA showed a significant strong direct/positive relationship ($p < 0.001$) to those of the variant, ≤ 10 th and > 90 th percentiles of TC, TG, LDL-C, HDL-C, VLDL-C, AC, TGC, sum of AC+TGC, product of AC TGC. A significant inverse/negative correlation ($p < 0.001$) was found between the values of ≤ 10 th percentile of DAB, DTA and those of > 90 th percentile of TC, TG, LDL-C, HDL-C, VLDL-C, AC, TGC, sum of AC+TGC, product of AC TGC, as well as between the values of > 90 th percentile of DAB, DTA and those of ≤ 10 th percentile of TC, TG, LDL-C, HDL-C, VLDL-C, AC, TGC, sum of AC+TGC, product of AC TGC.

Conclusion: The heterogeneity in the association was found between the values of ≤ 10 th percentile/ > 90 th percentile/variant of AS markers: DAB, DTA and LP: TC, TG, LDL-C, HDL-C, VLDL-C, AC, TGC, sum AC+TGC, product AC TGC. The genetic polymorphism of AS – the phenotypes of slow/fast/intermediate acetylators (three modal distribution) was stated. Knowledge of relationships between AS markers and LP may contribute to the formation of differentiated groups at risk for IHD and MS.

Dyslipidemia and type II diabetes mellitus risk

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Purpose: to assess risk of type II Diabetes Mellitus (DM) in European population of Novosibirsk at age 45-69 with dyslipidemia.

Methods and materials: In 2003-2005 within population screening 9360 subjects, including 4268 men (45,6%) and 5094 women (54,4%) at age 45-69 were investigated. Data of DM incidence in selected cohort were collected for 10 years from two sources: repeated screening of the same sample in 2006-2008 and database analysis of Novosibirsk city DM register for 2003-2014. Statistical analysis was performed with SPSS V-13. Association of dyslipidemia with DM incidence was assessed with multivariate and univariate Cox regression analysis.

Results: Hypertriglyceridemia (hyper-TG) prevalence in population sample with DM was 60%, three times more often in subjects with DM than without DM; 3 times more often in male sample – 69% and 23%, 2,7 times more often in female sample – 50% and 18%, $p < 0,001$. Frequency of HDL hypocholesterolemia (hypo HDL-C) in male and female subjects was 26,2%. In male frequency of hypo HDL-C is 2,3 times higher in subjects with DM, then without DM – 10,6% and 4,6%, $p < 0,001$, in female subjects – 2,2 times higher in DM subjects – 38,7% and 17,8%, $p < 0,001$.

Hyper-TG increased DM relative risk in 4,6 times (95% CI: 3,9; 5,2), $p < 0,001$, in men (OR=5,2; 95% CI: 4,2; 6,3), in women (OR=4,1; 95% CI: 3,4; 4,9). Hypo HDL-C increased DM risk in a less degree – in 2,7 times (95% CI: 2,3; 3,1), $p < 0,001$. According to univariate Cox regression analysis hyper-TG increased DM risk (OR=2,6; 95% CI: 2,2; 3,1), $p < 0,001$; hypo HDL-C (OR=2,5; 95% CI: 1,9; 3,0), $p < 0,001$,

Conclusion:

1. Hyper-TG prevalence in DM subjects at age 45-69 is 29,5%, hypo HDL-C -26,2%.
2. Hyper-TG and hypo HDL-C increase DM risk in subjects at age 45-69 in 2,5 and 2,6 times accordingly.

Keywords: diabetes mellitus, dyslipidemia, hypertriglyceridemia, HDL hypocholesterolemia

Epicardial adipose tissue thickness in patients with arterial hypertension and relation with metabolic parameters associated with cardiovascular risk

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Clinical and metabolic disorders associated with obesity are the main causes of development of cardiovascular syndrome.

Aim: to estimate the thickness of epicardial adipose tissue (EAT) in patients with arterial hypertension (AH) and to identify the relationship with metabolic parameters associated with cardiovascular risk.

Materials and methods: we examined 130 patients (male – 66; female 64; age 50,6±0,6 years) AH. Patients were divided into 2 groups depending on the level of total cholesterol (TC) in blood plasma: 1 – 64 patients with optimal ($\leq 5,0$; 4,5±0,7 mmol/l) cholesterol levels (control); 2 – 66 with high ($\geq 6,0$; 7,2±0,8 mmol/l) cholesterol levels. The measurement of EAT made on the apparatus Vivid 7, by modified parasternal projection. EAT was visualized as exonegative area, which was measured on the free wall of the right ventricle. The Protocol for laboratory investigations included evaluation of the following parameters: lipid profile (total cholesterol), triglycerides (TG), cholesterol of high density lipoproteins (HDL cholesterol), cholesterol of low density lipoproteins (LDL cholesterol), atherogenic coefficient (AC), carbohydrate metabolism (fasting glucose) and uric acid (UA). Evaluated circumference of waist (CW), calculation of body mass index (BMI).

Results: In the 1st group indicators epicardial fat was 5,4±0,9 mm, in the 2nd – 8,9±1,2 mm ($p=0,026$). Average blood glucose level in the 1st group was 4,2±0,8 mmol/l in the 2nd and 6,9±0,9 mmol/l ($p=0,027$). Analysis of lipid levels showed significant differences of mean values of TC, TG and LDL-C between groups (1st group – LDL-C to 2,6±0,3 mmol/l; TG – 1,4±0,2 mmol/l, KA – 3,8±0,1, UA – 280,3 ±0,02 mkmol/l). CW among the men was 100,4 ±4,4 cm, for women – 96,3±3,3 cm. Among 28 (43,3 %) people identified overweight (BMI = 30,3±2,2 kg/m²), 36 (56,7%) 1-2 grade obesity (BMI 38,9±2,1 kg/m²). In the 2nd group the lipid profile were significantly higher (LDL-C of 3,8±0,3 mmol/l; TG – 1,8±0,2 mmol/l, KA – 4,7±0,1, UA – 314±0,05 mkmol/l). CW among men was 108,4 ±2,4 cm, for women to 98,3±1,7 cm. Among the 17 (25,6 %) people identified overweight (BMI = 28,3±2,1 kg/m²), 49 (74,4%) 1-2 grade obesity (BMI of 38,4±2,4 kg/m²). In addition, in individuals with visceral obesity (CW=104,3±3,1 cm) in contrast to individuals with a uniform distribution of subcutaneous fat (CW=84,4±3,1 cm) were obtained reliable direct correlation between the thickness of EAT and metabolic parameters: TC, LDL ($r=0,71$; $p=0,001$), TG ($r=0,59$; $p=0,001$), CA ($r=0,69$; $p=0,001$) and blood glucose levels ($r=0,79$; $p=0,001$).

Conclusions: Thus the correlations between epicardial adipose tissue thickness and clinical and metabolic parameters (atherosclerotic, diabetogenic profile) may indicate the interaction of these factors that must be considered when assessing cardiovascular risk in patients with AH.

Keywords: arterial hypertension, obesity, metabolic syndrome, echocardiography

The clinical features of acute coronary syndrome in patients with diabetes mellitus subjected to PCI during hospitalization

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The aim of investigation was to reveal clinical – demographic characteristics of patients (pts) with non-ST-elevation acute coronary syndrome (NSTE-ACS) and diabetes mellitus (DM) subjected to PCI.

Methods. We observed 120 pts with NSTE-ACS, among them DM in 27 (23%) pts. Monitoring of patients continued 6-18 months.

Results. Among 27 pts with NSTE-ACS and DM prevailed aged group 60-69 years, 59% (16) males. Smoking was registered in 4 (15%) pts with NSTE-ACS and DM (less than in non-diabetic NSTE-ACS pts, $p = 0.002$). The following risk factors were observed: arterial hypertension – 93% (25) pts, $BMI \geq 25$ – 93% (25) pts, family history of cardiovascular disease – 19 (70%) pts (more frequent than in non-diabetic NSTE-ACS pts, $p = 0.002$). Previous myocardial infarction was in 37% (10) of pts, 10 pts (37%) had previous PCI. Aspirin was taken by 48% (13) of pts. Pts received oral hypoglycemic drugs (80.0%), insulin (20%). Most patients (70%) were hospitalized within 12 hours after the onset of ACS symptoms. Ischemic changes of ECG were determined in 56% (15) pts, predominated ST segment depression more than 0.5mm. The level of troponin T at admission >0.05 ng/ml was detected in 56% (15) pts. The level of glucose at admission was $9,3 \pm 0,7$ mmol/l (in pts without DM – $5,7 \pm 0.14$ mmol/l). Average LDL-CH level was 3.0 ± 0.2 mmol/l, $LDL \geq 1.8$ mmol/l was registered in 78% (21) of pts. All admitted pts received anticoagulants and dual antiplatelet therapy (aspirin in conjunction with either clopidogrel or ticagrelor), β -blockers, statins. In patients with NSTE-ACS and type 2 DM risk of adverse cardiovascular events during hospitalization (GRACE) was higher ($p = 0.038$) than in those without DM. Pts underwent coronary angiography, mainly by right transradial access (95%) within the first 48 hours (92%). Coronary stenosis $> 55\%$ revealed in 100% of patients, multivessel disease in 81% (22) pts, in 6 (22%) pts was determined stent stenosis de novo. One-vessel coronary disease was revealed in 7.5% of pts, two-vessel disease – 15.8% pts. Balloon angioplasty with stenting was performed in all pts, drug-eluting stents were implanted in 45% of pts. In 6 pts CABG was recommended. In pts with NSTE-ACS unstable angina was diagnosed in 60 pts, myocardial infarction was revealed in 60 pts. During hospitalization there were no lethal outcomes, one case of non-fatal ischemic stroke was observed on the 2-d day of hospitalization, in 2 pts was registered non-fatal myocardial infarction, in 1 patient – early postmyocardial angina. In 3 non-diabetic NSTE-ACS pts unstable angina was observed, in 2 pts – early postmyocardial angina. The development of combined end point (death from myocardial infarction, unstable angina, myocardial infarction) in pts with NSTE-ACS and DM was significantly earlier than in non-diabetic NSTE-ACS pts ($p < 0.008$). Thus, risk of cardiovascular events during hospitalization and observation (6-18 months) in pts with NSTE-ACS and DM was significantly higher than in non-diabetic NSTE-ACS pts. So, DM is considered to be an important risk factor of ischemic heart disease progression.

Keywords: acute coronary syndrome, diabetes mellitus, percutaneous coronary intervention (PCI), risk factors

A case of reversible diastolic dysfunction in patients with diabetes mellitus

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The patient V., women 59 years old, was admitted to the ICCU Moscow city hospital # 24 with symptoms of Acute heart failure (Killip 2 class). Echocardiography was urgently performed. Index of end diastolic volume of LA =44,3 ml/m², E/e' = 30, E/A=4,43, e'=0,04 m/s. Systolic function of non-dilated LV =47%. Systolic pressure of RV=44 mm Hg. IVC=22 mm and non collapsed during inspiration. There was mild fluid in pericardium. In blood test fasting glucose was 20,3 mmol/l. Troponin I was not increased. on ECG ST segment has no changes. The diagnostic search was based on data of HFpEF and restrictive cardiomyopathy. The patient was carried out examinations to exclude amyloidosis, sarcoidosis, hemochromatosis, systemic scleroderma, eosinophilic heart disease. All these conditions were excluded. Patient was treated by diuretics, ACE inhibitors, low-dosed selective BB and insulin therapy. Patients condition was improved: there was no oedema of fit, no short of breath. On echo, which was performed in 17 days later LV EF=53%, E/A=2,28, e'=0,07 m/s, E/e'=19,8. Fasting glucosac=6,4 mmol/l.

Diabetes mellitus is a common cause of heart failure with pEF. Also it is a one of cause of restrictive changes in myocardium. This case shows that glycemic status is very important part of pathogenesis of restrictive changes. Normalization of glycaemia can improve conditions in HF patients.

Keywords: Diabetes mellitus, Heart Failure, Diastolic Function, Restrictive Cardiomyopathy, Echocardiography

Features lipid profile in obesity, pre-diabetes and newly diagnosed type 2 diabetes

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Aim: To determine the nature of the changes and features of metabolic parameters influences on lipid profile among the patients with abnormal metabolic obesity, prediabetes and newly diagnosed type 2 diabetes mellitus (NDDM 2).

Material and Methods: This study enrolled volunteers aged 40 to 65, who were non-*smokers*, considered themselves healthy, and did not get any medical therapy. 65 of 200 examined individuals had impaired carbohydrate exchange (ICE): 16 – impaired fasting glucose, 23- impaired glucose tolerance, 26 – NDDM 2; 78 patients had varying degrees of obesity with signs of metabolic syndrome. The control group included 19 healthy volunteers with normal body mass index and without signs of metabolic abnormalities. In all contingents was investigated – fasting plasma glucose, C-peptide, insulin, with the expectation of HOMA-IR, total cholesterol (TC), cholesterol lipoprotein high and low density (HDL-C and LDL-C respectively) triglycerides (TG), ApoA1-, ApoB-lipoproteins (apo B) – a photometric methods, C-reactive protein (CRP) – immunoturbidimetric method, analyzer ADVIA 1650 (Siemens); HbA1c was measured using reference method (Bio-Rad Laboratories, USA). Statistical analysis was performed using the package of program STATISTICA 10 (StatSoft, USA).

Results: Along the insulin resistance there were found increased concentrations of total cholesterol, LDL-C by 1,2 times, Apo B by 1,5 times, TG by 2 times and CRP (1.7 and 2, 6 times respectively) according to the control in all groups of patients with obesity and ICE. Changes of the metabolism's parameters in obesity and ICE are the same type of character and are distinguished by the presence of hyperglycemia increase CRP by 1,5 time and greater severity of insulin resistance in the group with ICE. According to the results of correlation analysis the ties of moderate strength were established between the markers of insulin resistance, the concentration of CRP and TG, Apo B (straight), HDL-C, Apo-A (reverse). Moreover among the patients with ICE was revealed a direct link between fasting plasma glucose and concentration of total cholesterol, triglycerides, Apo B.

Conclusion: Violations of lipid metabolism in metabolic abnormal obesity, pre-diabetes and newly diagnosed type 2 diabetes are of the same type of character accompanied by an increase of total cholesterol, LDL-C, TG and Apo-B and both are associated with markers of insulin resistance and subclinical inflammation. The presence of hyperglycemia further contributes to the formation of dyslipidemia in the early stages of type 2 diabetes.

Keywords: lipid metabolism, obesity, prediabetes, newly diagnosed type 2 diabetes

Role of atherogenetic, metabolic, and psychic factors in patients with colorectal adenomas

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Introduction and aim: Proinflammatory states of the large bowel have a multifaced etiology, involving metabolism, atherogenesis, and also psychic conditions. Inflammation is regulated at many different levels including anxiety and depression, and is tightly associated with early pro-atherogenetic alterations and metabolic dysregulation. Inflammation is also a key factor for the development of colorectal cancer, and its main precancerous lesions, adenomas. This study aims at investigating the association among pro-atherogenetic factors, metabolic status, and psychic assessment, with the presence of colorectal adenomas.

Materials and methods: We designed a case-control observational study on patients undergoing colonoscopy. For each subject waist and hip circumferences, BMI, arterial pressure, fasten serum glycaemia, and a complete medical history with drug assumptions were collected. The subjects, depending on colonoscopy outcomes, may presented no lesion or various types of lesions including adenomas. Patients were evaluated blindly for the outcome of colonoscopy, with the following procedures: 1) carotid IMT using QIMT®-Esaote software (MyLab25-Gold ultrasound platform); 2) brachial-FMD (endothelium dependent dilation after 3 minutes of ischemia induced by a sphigmomanometer in the non-dominant arm, evaluating post-ischemic arterial dilation at minute 1 and 3 after cuff release); 3) psychometric test (Hospital Anxiety and Depression Scale, HADS). Proper statistical tests have been applied in order to compare differences between the two groups

Results: Eighteen patients had a complete assessment so far. Ten patients (M/F 6/4) had at least one adenoma at colonoscopy. Data analysis showed the following significant differences between groups: 1) HADS score for depression, mean±SD: adenoma vs no-adenoma, 4.9±3,2 vs 1.7±1,8, respectively, p=0.026; 2) Carotid QIMT median value in micrometers: adenoma vs no-adenoma, 793 vs 638, respectively; percentiles 25%: 724 vs 588, respectively; percentiles 75%: 1106 vs 769, respectively; p=0.037; 3) Body weight in kilograms, mean±SD: adenoma vs no-adenoma 66.4±8.7 vs 80.9±15.3, respectively, p=0.03; 4) Waist circumference in centimeters, mean±SD: adenoma vs no-adenoma 105.2±13.4 vs 89.5±4.7, respectively, p=0.009). An inverse correlation between patient age and HADS anxiety scores (Pearson index -0.477, p<0.05), and a direct correlation between higher values for fasten serum glycemia and carotid QIMT (Pearson index 0.48, p<0.05) were also observed.

Discussion and conclusions: Depression and not anxiety seems to be a factor characterizing patients with adenomas. The presence of higher values at the QIMT examination in the adenoma group may be a bridge between early signs of atherosclerosis and colorectal precancerous lesions. The association between waist circumference, body weight, and the presence of adenomas confirms evidence showing strong connections between metabolism and the risk of developing colorectal cancer. In conclusion, our study seems to provide interesting insights into the complex relation between systemic inflammation, evaluated through a multidisciplinary approach and the development of colorectal precancerous lesions.

Keywords: atherosclerosis, depression, colorectal adenoma

High Triglycerides, Low HDL Cholesterol and a Low LDL Cholesterol per Apolipoprotein B Ratio Predict Incident Diabetes in Patients with Established Coronary Artery Disease

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Patients with type 2 diabetes mellitus (T2DM) exhibit a typical pattern of dyslipidemia with low HDL cholesterol, high triglycerides and a low LDL cholesterol per apolipoprotein B (LDL-C/apoB) ratio reflecting small LDL particles. We hypothesized that high triglycerides, low HDL cholesterol and a low LDL-C/apoB ratio predict incident T2DM among non-diabetic patients with established coronary artery disease (CAD).

We enrolled 655 non-diabetic patients with angiographically proven stable CAD. Prospectively, the incidence of T2DM was recorded over a mean follow-up period of 6.1 ± 3.7 years. Diabetes was diagnosed according to ADA criteria.

From our non-diabetic coronary patients, 358 (54.7%) at baseline had normal fasting glucose (NFG) <100 mg/dl, and 297 (45.3%) had impaired fasting glucose (IFG) ≥ 100 mg/dl. During follow-up, T2DM was newly diagnosed in 17.4% of our patients. Baseline IFG compared to NFG was associated with a strongly increased risk of T2DM (26.6% vs. 9.8%; adjusted OR 3.34 [2.17-5.16]; $p < 0.001$). Low HDL cholesterol, high triglycerides, and a low LDL-C/apoB ratio after multivariate adjustment including fasting glucose significantly predicted incident diabetes in the total study cohort (OR 0.65 [0.49-0.86]; $p = 0.003$, 1.40 [1.13-1.74]; $p = 0.002$ and 0.54 [0.41-0.71]; $p < 0.001$, respectively) and also when we separately analyzed patients with IFG (OR 0.67 [0.46-0.97]; $p = 0.032$, 1.42 [1.03-1.96]; $p = 0.032$ and 0.56 [0.39-0.79]; $p = 0.001$, respectively) and NFG (OR 0.62 [0.40-0.96]; $p = 0.034$, 1.38 [1.03-1.86]; $p = 0.033$ and 0.49 [0.32-0.76]; $p = 0.001$, respectively).

We conclude that among patients with angiographically proven stable CAD the incidence of diabetes is high, particularly among those with IFG. Importantly, high triglycerides, low HDL cholesterol and a low LDL-C/apoB ratio significantly predict incident diabetes independently from baseline glycemia.

Keywords: dyslipidemia, type 2 diabetes mellitus, coronary artery disease, risk prediction

Remnant Cholesterol Predicts Cardiovascular Event Risk in Patients with Type 2 Diabetes Independently from The Baseline Coronary Artery Disease State

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Remnant cholesterol, which is calculated as total cholesterol minus LDL cholesterol minus HDL cholesterol recently has attracted interest as a marker of cardiovascular event risk. We aimed at investigating the power of remnant cholesterol to predict cardiovascular events in patients with type 2 diabetes (T2DM) as well as in non-diabetic patients in whom the baseline coronary artery disease (CAD) state was verified angiographically.

We enrolled 1774 consecutive patients undergoing coronary angiography for the evaluation of established or suspected stable CAD. Prospectively, cardiovascular events were recorded over a mean follow-up period of 7.5 ± 2.9 years. Diabetes was diagnosed according to ADA criteria.

During follow-up, 32.5% of our patients suffered cardiovascular events; the event rate was significantly higher in patients with T2DM (n=513) than in nondiabetic subjects (40.5 vs. 29.3%; $p < 0.001$). Remnant cholesterol significantly predicted cardiovascular events in the total study population, among patients with T2DM, as well as among non-diabetic subjects both univariately (HR 1.18 [1.10-1.27], $p < 0.001$, 1.20 [1.05-1.38], $p = 0.008$ and 1.19 [1.09-1.30], $p < 0.001$, respectively) and after multivariate adjustment including presence as well as extent of baseline CAD (HR 1.15 [1.07-1.24], $p < 0.001$, 1.21 [1.05-1.39], $p = 0.009$ and 1.15 [1.05-1.25], $p = 0.002$, respectively).

From our data we conclude that remnant cholesterol predicts cardiovascular event risk in patients with type 2 diabetes as well as in non-diabetic patients independently from the baseline CAD state.

Keywords: remnant cholesterol, cardiovascular disease, biomarker, risk prediction, type 2 diabetes mellitus

Significance of the body weight in endothelial dysfunction changes and systemic inflammation progression in coronary artery disease patients

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Endothelial dysfunction is regarded as a key event in the development and progression of atherosclerosis. It is suggested that dysfunction of the endothelium in large and medium-sized arteries plays a central role in atherogenesis. A recent study has documented the presence of an endothelial dysfunction in small resistance vessels of obese subjects, but it has not yet been ascertained whether an endothelial dysfunction of a large conduit artery is detectable in uncomplicated obesity and, in particular, whether abdominal fat plays a role in determining the degree of this early sign of vascular involvement.

Our aims was to investigate the influence of body weight values on the main markers of endothelial dysfunction (ED) and systemic inflammation (C-reactive protein (CRP), interleukin-6 (IL-6)) in patients with coronary artery disease (CAD).

Material and methods: The study involved 58 patients with coronary artery disease in the form of stable exertional angina II functional class, mean age – 54.5 ± 3.2 years, 25 of them women. Depending on body mass index (BMI) identified 2 groups: Group 1 – 26 patients with a BMI of 28.4 ± 1.3 kg/m² group – 32 patients with a BMI of 33.6 ± 2.5 kg/m².

The following anthropometric variables were evaluated in all subjects: weight, height and BMI. Serum total cholesterol, triglycerides and HDL cholesterol were measured. LDL cholesterol was calculated by using Friedwald formula. Using high resolution vascular ultrasound, we measured brachial artery responses to reactive hyperemia (with increased flow causing endothelium-dependent dilatation) and sublingual nitroglycerin (causing endothelium-independent dilatation). Were analyzed indicators of endothelium-dependent vasodilatation ((EDVD), an increase of $\geq 10\%$ of the original diameter during reactive hyperemia), endothelium-independent vasodilatation ((ENVD), $\geq 20\%$ increase in the sample with nitroglycerin) Also we analyzed results of quantitative determination of C-reactive protein (CRP), interleukin-6 (IL-6).

Results: At rest, the diameter of the brachial artery was 0.48 ± 0.02 cm patients of group 1 and 0.59 ± 0.02 cm patients in group 2. When EDVD reactive hyperemia increased by 15% in patients of group 1 and remained virtually unchanged in the 2nd group (respectively: 0.55 ± 0.02 cm; $p < 0.05$; 0.59 ± 0.03 cm; $p > 0.05$). The diameter of the brachial artery after 5 min after administration of nitroglycerin in patients in Group 1 increased by 19.4% and in the 2nd only 9.7% (respectively: 0.56 ± 0.02 cm ($p < 0.05$); 0.01 cm ± 0.63 ($p > 0.05$). Indicators of IL-6 had no statistical difference in the two groups (respectively: 6.85 ± 0.27 pg/ml; 6.91 ± 0.33 pg/ml control 6.54 ± 0.18 pg/ml). The level of CRP slightly increased in patients of group 1 was significantly increased in patients in group 2 (respectively: 2.68 ± 0.16 mg/ml ($p > 0.05$); 4.82 ± 0.14 mg/ml ($p < 0.05$); control 2.12 ± 0.06 mg/ml).

Conclusions: In patients with stable exertional angina II functional class with increasing BMI occurs inhibition of endothelial function and activation of systemic inflammation, manifested by decrease EDVD and ENVD and rising CRP, which adversely affects on the course of coronary artery disease and induces the development of vascular complications.

This risk appears to stem from multiple abnormalities in adipose tissue function leading to a chronic inflammatory state and to dysregulation of the endocrine and paracrine actions of adipocyte-derived factors. These, in turn, disrupt vascular homeostasis by causing an imbalance between the NO pathway and the endothelin 1 system, with impaired insulin-stimulated endothelium-dependent vasodilation.

Keywords: endothelial dysfunction, systemic inflammation, coronary artery disease, endothelium-dependent vasodilatation, endothelium-independent vasodilatation

Occurrence of overweight and obesity among doctors and nurses

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Overweight and obesity are risk factors for cardiovascular disease, cancer pathology, diabetes. According to the UN report, in 2015, Russia ranks 19th in the world in the number of people with overweight and obesity.

Objective: identification of a number of anthropometric parameters of doctors and nurses by profession most knowledgeable about the principles of a balanced diet and healthy lifestyle.

Material and methods: We observed 36 nurses at the age of $41,3 \pm 13,8$ years and 30 doctors aged $46,7 \pm 10,7$ years. All of the subjects were women. Anthropometry was performed using the monitor OMRONBF 508 body composition and measuring waist measuring tape.

Results: No differences between the groups of doctors and nurses have been identified. About a third of the subjects in both groups were detected exceeding the permissible standards for parameters such as the percentage of body fat and body mass index. Waist circumference greater than the allowable limit by more than half of the surveyed (52.9% of nurses and 56.7% of physicians). The percentage of visceral fat was increased to a lesser extent (from 22.0% to 16.7% of nurses and doctors) that are likely to be associated with women patients. According to the body mass index, obesity was diagnosed in 25% of nurses and 30% of doctors and overweight – in 30.6% of nurses and 23.3% of physicians.

Conclusion: Doctors and nurses revealed a high incidence of overweight and obesity, as well as exceeding the permissible norms of waist circumference, body fat and visceral fat in the body. These changes are likely to be associated with high-intensity health workers, diet disorders, stress.

Keywords: overweight, obesity, risk factors, doctors, nurses

Insulin Downregulates Apolipoprotein A-I Gene Expression in Human Hepatoma Cell Line HepG2

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Apolipoprotein A-I (apoA-I) plays a key role in reversed cholesterol transport as a main part of HDL. ApoA-I has a well established role as an anti-atherogenic, anti-inflammatory and anti-thrombotic agent. Liver is the main site of apoA-I production and so the regulation of apoA-I expression and secretion in the liver is crucial for atheroprotection. We have examined the regulation of apoA-I expression by insulin in human hepatoma cell line HepG2.

FOXO1 and FOXA2 are the well-characterized transcription factors that are inactivated by insulin. FOXA2 is known to activate apoA-I expression by binding to site B of its hepatic enhancer (HE). Administration of 100 nM of insulin resulted in apoA-I expression and secretion downregulation after 48 hours of incubation. siRNA against FOXO1 or FOXA2 abrogated the effect of insulin. We transfected HepG2 cells with plasmids bearing luciferase gene under control of intact HE or HE with mutated site B or C. Mutation either site reversed insulin-dependant downregulation of apoA-I expression. DNA-affinity precipitation and ChIP confirmed that FOXO1 indeed bound site B of HE. LXR α and LXR β are known to both participate in insulin signaling and interact with site C of HE to lower apoA-I expression. Because mutation of site C also reversed insulin-dependant decrease in apoA-I gene activity, we treated HepG2 cells with LXRs ligand TO901317. TO901317 abolished insulin-driven inhibition of apoA-I transcription. siRNA against LXR α and LXR β displayed the same effect.

To see whether LXRs acted in concert with FOXO1 and FOXA2 or independently, we treated cells transfected with siRNA against one of four factors with TO901317. Interestingly, siRNA against FOXA2 and LXR α , yet not FOXO1 or LXR β appeared to abrogate TO901317-driven downregulation of apoA-I gene activity. ChIP revealed that insulin treatment of HepG2 cells resulted in detachment of FOXO1 and LXR β from HE, yet failed to trigger the departure of either LXR α or FOXA2. In agreement with ChIP results, insulin caused nuclear exit of FOXO1 and LXR β . We employed immunoprecipitation to see if any of the factors formed complexes with each other. IP showed that FOXA2 formed the complex with LXR α while FOXO1 bound LXR β in HepG2 cells.

Here we have shown that high doses of insulin downregulate apoA-I expression and secretion in HepG2 cells. It was shown for the first time that FOXO1 binds to site B of apoA-I HE and forms a complex with LXR β . Insulin disrupts the interaction between FOXO1/LXR β and HE and causes the nuclear-cytoplasmic translocation of the complex. On the other hand, FOXA2 forms a complex with LXR α , and this interaction is necessary for both ligand-dependant and independent downregulation of apoA-I expression by LXR α .

Keywords: Apolipoprotein A-I, Insulin, Liver X Receptor, Forkhead box O1, Forkhead box A2

Neuroprotective effect of liraglutide in patients with metabolic syndrome

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Introduction: Metabolic syndrome (MS) is one of the leading problems of contemporary medicine. Chronic brain ischemia is a very frequent and serious MS complication. Currently new class of antidiabetic medications, glucagon-like peptide-1 receptor agonists (GLP-1Ra), appeared on pharmacological market. They have proved not only to lower blood glucose level, but also to decrease arterial blood pressure and to improve lipid metabolism, thus to influence all the MS components. GLP-1Ra have demonstrated cardioprotective effect. Specific receptors are widely presented in central nervous system and in endothelium, therefore these medications might also have neuroprotective effect.

Aim: To investigate potential neuroprotective effect of GLP-1Ra in MS patients.

Materials and methods: Patients with MS aged 40 to 75 (n=40) with unsatisfactory glucose control on metformin monotherapy were included in the study. Metformin dose was titrated for 3 months, afterwards patients were divided into group 1 (n=30) (those who reached target HbA1c level and continued to receive metformin monotherapy for 6 months more), and group 2 (n=10) (those who did not reach target HbA1c level and were administered liraglutide, GLP-1Ra, in addition to metformin, for 6 months more). At baseline and every 3 months following parameters were assessed: von Willebrand factor (vWF) activity, endothelin-1, tissue plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1) as endothelial dysfunction markers and neuron-specific enolase (NSE), S100 protein as neuroglial damage markers.

Results: Glycemic control improvement resulted in decrease of NSE, tPA, PAI-1, endothelin-1 in 3 months in group 2 (Δ NSE 11.68 (7.61;22.45) μ g/L, Δ tPA 0.15 (0.02;1.48) ng/mL, Δ PAI-1 23.4 (20.4;37.9) ng/mL, Δ endothelin-1 1.105 (1.05;1.23) pmol/L) and in group 1 (13.7 (6.6;17.03) μ g/L, 0.56 (0.29;1.24) ng/mL, 24.0 (3.09;55.7) ng/mL, 0.433 (0.257;0.671) pmol/L, respectively), $p > 0.05$. Liraglutide administration additionally decreased these factors in group 2, comparing to group 1, with similar glucose level. Total lowering (Δ) of NSE during 9 months of observation was 36.33 (27.65;38.76) and 16.33 (11.59;23.7) μ g/L in group 2 and 1, respectively, Δ tPA 3.35 (3.03;4.0) and 0.85 (0.56;1.42) ng/mL, Δ PAI-1 77.16 (66.35;109.2) and 46.45 (10.2;70.1) ng/mL, Δ endothelin-1 2.92 (1.858;3.087) and 0.58 (0.454;1.14) pmol/L, $p < 0.05$.

VWF activity level decreased significantly only in group 1 in 3 months (Δ 18.2 (1.65;21.0)%). Administration of liraglutide resulted in beneficial lowering of vWF activity and its total reduction (Δ) after 9 months was 50.8 (27.55;77.2;) and 30.7 (25.6;38.1)% in groups 2 and 1, respectively, $p < 0.05$.

S100 level decreased in groups 2 and 1 in 3 months for 30.7 (28.8;167.0) and 87.7 (14.9;112.0) ng/L, respectively, but liraglutide did not cause beneficial reduction of S100 after 9 months (Δ 85.38 (74.75;181.5) and 124.05 (104.65;169.15) ng/L in groups 2 and 1, respectively, $p > 0.05$).

Conclusion: Glycemic control improvement has neuroprotective effect which results in amelioration of endothelial dysfunction and neuroglial damage. Liraglutide has an independent neuroprotective effect, not related to glucose-lowering action.

Keywords: metabolic syndrome, glucagon-like peptide-1 receptor agonist, liraglutide, neuroprotection, endothelial dysfunction

The indices of lipid and carbohydrate metabolism and local fat depot in patients with metabolic syndrome

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Objective: to study the relationship of lipid profile and carbohydrate metabolism and local fat depots in metabolic syndrome.

Materials and methods: 803 patients with metabolic syndrome were investigated in age 60,28 (53;67) years, 299 men and 504 women. Anthropometric, biochemical and ultrasound investigations were provided. Metabolic syndrome was diagnosed in the presence of central obesity (waist circumference >80 cm in women and >94 cm in men) and two additional criteria from: arterial hypertension, triglycerides (TG) more than 1,7 mmol/l, LDL greater than 3,0 mmol/l, HDL in women <1,2 mmol/l, in men <1,0 mmol/l, fasting plasma glucose level more than 6,1 mmol/l or impaired glucose tolerance. The following local fat depot were determined by ultrasound: the epicardial fat thickness, the intraabdominal fat thickness (IFT), NAFLD, steatosis of the pancreas. Statistical analysis was performed using the software package Statistica 6.0.

Results: Waist circumference was 107,2 (100;113) cm in men, 107,7 (100; 114) cm in women. Arterial hypertension was present in all patients. Disorders of carbohydrate metabolism were diagnosed in 433 patients (54%): diabetes mellitus type 2 – in 290 people, impaired glucose tolerance – in 69, impaired fasting glucose – in 74 patients. The level of triglycerides was 2,03 (1,29;2,38) mmol/l, LDL – 3,7 (2,9; 4,4) mmol/l, HDL 1,07 (0,89;1,22) mmol/l and 1,28 (1,02;1,49) mmol/l in men and women respectively. IFT was significantly higher in men: 58,5 (47,4; 67) mm versus 50,9 (39;60) mm in women ($p=0,000008$), the epicardial fat thickness was higher in women: 10 (9;11) mm versus 9,04 (8;10) mm ($p=0,003$). The level of TG shows the connection with the liver size ($r=0,22$; $p=0,000001$), the levels of AST and ALT ($r=0,12$; $p=0,002$ and $r=0,19$; $p=0,000001$, respectively), with the size of the head of pancreas ($r=0,14$; $p=0,002$) and CRP level ($r=0,32$; $p=0,003$). HDL showed negative correlation with ultrasound data in the liver size and pancreas head size ($r= -0,13$; $p=0,01$ and $r= -0,14$; $p=0,001$, respectively). The presence of carbohydrate metabolism disorders were associated with fatty infiltration of the liver and pancreas ($r=0,12$; $p=0,003$ and $r=0,13$; $p=0,00008$, respectively), as well as epicardial fat thickness ($r=0,16$; $p=0,025$) and IFT ($r=0,2$; $p=0,0005$).

Conclusion: Thus, hypertriglyceridemia and reduced HDL play the greatest role in the formation of NAFLD, and steatosis of the pancreas in metabolic syndrome. Disorders of carbohydrate metabolism, as a consequence of insulinresistance, are associated with epicardial and intraabdominal obesity in metabolic syndrome.

Keywords: lipid metabolism, carbohydrate metabolism, local fat depot, metabolic syndrome

Physiological changes of adipokines during the menstrual cycle

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Context: The cyclical effects of hormones during the menstrual cycle (MC) are responsible for driving ovulation. The information about roles of adipokines within the scope of MC are not definite. Leptin plays a role in sexual function and regulating the onset of puberty. Thin girls often fail to ovulate or release an egg from an ovary during menstruation cycles. Leptin also acts on specific receptors in the hypothalamus to inhibit appetite. Levels of leptin are increased in women suffering from premenstrual syndrome.

Objective: The aim of our study was to describe physiological changes of selected steroids and adipokines at healthy women during the MC.

Methods: Twenty-seven women with regular menstrual cycles were included in the study. Each sample was collected in cooled EDTA tubes, centrifuged at 2000 rpm in a refrigerated centrifuge, and stored at -80°C . For all samples we measured luteinizing hormone, follicularstimulating hormone, sex hormone-binding globulin, testosterone, dehydroepiandrosterone (DHEA), estradiol, 7α -DHEA, 7β -DHEA, 7-oxoDHEA, 17-hydroxyprogesterone, progesterone, cortisol, adrenocorticotrophic hormone by RIA and IRMA. Levels in plasma of hormones associated with food intake (c-peptide, ghreline, GIP, GLP, GLP-1, glucagon, insulin, leptin, PAI-1, resistin and visfatin) were measured using magnetic bead-based multiple assays (x-MAP technology, Luminex Corporation). Two kits were used: the 10-plex Bio-Plex Pro Human Diabetes assay and the 2-plex Bio-Plex Pro Human Adiponectin and Adipsin assay (both Bio-Rad Laboratories).

Patient(s): Twenty-seven women with regular menstrual cycles (cycle length 28 ± 2 days) were included in the study. The average age of the women was 31.8 ± 3.56 , and average BMI 22.9 ± 2.8 . The women used no hormonal contraceptives or other medicines influencing the production of steroid hormones, and were non-smokers. Intervention(s): Fasting blood samples were taken in the morning between 7 and 8 am. The first sampling was done at the start of the menstrual cycle (1st or 2nd day). Subsequent samples were taken at regular intervals every three days, for a total of 10 samples taken during the study.

Results: Classical changes in gonadotropins, estrogens and progesterone during the menstrual cycle are accompanied by less striking but significant changes in 17-hydroxyprogesterone and testosterone. No significant changes show dehydroepiandrosterone and its 7-oxygenated metabolites. Adipokines show a tendency to increase during ovulation, while ghrelin and resistin decrease. There is also a remarkable association of sex hormone binding globuline on the day of the cycle.

Conclusions: Our results demonstrate that changes to adipokines during the menstrual cycle are not substantial. Differing leptin levels are characteristic for premenstrual syndrome. Precise descriptions of physiological changes in healthy women are important in helping us understand the significance of the changes accompanying various pathological states.

Acknowledgement: The project was supported by grant GAUK 1254314.

Keywords: adipokines, menstrual cycle, obesity

Adiponectin modulates apolipoprotein production in THP-1 macrophages

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The aim: to evaluate the effects of adiponectin on production of apolipoproteins A-1 and E by human THP-1 macrophages.

Methods: PMA differentiated human leukemia THP-1 macrophages (3 and 5 days of differentiation) incubated for 24 h with 10 mg/ml adiponectin, 10 mg/ml bovine albumin, 10 ng/ml TNF α or RPMI in serum free media. Apolipoproteins gene expression level was determined by RT-PCR, secretion of these proteins was estimated by ELISA and immunodot.

Results: Adiponectin didn't change the expression levels of apo A-1 and apo E, although TNF α stimulated the former. The expression level of ABCA-1, the "partner" of apoA-1, increased under the impact of adiponectin. Adiponectin stimulated the apo A-1 secretion and inhibited secretion of apo E.

Conclusions: Adiponectin modulates the apolipoproteins A-1 and E secretion by human macrophages. This effect in addition to ABCA-1 stimulation can participate in the antiatherogenic properties of adiponectin.

Keywords: adiponectin, macrophages, apolipoproteins

Efficacy and Safety of Fenofibrate in the Treatment of Dyslipidemia in Patients with Metabolic Syndrome Associated with Non-alcoholic Fatty Liver Disease

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Background: Metabolic syndrome (MS) is known to present a complex of metabolic, hormonal and clinical disorders recognized to be a risk factors for the development of cardiovascular diseases. One of the main objectives of the treatment of MS is correction of lipid disorders. Typical pattern of dyslipidemia in patient with MS includes increased triglycerides (TG), decreased high-density lipoprotein cholesterol (HDL-C), increased low density lipoprotein cholesterol (LDL-C), increase of small dense LDL particles serum levels. This pattern of dyslipidemia is known to have a good responsiveness to fibrates. MS is often associated with non-alcoholic fatty liver disease (NAFLD). Lipid-lowering agents, first of all statins, but also fibrates, in some cases, may exert hepatotoxicity. In this regard, NAFLD patients receiving antihyperlipidemic agents present a cohort requiring the most careful monitoring of liver function.

Objective: To study the effectiveness and safety of fenofibrate in the correction of dyslipidemia in patients with MS associated with NAFLD.

Material and methods: 19 women with MS associated with NAFLD were included in the study. Standard lipid panel (total cholesterol, LDL-C, HDL-C, TG), transaminases (ALAT and ASAT) and alkaline phosphatase (AP) serum level were determined by means of biochemical analyzer "COBAS" INTEGRA 400 Plus. Diagnosis of NAFLD were based on clinical, laboratory and ultrasound criteria. All patients received standard baseline treatment according to existing guidelines. For correction of dyslipidemia all patients received micronized fenofibrate ("Traykor", Abbott, USA) in daily dose of 145 mg. No other lipid-lowering agents had been taken within 3 months prior to inclusion to the study and during the entire period of observation. Laboratory test had been made three times: before the beginning of fenofibrate treatment, in 4 weeks and in 3 months after starting fenofibrate intake.

Results: Fenofibrate exerted a positive effect on lipid profile: achieving the target level of TG (all patients at month 3) and HDL-C (84.2% of patients at month 3). All patients had shown also a clear downward trend of total cholesterol and LDL-C levels. No one case of clinically significant (3 times higher than upper normal limit) ALAT, ASAT or AP increase was revealed during the observation period. Control examination in 3 months after the beginning of treatment in a comparative analysis with baseline data had not reveal any one patient having significant dynamics nor for the liver size, or for its parenchyma ultrasound characteristics.

Conclusions: Fenofibrate in 145 mg daily dose after 3 months of treatment leads to a modification of serum lipids spectrum allowing achieving target levels of TG and HDL-cholesterol in the vast majority of patients with MS associated with NAFLD and does not cause hepatotoxic or other clinically significant side effects.

Keywords: fenofibrate, dyslipidemia, metabolic syndrome, non-alcoholic fatty liver disease

Lipoprotein (a) in dyslipidemic subjects: Association with haemostatic markers of endothelial dysfunction, markers of insulin resistance, metabolic syndrome, and IMT.

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Lipoprotein (a) [Lp(a)] is an LDL-like particle that contains an apolipoprotein B 100 molecule covalently bound to a plasminogen-like glycoprotein, apolipoprotein (a) [apo(a)]. Epidemiological evidence supports a direct and causal association between Lp(a) levels and coronary risk. On the contrary, prospective findings demonstrate inverse association of Lp(a) levels with risk of type 2 diabetes [T2D]. The potential reason for an inverse association between Lp(a) and incident T2D are unknown. Some human and animal studies suggest an effect of insulin in reducing Lp(a) levels. Thus Lp(a) might be another lipoprotein, that is associated with metabolic syndrome characterized by insulin resistance. Furthermore, due to the high homology between apo(a) and plasminogen, Lp(a) may potentially interfere with fibrinolysis and increase the risk of thrombosis.

The aim of our study was to evaluate: 1) the association of Lp(a) with haemostatic markers of endothelial dysfunction, 2) the association with indicators of insulin resistance and metabolic syndrome (MS), and 3) impact of high levels of Lp(a) ($\geq 0.5\text{g/l}$) on IMT in dyslipidemic subjects.

Plasma levels of Lp(a), fasting glucose, homeostasis model assessment (HOMA), C-peptide, proinsulin, fibrinogen, vWF, t-PA, PAI-I, and other conventional risk factors for atherosclerosis were assessed in 607 (295 males/312 females) dyslipidemic subjects. Exclusion criteria were hypolipidemic therapy in the last 6 weeks, presence of atherosclerotic cardiovascular disease and all causes of secondary dyslipidemia, including diabetes mellitus. IMT was evaluated in 369 (61%) subjects.

In the whole group, Lp(a) levels correlated positively with LDL-C, HDL-C, ApoB, and inversely with TAG, AIP, insulin, HOMA, BMI, and the number of metabolic syndrome components ($p < 0.05$ for all). Subjects with MS had significantly lower levels of Lp(a) in comparison with those without MS ($p < 0.001$). IMT in subjects with Lp(a) $\geq 0.5\text{g/l}$ was significantly higher than in those with Lp(a) $< 0.5\text{g/l}$ after adjustment for age, sex, BMI, TC, SBP, and smoking ($p < 0.05$).

Conclusion: Higher IMT in subjects with Lp(a) $\geq 0.5\text{g/l}$ supports proatherogenic role of this LP. Lp(a) concentrations did not correlate with haemostatic endothelial markers. Inverse association of Lp(a) with markers of insulin resistance and lower levels of Lp(a) in subjects with metabolic syndrome suggests that insulin resistance might be one of the factors influencing Lp(a) levels in T2D.

Keywords: lipoprotein (a), metabolic syndrome, lipids, haemostatic endothelial markers, IMT

The role of individual triglycerides in the pathology of coronary artery disease

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Coronary artery disease is the leading cause of death as compared to other cardiovascular diseases. Many scientists are inclined to believe that high cholesterol and changes in main components of the lipid profile are not the only cause and consequence of the pathology. Characteristics of the triglyceride species composition are also of great importance.

Oleic and palmitic triglycerides make up more than 90 per cent of all VLDL. Oleic fatty acid is esterified at an sn-2 position in oleic triglycerides; palmitic fatty acid is esterified at the same position in palmitic triglycerides.

The purpose of our research has been to study characteristics of the triglyceride species composition in patients with coronary artery disease.

Our study has been conducted on 146 conditionally healthy persons at an average age of 49,87±6,5 and 153 persons with CAD at an average age of 60,59±9,5.

Plasma triglyceride levels were assessed by HPLC-MS. Separation was carried out by high-performance DIONEX Ultimate 3000 liquid chromatography system on a Reprosil-PurC18-AQ 3µm column, 150×4.6 mm, by applying a linear gradient (acetonitrile/acetone). Detection was performed using ABSCIEX QTRAP 5500 mass spectrometer. The mass spectrometer was operating in positive ion mode. In this study, we applied atmospheric pressure chemical ionization (APCI).

The present research showed a statistically significant difference in levels of oleoyl-oleoyl-oleate (3,269 mM/L in conditionally healthy persons compared to 2,462 mM/L in persons with coronary artery disease ($p \leq 0.001$)), and oleoyl-oleoyl-palmitate (4,032 mM/L compared to 3,525 mM/L ($p \leq 0.05$) respectively).

The figures presented above show that persons with coronary artery disease have a reduced concentration of oleic triglycerides. However, oleic triglycerides are energetically more favourable, for they can be faster and easier hydrolyzed by enzymes whereas palmitic triglycerides have a low rate of hydrolysis and tend to be involved in the atherosclerotic process.

Thus, the data obtained lead to the conclusion that there is a disorder in the triglyceride species composition in patients with coronary artery disease.

Keywords: triglycerides, coronary artery disease, HPLC-MS, palmitic fatty acid, oleic fatty acid

Gene variants determine parameters of metabolic syndrome in children after intensive regime change

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Objectives: The study was aimed to determine whether there is a relationship between common *FTO* (rs17817449) and *MC4R* (rs17782313) gene variants and body mass reduction or weight loss after one month lifestyle intervention in overweight/obese children.

Design and Methods: We have genotyped 357 unrelated non-diabetic Czech children (age 13.7 ± 4.9 years, average BMI at baseline 30.8 ± 4.6 kg/m²). Before and after 4 weeks of lifestyle intervention (comprising a reduction of energy intake to age matched optimum and a supervised exercise program consisting of 5 exercise units per day, 50 min each), biochemical and anthropometrical measurements were performed.

Results: The mean weight loss achieved was 6.2 ± 2.1 kg ($P < 0.001$). Significant associations between BMI decrease and *FTO* and *MC4R* variants were found. Carriers of the *FTO* GG genotype and/or *MC4R* CC genotype lost significantly more body weight in comparison to the noncarriers ($P < 0.0009$ for BMI and $P < 0.002$ for body weight). The differences remain significant after adjustment for sex age and baseline values ($P = 0.004$ for BMI and $P = 0.01$ for body weight).

Conclusions: *FTO* and *MC4R* gene variants modify the impact of an intensive lifestyle intervention on BMI decrease in overweight/obese children. Carriers of the *FTO* GG genotype and *MC4R* CC genotype benefit significantly more from the lifestyle intervention.

Keywords: children, gene, obesity, metabolic syndrome, regime

Pharmacol treatment of HLP

The role of omacor treatment in morphological changes of venous grafts in patients after surgical myocardial revascularisation

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Objective: To evaluate a preoperative omacor treatment effects in morphological changes of venous grafts in patient after surgical myocardial revascularisation.

Methods: This study was conducted as parallel, opened and randomized work which enrolled 189 patients suffering CAD with planned CABG surgery (125 male, 64 female – mean age 64,2±9,4 years). Patients in control group were prescribed only standard treatment, patients in the treatment group were treated using mentioned above standard therapy plus Omacor 2g/daily during 14 days before surgery. The samples of the great saphenous vein were obtained during the CABG surgery. Histological and immunohistochemistry tests were performed.

Results: Circular hyperplasia of vein intima was observed in 42% of cases in control group and in 40% of cases in treatment group. Morphometric study showed the average thickness of the intima segments of veins was 0,13±0,11 mm, media – 0,22±0,08 mm in the control group and 0,12±0,11 mm, media – 0,20±0,06 in treatment group. A significant difference between groups in terms of epithelial desquamation was established: 48% of cases in the control group and 15% - in the main. In the control group the number of layers of smooth muscle cells of venous conduit were 10-19 (average 10,31±3,66), in the treatment group – up to 9 (average 7,85±2,65). The immunohistochemical analysis showed relatively low proliferative activity in epithelial cells in the treatment group (3,5 and 6,4 respectively, $p < 0.05$).

Conclusions: Omacor is improving the functional condition of the great saphenous veins, which using as venous grafts for CABG surgery.

Keywords: venous grafts, surgical myocardial revascularisation, omacor treatment effects

Studying the effectiveness of Omacor on lipid metabolism in patients with chronic heart failure

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Purpose: To study the effectiveness of Omacor on lipid metabolism in patients with chronic heart failure (CHF).

Material and methods: The study included 184 patients with CHF. The study included patients with a total cholesterol (CL) level of more than 4.5 mmol/l. The patients were divided into 2 groups: 1 group consisted of 88 patients treated with atorvastatin group and 2 of 96 patients taking Omacor in a dose of 1 g. administered for 6 months. All patients lipid profile was determined at baseline and after 6 months of treatment.

Results: In one group of patients treated with atorvastatin after 6 months of treatment there was a significant decrease in CL by 18.9% and amounted to $4,24 \pm 0,148$ mmol / L ($P < 0.05$) and LDL cholesterol by 24.3% and amounted to 3.01 ± 0.01 mmol / l. In the second group of patients after 6 months of treatment with Omacor in combination therapy there was a decrease in total cholesterol levels by 22.3% and the level of CL was $4,052 \pm 0,168$ mmol / l ($P < 0.01$), LDL by 26.4% mmol / l ($P < 0.001$), accounting for $- 2,91 \pm 0,245$ mmol / l. It noted an increase in HDL in patients with Group I and II of 10.2% and 12.7%, respectively. In the group treated with atorvastatin in 4 patients in the group taking Omacor in 2 patients omechalis side effects such as indigestion, which took place after the withdrawal of the drug. In the dynamics of observation in both groups at 3 and 6 months bilirubin, ALT and AST in the blood. The results showed that in both groups improve these parameters were observed.

Conclusion: Thus, in patients with CHF the six-month treatment with atorvastatin and Omacor lipid metabolism improved, which was characterized by significant decrease in CL and LDL cholesterol, increase HDL cholesterol, but in the group treated with a combination of atorvastatin and Omacor lipid-lowering effect was more pronounced.

Keywords: chronic heart failure, lipid metabolism, Omacor

Effects of Fimasartan on Carotid Atherosclerosis Progression after Mechanical Injury in ApoE Knockout Mouse

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Aim: The beneficial effects of angiotensin receptor blockers (ARBs) in atherosclerosis have been demonstrated in numerous studies. We investigated the effects of fimasartan in reducing atherosclerosis progression and systemic inflammation after carotid artery injury in ApoE knockout mouse.

Methods: Male ApoE knockout mice were randomly allocated to Group 1 (without carotid artery injury, $n=20$), Group 2 (without carotid artery injury + fimasartan, $n=21$), Group 3 (carotid artery injury, $n=25$) and Group 4 (carotid artery injury + fimasartan, $n=24$). Fimasartan (3mg/kg in distilled water) was orally injected on daily basis, and left carotid artery injury was induced with 0.014 inch guidewire. At 28 days, hematoxylin & eosin and elastic stains were used to measure cross-sectional atherosclerotic plaque from carotid artery. Moreover, inflammatory markers such as MMP9, IL-6, TNF α and ICAM were analyzed by ELISA, and anti-inflammatory cytokines such as IL-10 was measured in peripheral blood.

Results: Histomorphometric staining showed significantly reduced neointimal hyperplasia in Group 2 ($2.30\pm 0.66\%$) compared to Group 1 ($12.31\pm 2.97\%$, $p<0.05$). In addition, Group 4 ($32.03\pm 4.62\%$) showed significantly reduced neointimal hyperplasia compared to Group 3 ($50.06\pm 7.50\%$, $p<0.05$). All fimasartan treated groups revealed decreased smooth muscle cell proliferation and CD68+ macrophages in carotid artery. Furthermore, inflammatory cytokines such as MMP9 and IL-6 were significantly lower in Group 4 ($0.32\pm 0.02\text{ng/mL}$ and $11.68\pm 2.13\text{pg/mL}$) compared to Group 3 ($0.54\pm 0.13\text{ng/mL}$ and $16.68\pm 3.03\text{pg/mL}$, $p<0.05$, respectively). In particular, TNF α and ICAM were significantly decreased in Group 2 ($5.83\pm 2.28\text{pg/mL}$ and $3.76\pm 0.84\text{ng/mL}$) and Group 4 ($7.32\pm 0.95\text{pg/mL}$ and $5.04\pm 1.47\text{ng/mL}$) compared to Group 1 ($6.64\pm 1.34\text{pg/mL}$ and $4.42\pm 0.88\text{ng/mL}$) and Group 3 ($9.28\pm 1.57\text{pg/mL}$ and $6.31\pm 1.60\text{ng/mL}$, $p<0.05$, respectively). IL-10 increased significantly in Group 4 ($29.20\pm 0.52\text{pg/mL}$) compared to Group 3 ($26.18\pm 1.14\text{pg/mL}$, $p<0.05$).

Conclusions: Fimasartan reduced neointimal hyperplasia with decreases in macrophages in carotid atherosclerotic plaque and with reductions in systemic inflammation in ApoE knockout mice.

Keywords: Atherosclerosis, Angiotensin Receptor Blockers (ARB), Fimasartan, ApoE knockout mouse, Cytokines

Compliance to statins and antiaggregants therapy in patients 5 years ago suffered of acute coronary syndrome (experience of regional cardiovascular centre)

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Purpose: to evaluate compliance to the therapy by statins and anticoagulants in patients after Acute Coronary Syndrome (ASC) in 5-years follow-up period.

Materials and methods: we studied long-time follow-up results of observation in randomly formed cohort of 100 alive patients (males – 42 (42%), females – 58(58%)), average age – 69,4±9,3 years), hospitalized in 2011 to CCU with ACS. 73(73)% patients met first coronary event, 27(27%) – recurrent ACS. Finally in 67(67%) cases myocardial infarction with ST segment elevation (STEMI) was diagnosed, in 33(33%) – nonSTEMI. In 81(81%) patients Q- MI was registered, in 19(19%) – non-Q-MI. To all patients coronarangiography followed by stenting of infarct-related artery with bare stents OMEGA Boston Scientific was performed. At discharge all patients were recommended to take dual antiaggregant therapy (DAT) and statins. 5 years after discharge we contacted with patients by phone to assess medical history and compliance to the therapy.

Results: by fifth year after primary discharge all patients took at least ASA. DAT as were prescribed administered 68(68%) patients. Only 40(40%) patients continued statins (preferably atorvastatin (82%), average dose 26,3 ± 6,2 mg/day), but generally doses of them were not adjusted. Only 5 (5%) used laboratory control of lipids and only 2 (2%) had target value of LDL-C. Compliance in females was better then males.

87(87%) patients experienced angina pectoris I-II by CCS, 38(43,7%) of them continued statins, 50(56,3%) stopped), 13(13%) – had angina of III class, 2(15,4%) of them continued statins ($p < 0,05$). 83(83%) patients described symptoms of chronic heart failure (CHF) I-II by NYHA, 34(41%) of them kept good compliance to statins), 17(17%) – had CHF NYHA III, 5 (29,4%) of them continued statins) ($p < 0,05$). In 5 years 14(14%) patients were re-hospitalized (3 – not about ACS, all took statins permanently; 2-with recurrent AMI, 1 – with ischemic stroke. 3 patients required additional stenting, 2 – CABG.

Conclusion:

1. In 5 years after acute coronary event patients kept compliance to antiaggregants better then to statins.
2. Patients who stopped statins met higher rate of severe angina pectoris and CHF.
3. Control of LDL-C levels and reaching of their targets was really poor.

Keywords: ACS, 5-years follow-up, statins, antiaggregants

The effects of atorvastatin treatment on the mean platelet volume and red cell distribution width in patients with dyslipoproteinemia and comparison with plasma atherogenicity indicators – a pilot study

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Objectives: The mean platelet volume (MPV) and red cell distribution width (RDW) have recently arisen interest because of their association with an increased cardiovascular risk. The aim of our study was, therefore, to determine whether an association exists between MPV, RDW and lipoprotein sub-fractions, and to show the impact of statin therapy on these new possible biomarkers of atherosclerotic risk.

Design and Methods: A cohort of 40 patients with hypercholesterolaemia (29 females, mean age 62.9 ± 9 years), without previous hypolipidaemic treatment were enrolled. The patients were treated with atorvastatin 40 mg/day for 12 weeks. Total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density cholesterol (HDL-C), triglycerides (TG), LDL-C sub-fractions [large LDL-C 1-2 and small dense (sd)-LDL-C 3-7], apolipoproteins (apoA1, apoB), apoB/apoA1 ratio, atherogenic index of plasma (AIP), haematological parameters (including MPV, RDW) and safety parameters (renal, hepatic) were measured before and after 12 weeks of atorvastatin treatment.

Results: At baseline, a strong correlation between HDL-C, TG, sd-LDL-C, apoB, apoB/apoA1, AIP with MPV ($r=-0,55$, $p<0,001$; $r=0,57$, $p<0,001$; $r=0,73$, $p<0,001$; $r=0,41$, $p<0,05$; $r=0,52$, $p<0,001$; $r=0,61$, $p<0,001$, respectively) and RDW ($r=-0,49$, $p<0,001$; $r=0,62$, $p<0,001$; $r=0,67$, $p<0,001$; $r=0,41$, $p<0,05$; $r=0,43$, $p<0,05$; $r=0,65$, $p<0,001$, respectively) was found. After 12 weeks of treatment with atorvastatin, MPV and RDW values underwent significant modification only in those patients displaying the strongest lipid-lowering effect.

Conclusions: Values of MPV and RDW seem to reflect a pro-atherogenic lipoprotein profile mainly represented by the presence of sd-LDL-C.

Inhibition of mevalonate diphosphate decarboxylase in the cholesterol biosynthesis pathway causes replication stress

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Cholesterol biosynthesis is tightly linked to cell proliferation. Several products synthesized by this pathway are required for cell cycle progression, such as non-sterol isoprenoids for the G1-S transition and cholesterol for both the G2-M transition and cytokinesis. In line with this, proliferating cells strongly express not only the LDL receptor, but also enzymes involved in cholesterol biosynthesis in order to provide cells with cholesterol-biosynthesis derived intermediates. Restricted access to those metabolites can lead to cell proliferation arrest. Mevalonate diphosphate decarboxylase (MVD) catalyzes the conversion of mevalonate-PP into isopentenyl-PP in the cholesterol biosynthetic pathway. In the present work we aimed to study the effects of MVD inhibition on both cell proliferation and cell cycle progression. For this we used human p53-deficient HL-60 cells cultured in cholesterol-free ITS+ medium. Inhibition of MVD was accomplished by using fluoromevalonate, a competitive inhibitor of the enzyme. At the concentrations used, fluoromevalonate inhibited, but did not block, cholesterol biosynthesis and produced the accumulation of mevalonate-PP. Remarkably, fluoromevalonate also decreased cellular concentrations of ATP and dNTPs. These effects were accompanied by cell cycle arrest at S phase, the appearance of γ -H2AX foci in the nucleus and Chk1 activation, all of which indicate replication stress and DNA damage response. The inhibition of Chk1 in fluoromevalonate-treated cells by either UCN-01 or specific siRNA caused premature entry into mitosis, with the appearance of aberrant mitotic figures, followed by cell death. Provision of a mixture of deoxyribonucleosides, which are dNTP precursors, prevented the DNA damage and counteracted in part the effects of fluoromevalonate on cell proliferation. These results point to depletion of dNTPs as the cause of the inhibition of DNA replication in cells treated with fluoromevalonate, leading to DNA damage. In response to DNA damage, cells activated Chk1, which impeded the entry into mitosis. Replication stress induced by MVD inhibition may result in genomic instability.

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Keywords: cholesterol biosynthesis, mevalonate, deoxyribonucleotides, DNA damage, fluoromevalonate

Assessment of the quality of lipid-lowering therapy according to outpatient registry data.

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Objective: To determine doctors' adherence to clinical recommendations on lipid-lowering therapy in outpatient practice.

Material and methods: We used outpatient registry data (RECVASA) in which all patients with ischemic heart disease (IHD), hypertension, chronic heart failure, atrial fibrillation who visited the primary physician or cardiologist in one of three outpatient clinics in Ryazan city in 2012-2013 were included. A special algorithm to assess a quality and safety of lipid lowering therapy was created. This algorithm was based on current clinical recommendations and official indications and restrictions to prescribe any particular hypolipidemic drug (primarily statins). The quality of therapy was analyzed separately for patients with IHD, history of myocardial infarction, cerebral stroke and diabetes mellitus. In addition, patients with concomitant liver diseases and/or deteriorated liver function were selected.

Results: Overall, statins were prescribed to 809 (22%) of 3690 patients included in the registry. In 803 patients (21.8%) no cholesterol (CH) level data were available during one year prior to the inclusion in the registry, however, 117 of them (14.6%) received statins. Among 2887 patients with known CH level 692 patients (24.0%) received statins while 2195 patients (76.0%) did not receive this drugs. Of the 692 patients who received statins only 251 (36,3%) had the level of serum CH less than 5.0 mmol/l. Statins were prescribed to 28.7% of patients with CHD, 42.3% of patients with myocardial infarction, 50% of patients with recurrent myocardial infarction, 9.8% of patients with stroke and 18.9% of patients with diabetes mellitus. 71 (8,8 %) patients to whom statins were prescribed had a history of hepatitis and 354 (43,6 %) patients had a history of other liver diseases, however, control of serum bilirubin and hepatic transaminases was performed only in one third of them.

Conclusions: In current outpatient practice statins were not properly prescribed for patient with cardiovascular diseases according to clinical recommendations. The efficacy and safety of statin therapy were not always under appropriate physicians' control. Adherence of doctors to clinical recommendations on lipid-lowering therapy in outpatient practice should be improved.

Keywords: cardiovascular disease, statins, registry, assessment of efficacy and safety

Improvement of lipid-lowering therapy efficacy and tolerability in patients at high cardiovascular risk and concomitant liver disease with ursodeoxycholic acid

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Aim: To evaluate the effectiveness and tolerability of the therapy with statins and ursodeoxycholic acid (UDCA) and therapy with statins in patients with high cardiovascular risk and concomitant liver disease by using Propensity Score matching.

Material and methods: 262 patients aged 60.1±8.9 years, taking statins for the secondary prevention of cardiovascular complications were included into a 6-month observational cohort study. The UDCA intake was recommended to all the patients due to the presence of liver, gallbladder and/or bile duct diseases. One part of the patients (n=179) strictly followed medical recommendations and used UDCA, while the other part of the patients (n=62) have not done it. Clear information about UDCA intake wasn't available for 21 patients. Propensity Score matching method allowed forming two groups with 52 patients in each. The effect of UDCA in two groups was compared after 6 months of treatment.

Results: Both groups were similar in main clinical and demographic characteristics such as age, sex, weight, biochemical indicators, levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). Compared to initial data a significant decrease in the levels of TC and LDL-C were found in patients treated with statins in combination with UDCA (up to 4.0 mmol/L and 1.92 mmol/L, respectively; $p<0.001$) while in patients treated with statins these effects were less significant (up to 4.52 mmol/L and 2.6 mmol/L, respectively; $p<0.05$). No ALT, AST, CPK and LDH activity deterioration and no bilirubin serum level increase were found. After excluding the impact of additional factors it was found that the treatment with statins and UDCA leads to a greater reduction in TC and LDL-C than statin therapy alone ($p<0.05$). Target level LDL-C (<1.8 mmol/L) was reached in 31% of patients treated with statins in combination with UDCA and was not achieved in patients without UDCA ($\chi^2=18.9$, $p<0.001$).

Conclusion: A high adherence to UDCA therapy was demonstrated. Combined therapy with statins and UDCA was effective and safe in patients with high cardiovascular risk and concomitant liver diseases. Co-administration of statins with UDCA is promising in the treatment of hyperlipidemia in patients with low tolerance to statins, however, additional controlled studies are required.

Keywords: dyslipidemia, statins, high cardiovascular risk, liver disorders, ursodeoxycholic acid

Pitavastatin Lowers Plasma Levels of CoQ10 less than Equipotent Doses of Rosuvastatin or Atorvastatin

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Background: Reduction of CoQ10 following statin therapy is considered a possible mechanism for causing muscle-related adverse events and in addition, possibly related to risk of incident diabetes. Preserving CoQ10 levels may help to improve insulin sensitivity and reduce insulin resistance. CoQ10 has been found to be deficient in patients with diabetes and may be able to counteract various metabolic disturbances associated with insulin resistance and diabetes. Recent meta-analyses have shown that treatment with statins have varying effects on CoQ10 depletion and these effects are both dose dependant as well as statin dependant. Lipoprotein Insulin Resistance (LpIR) is a new biomarker strongly associated with increased insulin resistance and potentially incident diabetes and may be an early indicator of type 2 diabetes risk.

Hypothesis: In an adult patient population with impaired glucose metabolism and dyslipidemia, an equipotent dose of pitavastatin based on LDL-C reduction will lower CoQ10 less than rosuvastatin or atorvastatin and decrease the LpIR score to a greater degree than these statins thereby potentially decreasing insulin resistance and the risk of incident diabetes.

Method: Single site double blind study of 134 patients with impaired glucose tolerance randomized to pitavastatin (4 mg/qd), rosuvastatin (5 mg/qd) and atorvastatin (20 mg/qd) for 12 weeks. The primary endpoint was to determine the difference in plasma levels of total CoQ10, ubiquinol, and ubiquinone, before and after 12 weeks of therapy, between the three groups. A secondary analysis of the data measured serum LPIR at baseline and following treatment. Nine patients were unable to complete the study. Non-parametric Kruskal Wallis tests were done to assess treatment differences in the change in CoQ10, ubiquinol, and ubiquinone from baseline.

Results: Comparable LDL-C reduction was noted among the 3 groups, (p-value=0.2626), however, pitavastatin decreased CoQ10 levels, in particular ubiquinol, significantly less than atorvastatin and rosuvastatin (p-value=0.0401). No statistically significant treatment difference was observed in ubiquinone levels (p-value=0.6988), however the significant change in ubiquinol (p-value 0.0401) allowed total CoQ10 (p-value=0.0697) to be marginally significant. No statistically significant treatment differences were observed in the metabolic or lipid measures. Among the lipoprotein particles and apolipoproteins, LDL-particle number showed a significant difference between treatment groups (p-value=0.0087); as subjects in the rosuvastatin arm exhibited the smallest decrease in LDL-particle number, while those in the atorvastatin arm exhibited the largest decrease, followed by pitavastatin. In the LpIR data analysis, mean LpIR did not change significantly from pre- to post-treatment for any treatment condition, however, both pitavastatin and atorvastatin showed non-zero decreases in LpIR, with the greatest change being with pitavastatin, whereas rosuvastatin did not.

Conclusion: Pitavastatin showed the smallest reduction in CoQ10 as well as greatest reduction in LPIR compared to arotvastatin and rosuvastatin. Pitavastatin may be preferred when considering statin therapy for patients needing potent LDL-C and LDL-P reduction but with increased insulin resistance, impaired fasting glucose, or at risk of developing diabetes. Further studies are necessary to determine the clinically relevant changes in levels of CoQ10 and in markers of insulin resistance and incident diabetes with statin therapy when considering treatment regimens.

Keywords: Pitavastatin, Rosuvastatin, CoQ 10, LpIR

New lipid-lowering property of the active drug Hypoxen (experimental study)

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The screening and science research of new effective substansies for treating atherosclerosis is one of important labour-intensive medical problem of biochemistry and pharmacology. Hypoxen (**H**) is the modern non-toxical Russian drug with exceptional antihypoxant and antioxidant properties. **H** had used widely as the remedy of urgent, complex therapy of cardiovascular and other somatic disorders. It is known that rats are more resistant and steady to creation of alimentary model of hypercholesterolaemia and atherosclerosis than rabbits. In our experimental studies we used the special hyperlipidemic(atherogenic) diet containing rich doses of food cholesterol, saturated fats and vitamine D. It was shown the significant hypolipidemic effect of **H** in dose 50 mg/kg per os in rats, guinea-pigs and rabbits fed by special hyperlipidemic diet during 30 days. We observed the pronounsed decrease of content of total cholesterol, LDL-cholesterol, triglycerids, lipid oxidative products in serum and liver. It was founded the protective action of **H** from lipidosis of aortas of rabbits. These alterations were more significant than others in comparison with well-known hypolipidemic medicine agent Gemfibrosil. The data obtained had proposed the further investigations to confirm of the revealed valuable action of antihypoxant drug Hypoxen.

Keywords: special diet, correction, experimental model, antihypoxant, Hypoxen

Adherence to prescribed therapy and its influence on the serum lipid levels among patients with coronary artery disease

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Dyslipidemia is a primary risk factor of coronary artery disease (CAD). Compliance with a lipid-lowering therapy is an important factor, improving the prognosis of these patients. Questions of adherence to lipid-lowering therapy are widely discussed. Non-compliance is often unrecognized in clinical practice. One of the possible factors, lowering the patient's compliance, is comorbid pathology. The anxious and depressive symptoms can also cause the decrease of adherence to prescribed therapy.

The purpose of the study was to determine the association between lipid disturbances and the level of adherence among patients with CAD. Furthermore, we investigated the possible influence of the anxious and depressive symptoms on the level of compliance.

Materials and methods: 53 hospitalized patients (76% male and 24% female) with stable CAD and dyslipidemia were included in our study. All the patients had signed a voluntary informed consent. 70,37% of them had stable angina pectoris, 29,63% – had stable angina pectoris with concomitant atrial fibrillation. A middle age of the patients was $58,3 \pm 4,6$ years. The levels of plasma lipids were estimated. Adherence was rated by Morisky Medication Adherence Scale (MMAS-4). Also we used Charlson Comorbidity Index. Anxiety and depressive symptoms were measured by using of the Russian version of Hospital Anxiety Depression Scale (HADS). Statistical analysis was performed using Microsoft Excel 2013.

Results: low compliance (0-2 points, MMAS-4) was detected in 47% of patients, risk's group (3 points, MMAS-4) included 29,4% of them, 23,6% of patients were compliant (4 points, MMAS-4). A significant difference in the levels of lipid parameters wasn't found among compliant and uncompliant patients. But the tendency of lipids' levels to grow was observed. A significant inverse correlation was reported between the compliance to prescribed therapy and levels of the total cholesterol ($r = -0,31$), LDL ($r = -0,29$) and HDL ($r = -0,36$). The relation between patient's adherence and triglyceride's level ($r = -0,06$) wasn't found.

We have detected a high prevalence of comorbid pathology among observed patients. The mean Charlson Comorbidity Index was $4,0 \pm 2,1$ points. There was moderate negative correlation between the level of compliance and comorbidity ($r = -0,26$).

The affective symptoms were detected among 39,6% of patients. The subclinical level of anxious symptoms was observed among 18,7% of patients, clinical anxiety – among 9,4% of them. Depressive symptoms were detected among 28,3%, including subclinical depression among 20,6% of patients. Clinically expressed symptoms of depression were observed among 7,5% of them. The influence on the adherence was found only for anxious symptoms ($r = -0,3$).

Conclusions: Low compliance to prescribed therapy negatively affects the possibility of achieving target lipid parameters. The comorbid pathology and the anxious symptoms have impacted negatively on the patient's adherence.

Keywords: anxiety, depression, adherence, dyslipidemia, compliance

Results of simvastatin applying in the patients of senile age with CHD

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Purpose of a study: To estimate the ability of the influence of inhibitor GMG-Co A reductase (simvastatin) on the outcome of disease (lethal outcome from the basic disease or the sharp vascular event) and the exponential functions of cardiovascular system in patients it is older than 75 years with CHD.

Material and methods: Is executed observation in the course of 12 the months of 100 the patients of control group and 95 the patients of the group of the interference of senile age with stenocardia of 2-3 functional class, the randomization of groups is executed in such a way that there was no reliable difference between the groups of patients for the sex, the age, IM, gravity of basic disease and associated pathology, indices of lipid exchange, coagulogram, Echo-kg., thickness of complex “intima-media”, capability of humeral artery for endothelium- dependent vazodilatation, conducted treatment between the groups. Exception was application in the diagram of treatment in the patients of the group of the interference of the preparation of simvastatin at the daily dose 20 mg during entire period of observation.

Results of study: In 1 year of observation in the group of interference it developed 11 unfavorable outcomes, and in the group of the comparison – 22. With the calculation of the authenticity of the divergence of the curves of the development of end points to the end of the study by the method of the Coxe – $r = 0,044$. Reliable dynamics is obtained with the comparison of the following indices between the groups: class of stenocardia ($r < 0,05$), dynamics of the endothelium- dependent vasodilatation ($r < 0,05$), thickness of complex “intima -media” ($r < 0,001$), clearance of creatinine ($r = 0,04$, in dynamics $r = 0,01$), S-reactive protein ($r < 0,001$), TNFa ($r = 0,059$).

Conclusions: The application of simvastatina at the daily dose 20 mg in the investigated cohort group CHD of senile age led to improvement in their clinical state and reduction in the unfavorable outcomes of disease. The clinical effects of simvastatin at the dose 20 mg were accompanied by an improvement in the functional state of vascular wall and by the laboratory indices of the readiness of atherosclerotic platelets for the spontaneous break.

Keywords: senile age, Coronary Heart Disease, GMG-Co A reductase

Comparative study of atorvastatin and simvastatin efficacy in patients with ischemic heart disease

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Aim of the study: Comparative study of atorvastatin and simvastatin efficacy in patients with coronary heart disease (CHD).

Material and methods: The study included 40 patients with CHD with stable angina functional class (FC) I-II (mean age 55,7 ± 5,3 years). The patients were divided into two groups: I group consisted of 20 patients taking simvastatin 40 mg, II group – 20 patients taking atorvastatin 20 mg once a day with the basic therapy. All the patients carried out a comprehensive study of the definition of total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), and the parameters of quality of life (QOL) at baseline and after 8 weeks of treatment. To study the QOL of patients used the SF-36 questionnaire, 36 items grouped into 8 scales. Results are presented as estimates of 8 points on the scales, with a higher score indicates a higher level of QOL. As a result, each patient received 8 ratings from 0 to 100%.

Results of the study: Initially in patients of group I TC was 6,072 ± 0,23 mmol / l, LDL – 4,08 ± 0,16 mmol / l and HDL – 1,05 ± 0,14 mmol / l, in patients of group II TC was 6,335 ± 0,17 mmol / l, LDL – 4,063 ± 0,23 mmol / l and HDL – 0,95 ± 0,13 mmol / l. In patients of group I after 8 weeks of treatment, the level of TC decreased by 13.9% (P < 0.05), and a trend towards a decrease in LDL cholesterol by 4.3%. In group II, against the backdrop of 8 weeks of treatment was observed a significant decrease in TC. Which amounted to 5,032 ± 0,168 mmol / l, LDL – 2,638 ± 0,245 mmol / l, with a significant decrease in TC by 20.5% and LDL cholesterol by 35.1% (P < 0.05). It noted an increase in HDL in group I and II patients by 11.2% and 6.7% respectively.

In the analysis of the QOL study in patients studied lowest level of QOL in the study groups was observed on scales: physical functioning (PF), the bodily pain (BP), general health (GH), and vitality (VT). Evaluation of QOL in patients with CHD after 8 weeks of treatment showed that patients on the background of complex treatment with atorvastatin significantly recorded significant improvements in role physical scales (RP) (from 62,11 ± 10,13 to 79,17 ± 3,14; P < 0,05), GH (from 44,17 ± 8,26 to 67,14 ± 6,24; P < 0,05) and emotional role functioning (RE) (from 58,19 ± 11,12 to 68,19 ± 4,12; P < 0,05). On a scale PF, BP, VT showed a trend toward improvement. Patients in the group of simvastatin on the background of 8 weeks of treatment was observed significant improvement on scales RP (from 63,2 ± 11,15 to 75,2 ± 4,14; P < 0,05), and on the scale of PF, GH, VT, RE and showed a trend toward improvement.

Conclusion: The study show that the clinical efficacy of atorvastatin was higher compared to simvastatin.

Keywords: coronary heart disease, quality of life

Peculiarities of risk stratification for patients with unstable angina pectoris and type 2 diabetes mellitus

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Aim: The work was initiated to study peculiarities of lipid and carbohydrate metabolism in patients with unstable angina pectoris (UAP) and type 2 diabetes mellitus (DM).

Materials and methods: We examined 73 UAP patients with type 2 DM (mean age 54.61 ± 1.13 years), duration of IHD and type 2 DM being 5.69 ± 0.38 and more than 5 years in 54.8% ($n=40$), respectively. Clinical and medical history data was analyzed, hemodynamic parameters, such as, ECG, echocardiogram, HM ECG and reactive hyperemia test, as well as biochemical parameters, such as, lipid and carbohydrate profiles being assessed. The patients were divided into two groups by the character of outcome. Thus, 58 patients (79.5%) were included into the group of favorable outcome (FO), 15 patients (20.5%) comprising the one with unfavorable outcome (UO), such as, sudden death, fatal and non-fatal myocardium infarction within the two-year period observed. Anticoagulants, antiaggregants, nitrates, beta-adrenoreceptor blockers, ACE inhibitors, atorvastatin and gliclazidum (due to rejection of insulin) were the medications used for therapy. Student's criterion as well as χ^2 and Fisher's criterion were used for independent totals to assess difference confidence. Mean values were given as $M \pm m$. Differences at $P < 0.05$ were considered confident.

Results: We have analyzed carbohydrate metabolism by five parameters, such as, fasting glycemia, post-prandial glycemia, post-prandial glycemia differential and HbA1c in patients with type 2 DM with favorable and unfavorable outcome.

Screening of metabolic UO UAP markers showed that UO long-term risk is conferred by FG level ≥ 13 mmol/l, incidence being 13.8 and 40%, respectively ($P < 0.05$). PPGD incidence (+54% and more) was 46.9% in UO UAP patients versus 6.9% in FO patients ($P > 0.001$). In FO patients total cholesterol was lower than the parameter in UO patients ($P = 0.031$), no significant inter-group differences in HDL cholesterol being registered. LDL cholesterol was higher in UO patients ($P = 0.007$), the difference preserved at all stages of study. No inter-group differences in TG were found. As to lipid metabolism parameters, total cholesterol (> 200 mg/dl; $P = 0.041$) and LDL cholesterol (> 193 mg/dl; $P = 0.032$) were registered 1.5 times (93.3% versus 60.3%; $P = 0.032$) and 3.1 times (40 versus 13.1%; $P = 0.032$) more frequently in UO UAP patients.

Conclusion: Hyperglycemia, high fasting glycemia (> 13 mmol/l) or PPGD ($> 54\%$ and more) in particular, as well as increase in total cholesterol ≥ 200 mg/dl and LDL cholesterol > 115 mg/dl are the criteria affecting long-term UAP outcome in patients with type 2 DM.

Keywords: unstable angina pectoris, type 2 diabetes mellitus, risk stratification, carbohydrate metabolism, atorvastatin

Assessment of dynamics of carotid atherosclerosis on short-term intensive statins therapy: the plaques volume versus the intima-media thickness.

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Implementation of 3D vascular ultrasound and the new software in clinical and scientific practice allowed approaching studying of expressiveness of dynamics of atherosclerosis more precisely. The purpose of this study was assessment of changes of plaques volumes by 3D ultrasound (3D US) by new program module Qlab-VPQ during short-term intensive statins therapy, in comparison with dynamics of carotid intima-media thickness (IMT).

Materials and methods: 40 patients were included (7 women and 33 men) very high CVR, on rosuvastatin therapy 40 mg/d during 3 months. Mean age $61,5 \pm 3,5$ years (51 to 70 years). At the first visit and after 3 months standard carotid duplex US examinations with estimation mean IMT by automatic method was performed on all patients, using a 9-3MHz linear transducer (Philips iU 22). If atherosclerotic plaques was defined (according to Mannheim consensus), was performed 3D US examination using a VL13–5 linear volume transducer. The 3D images treated at the computer workstation by the semi-automatic module of the software of Philips Qlab-VPQ. For detection of statistical distinctions when comparing two visits Wilcoxon's method was used, correlation dependence was estimated by Spearman's method, reproducibility – by Bland-Altman's method. All descriptive data were expressed as median and interquartile range (Me; 25th; 75th percentiles).

Results: 70 heterogeneous plaques (from 40 patients) with a smooth surface and stenosis less 70%, was included in research. The echolucency and calcified plaque didn't include in the analysis. Plaques on the one and the several segments were estimated. The volume of plaques varied from 5,0 to 1024,0 mm³ (61(24,5; 122,5)), the total volume of all plaques from one patient was from 5,0 to 1 720,0 mm³ (85,0 (54,75; 195,5)). Our research showed, that the mean volume of plaques on 3 months of statins therapy significantly decreased: before treatment 85,0 (54,5; 196) mm³ and 83,5 (56; 192) mm³ after treatment ($r=0,045$). The reduction of mean volume of plaques was in the 21 patients (81,0 (69; 197) mm³ and 77,0 (60; 194) mm³ ($p<0,001$)). The mean volume of plaques was without changes in the 11 patients (74,0 (19; 127,5) mm³). The increase in mean volume of plaques was in the 8 patients (146,5 (75,75; 171,5) mm³ and 155,5 (79,25; 197,25) mm³ ($p=0,012$)). Reproducibility of this semi-automatic method of an assessment of volume of plaques CV=3,1%. Coefficient of correlation $r=0,99$ ($p<0,001$). The mean carotid IMT from 3 months of statins therapy didn't significantly change: before treatment 0,7 (0,63; 0,75) mm, after treatment 0,71 (0,63; 0,76) mm, ($r=0,14$).

Conclusions: our study show significantly reduction of volume of plaques from 3 months of intensive statins therapy was revealed. Whereas, such standard parameter, as the mean carotid IMT, didn't show significantly dynamics. It confirms that linear parameter, such as IMT «doesn't work» on the short-term of statins therapy, and volumes parameters it is better in this case. For measurement of volume of plaques it is possible to use the new semi-automatic Qlab-VPQ method, which has a good reproducibility.

Keywords: atherosclerosis, statins therapy, 3D vascular ultrasound, Qlab-VPQ, plaques volume

Specifics of the blood serum triglycerides composition in men with CAD treated with simvastatin

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Statins are common medications used to treat CAD. Their efficacy has been proved by various clinical trials, which demonstrated not only a reduction of atherogenic lipid levels by statins, but also a reduction in the frequency of complications of CAD by more than 25–40 percent.

Statins achieve their effects on the phylogenetically latest VLDL, which consist of more than 90 percent oleic and palmitic triglycerides. Oleic fatty acid is esterified at sn-2 position in oleic triglycerides; palmitic fatty acid is esterified at the same position in palmitic triglycerides. Further, oleic triglycerides are energetically more favourable substrates, for they show a higher rate of hydrolysis than palmitic triglycerides, which are known to be involved in the development of atherosclerosis.

Our research was conducted on 60 conditionally healthy men at an average age of $48,4 \pm 6,4$ and 83 men with CAD at an average age of $58,2 \pm 8,4$. Patients separated in two groups and treated with simvastatin in doses of 40 and 80 mg/day have been observed for two months.

Plasma triglyceride levels were assessed by HPLC-MS. Separation was carried out by high-performance DIONEX Ultimate 3000 liquid chromatography system on a Reprosil-PurC18-AQ $3 \mu\text{m}$ column, $150 \times 4.6 \text{ mm}$, by applying a linear gradient (acetonitrile/acetone). Detection was performed using ABSCIEX QTRAP 5500 mass spectrometer. The mass spectrometer was operating in positive ion mode. In this study, we applied atmospheric pressure chemical ionization (APCI).

The group of men with coronary artery disease showed a statistically significantly reduced concentration of oleoyl-oleoyl-oleate, oleoyl-oleoyl-palmitate, and palmitoyl-palmitoyl-oleate compared to the group of conditionally healthy men.

Without due regard to the dosage administered, after two months of treatment with simvastatin, levels of oleoyl-oleoyl-palmitate were statistically significantly reduced compared to that before treatment.

Thus, the present study found that men with coronary artery disease had reduced concentration of oleic triglycerides. Simvastatin treatment induced a more significant reduction in oleoyl-oleoyl-palmitate levels.

Keywords: triglycerides, simvastatin, CAD, HPLC-MS

Varia

Complicated course of atherosclerosis and hemodynamic disturbances in reconstructive surgery of vessels

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Peculiarities of the atherosclerotic process is largely determined by damage of the endothelium on the background of hemodynamic disturbances.

The purpose of this study was to investigate the association between the characteristics of variations in blood pressure and characteristics of course of the postoperative period in patients with atherosclerosis.

Materials and methods: Study is based on an observation of the 58 patients who underwent reconstructive operations on major arteries. Among them, 30 people were required to perform drug correction of hemodynamic parameters (study group) and 28 patients who did not require this (control group). In examined patients were analyzed lipid spectrum of the blood, characteristics of carbohydrate metabolism, body weight and waist circumference, blood pressure variability index (arithmetic mean between the maximum and minimum values for 10 hours of observation), and the results of surgical interventions (adverse cardiovascular events).

Results: Index of variability of blood pressure turned out to be informative in assessing the circumstances of the risk of adverse cardiovascular events. Adverse prognostic variability values were more than 20 mm Hg. Cardiovascular complications were observed in patients with variable pressure less than 9 mm Hg significantly less frequently. Variability within 10-19 mm Hg should be regarded as “grey” area. The most dangerous (in terms of the need for medical correction) had abnormalities of blood pressure according to an embodiment of hypotension.

Another predisposing factor for significant prognostic deviation in blood pressure should be considered a long experience of smoking, determining the increase in the probability of hemodynamic instability doubled from baseline.

Conclusions: Increased risk of adverse cardiovascular events is observed in patients with advanced atherosclerosis on a background of high levels of blood pressure variability.

Keywords: hemodynamic disturbances, atherosclerosis

Does physical activity influence the development of atherosclerotic process?

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The role of physical activity remains unspecified for the rehabilitation of patients with advanced atherosclerosis.

The purpose of research – the identification of an association between daily physical activity and features of the atherosclerotic process.

Materials and methods: Study is based on observations on 78 patients with manifestations of peripheral atherosclerosis (PAD). The study group included 59 patients with low daily physical activity in the control group – 12 patients with high levels of activity.

For the analysis of daily physical activity International Physical Activity Questionnaire (IPAQ) index was used. Parameters of blood pressure, heart rate, the degree of ischemia of the lower limbs by Fountain – A.V. Pokrovsky, version of hypertension, peculiarities of coronary heart disease were registered. The results were separated on a scale of arithmetic values (mean) ± standard deviation (SD). Comparing groups of arithmetic values was carried out by using the non-parametric Mann-Whitney criterion. The difference in categorical variables were analyzed by the Pearson χ^2 and Fisher test. Differences were considered statistically significant at $P < 0.05$. Mathematical processing was carried out using the software package STATISTICA 10.

Results: The presence of high physical activity predicts quite favorable obliterans treatment process, manifested disbaziya (mainly, II b stage chronic ischemia). Evidence of the optimistic prognosis of the named category of patients is the minimum number of repeat interventions on the reconstructed segment.

Rehabilitation measures appear to be ineffective in people with low physical activity due to resistant flow of hypertension, displayed on the state of target organs (the myocardium, renal parenchyma).

Confirmation of the latter fact is the presence of coronary artery disease in patients with low physical activity (such as stenocardia and postinfarction cardiosclerosis) on the background of peripheral atherosclerosis.

Conclusions: A significant physical activity is one of the decisive factors for successful rehabilitation of patients with multifocal atherosclerosis, in its turn low physical activity predisposes to progression of peripheral atherosclerosis, which should be considered in the development of rehabilitation programs.

Keywords: physical activity, rehabilitation, atherosclerosis

Impact of Individual Acute Phase Serum Amyloid an Isoforms on HDL Metabolism in Mice

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The acute phase reactant serum amyloid A (SAA) is an HDL apolipoprotein that exhibits biological activities as a pro-inflammatory mediator, but its physiological function(s) are poorly understood. Possible functional differences between SAA1.1 and SAA2.1, the two major SAA isoforms, are also unclear. Mice deficient in either SAA1.1 or SAA2.1 were used to investigate SAA isoform plasma clearance rates and effects on HDL structure, composition and apolipoprotein catabolism. The absence of either isoform did not affect the size of the normally enlarged HDL found in acute phase wild type mice, and did not result in significant changes in HDL lipid composition. Plasma clearance rates of normal and acute phase HDL apolipoproteins were determined using native HDL particles. The fractional clearance rates (FCR's) of apoA-I, apoA-II and SAA were distinct, indicating that neither normal nor acute phase particles are cleared as intact particles. No significant difference was found between the FCR's of SAA1.1 and SAA2.1 in acute phase mice, suggesting that the selective deposition of SAA1.1 observed in amyloid plaques is not associated with a difference in the rates of plasma clearance of the isoforms. In the absence of the HDL receptor SR-BI, the clearance rate of SAA was reduced by about 30% and remained significantly greater compared to that of apoA-I and apoA-II, indicating a relatively minor role of SR-BI in SAA clearance. These studies contribute to our understanding of the metabolism of SAA and its effects on acute phase HDL composition and catabolism.

Keywords: serum amyloid A, HDL, Inflammation, lipoprotien metabolism, acute phase

Pregnancy and lipid status in view of heredity, burdened by early cardiovascular disease

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Relevance: hypercholesterolemia is one of the major risk factors for cardiovascular (CV) disease. At same time some authors considered increased level of cholesterol during pregnancy as physiological. However, number of studies allows us to consider elevated levels of cholesterol during pregnancy as a predictor of future CV events. The importance of objective assessment of fluctuations of atherogenic lipids during gestation is very relevant due such reason as existing prohibition of receiving statins during pregnancy and lactation.

Aim – to study the dynamics of total cholesterol and triglycerides in different trimesters of pregnancy in view of features of negative heredity for early CV disease.

Materials and Methods: The 58 individual cards of pregnant women aged 21 to 38 years (mean age $29,3 \pm 1,5$) was analysed. The following parameters were evaluated: height and weight to calculate body mass index; family history, which took over the fact of early CV disease in close relatives (up to 55 years for men and 65 for women), cholesterol and triglyceride levels in each trimester of pregnancy. In view of the presence/absence of family history two groups were identified: 1st group (n = 28) – pregnant women with burdened family history of early CV disease and 2nd group (n = 30) – pregnant women without such family history.

Results: The groups were matched for age ($29,8 \pm 1,3$ and $28,3 \pm 1,5$, respectively, in groups 1 and 2). Baseline BMI values in both groups did not differ in the same $-23,89 \pm 1,5$; $23,98 \pm 1,3$ kg/m² respectively.

Cholesterol levels in I-trimester in both groups were normal values: $4,6 \pm 0,2$ and $4,7 \pm 0,15$ mmol/l ($p > 0,05$). In the II-trimester the mean value of cholesterol in the group with burdened family history was significantly higher compared with the comparison group – $6,2 \pm 0,3$ and $5,1 \pm 0,2$ mmol/l, respectively. The values of the analyzed indicator in III-trimester amounted to $5,6 \pm 0,4$ in 1st group and $5,8 \pm 0,3$ mmol/l in 2nd group ($p > 0,05$).

Dynamics of triglycerides in group with favorable heredity characterized by gradual enlarge in values with increasing gestational age. In another group with negative family history maximum value of this indicator recorded in II trimester, and improvements over baseline was 80%.

Conclusions: in pregnant women with history of early cardiovascular disease in close relatives in the II trimester is recorded higher level of cholesterol and triglyceride levels compared with women who have not burdened heredity. Probably, significant hormonal changes that occur during pregnancy, contribute to improvement of these indicators in the presence of unfavorable heredity. It is also possible that described lipid changes can detect predisposition to their increasing in the future life of this group of women. It is need further prospective studies to address the question of possible relationship of the detected biochemical abnormalities with increased cardiovascular risk in these women in the future.

Keywords: pregnancy, heredity, cholesterol, triglycerides

Hypoxia-induced immune organs and cells response in experiment background infection.

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Immunohistochemical and light microscopic investigations develop that hypobaric hypoxia in barocamera (15 days duration) on the Wistar male rats (N=30) induces involution of lymph node cortex, particularly T-dependent zone, but stimulates B-dependent medullary cords and lymphoid nodules plasmacytization increasing their volume and cellularities.

Spleen reacts on this hypoxia regime by enlargement of lymphoid nodules activation of follicular dendritic cells. Hypobaric Hypoxia promote activity of mononuclear phagocytic system cells which enhance the expression of corresponding immunohistochemical markers: CD34 and CD133.

Conclusion: Hypobaric hypoxia depressed cellular immune response and activates phagocytic cells and B-dependent system.

Keywords: Hypobaric hypoxia, immune organs, immunohistochemistry

Comparative study of the psychogenic trauma influence on lipid metabolism in male and female rats

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The influence of psychogenic trauma – threats to life in rats of both genders in different periods after the injury was studied. Psychogenic trauma simulated stressful effects on rat tiger python. It was found a sharp decrease in HDL cholesterol in male rats immediately after a single psychogenic effect that lasts at least for one month and a half. A year after such exposure abnormalities in lipid spectrum in blood serum and liver observed. Repeated psychogenic effects lead to persistent disturbances of lipid metabolism. In female rats, a single psychogenic stress leads to an increase in HDL-C immediately after the stress, but after a week this parameter drops, but not so drastically as in male rats, and after two week returns to baseline. Repeated psychogenic stress in female rats also leads to disruption of lipid metabolism, but not as resistant as in the males. Moreover, the degree of such disturbances depends on the phases of the estrogen cycle.

Keywords: psychogenic trauma, lipid metabolism, HDL-cholesterol

Vegetative regulation in patients with chronic obstructive pulmonary disease in combination with obstructive sleep apnea syndrome

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Object: To perform an analysis of patients' cardiac rhythm variations in presence of chronic obstructive pulmonary disease in combination with obstructive sleeping apnea syndrome and obesity.

Research methods: The research included 81 male patients with COPD, matched by age to 2nd stage of airflow speed limitation (GOLD II). The patients were divided into three groups. All patients got cardio-respiratory monitoring test with "Cardiotekhnika 04-3PM" apparatus (INKART, St. Petersburg, Russia) during 20±4 hours with equal software. Time and spectrum analysis methods were used in order to examine heart rate vegetative regulation parameters. The following time analysis parameters were checked: SDNN, ms – standard deviation of all R-R sinus intervals; SDNNi, ms – 5 minute intervals standard deviation average; SDANN-i, ms – 5 minutes intervals standard deviation of RR intervals averaged values; pNN50 (%) – RR consequent intervals difference for more than 50ms percentage. During spectrum analysis were examined the following parameters: HF, ms² – high-frequency; LF, ms² – low-frequency; VLF, ms² – very low frequency; ULF, ms² – ultra-low frequency; TP, ms² – spectrum total power, LF/HF – power ratio of low frequency and high frequency range.

Data statistical processing was performed with use of Statistica 6.0 (Stat Soft, USA, 1999) programs. OSAS stage was set with consideration of Apnea-Hypopnea Index.

Results: 1st group of 32 patients (39,5%) with COPD, 2nd group – 26 patients (32%) with COPD and OSAS with normal weight, 3rd group of 23 patients (28%) with COPD and OSAS and I and II stages of obesity. During time parameters analysis lower SDNN parameter in groups 2 and 3 was noticed in comparison with the first group where $p = 0,001$. At this there was no statistically significant difference stated between 2 and 3 groups. SDANN parameter in group 3 was the lowest in comparison with 1 and 2 groups ($p = 0,001$ and $p = 0,029$ respectively). RMSSD decrease for 37% in group 3 was stated in comparison with group 1 ($p = 0,0001$). pNN50 parameter was also lower in groups 2 and 3 ($p = 0,04$; $p = 0,00001$) in comparison with 1 group. Statistically significant difference between group 2 and group 3 was not stated. During spectrum parameters analysis the VLF parameter was essentially lower in group 3 comparing to groups 2 and 1 ($p = 0,01$; $p = 0,00001$). There was stated power reduction in low (LF) and high frequency (HF) range. Statistically significance was marked in group 1 in comparison with groups 2 and 3 ($p = 0,03$; $p = 0,00001$). Spectrum total power decrease was registered in all present groups, the lowest parameter was in group 3. Maximum LF/HF parameter was stated in the group 2, which indicates sympathicotonia domination in the present group of patients, however significant difference in parameters was noticed in comparison with group 1 (COPD isolated) ($p = 0,04$).

Conclusion: COPD and OSAS combination is characterized by significant sympathicotonia and heart rate variability spectrum and time absolute value parameter decrease. The most significant abnormalities were stated in comorbidity of COPD and OSAS and obesity.

Keywords: chronic obstructive pulmonary disease, obstructive sleeping apnea syndrome, obesity, heart rate vegetative regulation

Proosteogenic genes are activated in endothelial cells of patients with thoracic aortic aneurysm

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Purpose: Aortic aneurysm (AoA) remains among the most dangerous cardiologic complications, but cellular and molecular reasons of this pathology are not fully understood. Recently it has been shown that *NOTCH1* haploinsufficiency in endothelial cells derived from iPS and also inhibition of *NOTCH1* in aortic valve endothelial cells gives rise to the activation of proosteogenic pathways. We have previously shown that Notch signaling is impaired in the endothelial cells of patients with aortic aneurysm associated bicuspid aortic valve (BAV) and tricuspid aortic valve (TAV). The aim of the present study was to elucidate whether the expression of proosteogenic genes is elevated in the endothelial cells of the patients with thoracic aortic aneurysm.

Methods: Human aortic endothelial cells (HAECs) were isolated from tissue fragments of BAV- and TAV-associated thoracic aortic aneurysm patients and from healthy donors used as controls. The baseline level of target genes was estimated by qPCR.

Results: We checked expression of about 40 genes related to proosteogenic and proinflammatory cellular response. Endothelial cells of AoA patients had significantly higher mRNA levels of *BMP2*, *DKK1*, *TCF4*, *STAT6*. In contrary, the expression of *CDC20*, *CYP11B1*, *GREM1* was lower in the HAECs of the patients.

Conclusions: Our data show that proosteogenic genes, such as *BMP2*, are up regulated in the endothelial cells of the patients with thoracic aortic aneurysm. Our data also show implication of Wnt signaling along with Notch signaling in changing the properties of endothelial population of AoA patients and thus presumably to the pathogenesis of thoracic aortic aneurysm.

Keywords: Aorta, Aortic aneurysm, Notch, Endothelial cells

Influence of cardiorehabilitation on clinical outcomes, physical performance, blood lipids in patients after endovascular intervention in the long-term period

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Goal: Influence of cardiorehabilitation comprehensive program on the development of cardiovascular events (CVE), indicators of physical performance (PP), the levels of blood lipids in patients undergoing percutaneous coronary intervention (PCI) after 10 years of observation.

Materials and methods: The study included 77 patients who underwent PCI in 2004–2005 years. Patients were randomized into 2 groups: the main – «O» (n = 41 patients), who have been performed a shortened (1.5 months) program of physical training (PT) and a course of education “School for patients undergoing PCI”. The second group – control «K» (n = 36 patients), who participated only in the educational school. All patients received standard therapy according to the underlying disease. After 1 year and 10 years patients were examined: stress test on veloergometer (VEM-test), a blood test for lipids total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG)). After 10 years, the patients responded to a telephone survey of a specially developed questionnaire, 45 patients were invited to the clinic: 27 patients in the group «O» (mean age 63 ± 6.9 years) and 18 in the group «K» (mean age 62.4 ± 7.0 years).

Results: The total number of the CVE, including mortality, need for revascularization after 10 years after the end of the rehabilitation program was in the group «O» 23 cases, in group «K» 23 cases. In the group «O» 4 patients died (9.8%), 3 of them due to the CVE, in group «K» – 8 patients (22.2%), 5 of them due to CVE. Recurrent myocardial infarction occurred in 3 patients (7.3%) from the group «O» and in 3 (8.3%) from the group «K». In the group «O» identified 1 case of transient ischemic attack (2.4%) and 1 case of stroke (2.4%). In the «K» group 1 patient suffered a stroke (2.8%).

According to the VEM-test there was a significantly increased level of load capacity in the group «O» after 10 years of follow up by 37.5% (936 ± 315.7 kgm/min, $p < 0.01$) compared to baseline (585.2 ± 224.4 kgm/min), exercise duration by 23.3% (13.3 ± 2.5 m., 10.2 ± 2.2 min., respectively, $p < 0.05$) and the total amount of work by 37.5% (56.2 ± 18.9 Jxmin., 35.1 ± 13.5 Jxmin., $p < 0.01$). All of the parameters in the «K» group were not significantly different from baseline. After 10 years trained patients had had lower levels of total cholesterol (in the group «O» 4.7 ± 1.1 mmol/l vs in group «K» 5.6 ± 1.4 mmol/l, $p < 0.05$). After 10 years of follow up there was no difference in levels of LDL-C, HDL-C, TG in two groups of patients.

Conclusion: After 10 years of follow up in patients who had performed complex, but shortened program of cardiorehabilitation the better indexes of PP were preserved, compared to group «K».

Keywords: cardiorehabilitation, secondary prevention, controlled physical training

LDL aggregation inhibitors do not reduce their atherogenic potential

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Objectives: LDL isolated from the blood of patients with CVD are prone to association and these LDL associates accumulate in cells, i.e. they are atherogenic. We have found amphiphilic compounds – poloxamers – inhibitors of LDL association process. We assume that poloxamers can influence on intracellular lipid accumulation caused by the addition of LDL from CVD patients

Methods: We used Poloxamers P85, L64, L61 and L81 (BASF; Wyandotte, MI). The total LDL fraction was isolated by ultracentrifugation from the serum of patients with cardiovascular disease (men aged 40-74 years with carotid atherosclerosis). Human blood monocytes were isolated from the blood of healthy volunteers and matured to macrophages as described by Griffith et al.

Results: In the beginning we clarify, that the addition of Poloxamers P85, L61 and L64 in minimal concentration sufficient for LDL association inhibition, to cell culture did not influence on viability of cells. Then we preincubated cells with pluronics in various concentrations during 1 or 24 hours, washed it with PBS solution and then added LDL. Also we made an attempt to inhibit LDL association before its interaction with cells. So we preincubated LDL with poloxamers in different concentrations to inhibit LDL association and then we added this mixture to cell culture. As well as in previous experiments we didn't receive any differences in lipid accumulation in all concentration of Poloxamers.

Conclusions: Poloxamers inhibit LDL association, but do not influence on intracellular lipid accumulation induced by addition of LDL.

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Keywords: ldl aggregation, ldl association, poloxamer, atherosclerosis

Comparative assessment of different methods of vascular allografts recellularization efficiency

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Background: Currently there is a strong need for small diameter long tissue-engineered vascular grafts (TEVG). A promising material for these bioprotheses are decellularized human umbilical arteries (DHUA), which have the ideal properties for vascular bypass grafts. Effective recellularization of a vascular graft at the initial stage is a necessary condition for creation of a full-fledged TEVG.

Objective: To compare efficiency of different methods of DHUA recellularization in vitro.

Materials and Methods: Human umbilical arteries decellularized using original method were examined. Recellularization of vessels was performed using adipose-derived mesenchymal stem cells (ADMSC). DHUA segments of 10 cm length were filled with the cell suspension, fixed in the bioreactor and placed in CO₂ incubator for 1 hour. Efficiency of different methods of recellularization was evaluated in four groups: I – static recellularization of DHUA; II – static recellularization of DHUA rotating by 90 degrees every 15 minutes; III, IV groups – recellularization with low-speed reversible perfusion (LSRP) (1,0 mL/h). DHUA in groups I-III were fixed in the bioreactor in a lengthwise stretched position. In group IV vessels were put on a hollow plastic cylinder and had a spiral form. In each group cellular suspension with concentration of ADMSC 1×10^6 , 2×10^6 , 3×10^6 and 4×10^6 /1 mL (n=3 for each concentration) was used. LSRP was accomplished by the use of peristaltic infusion pump.

Recellularization efficacy was evaluated by the number of adherent cells and uniformity of their distribution on the inner surface of the DHUA. For this purpose vessels were washed with 10 ml of phosphate-buffered saline (PBS) after incubation. Washing solution was centrifuged and the precipitated cells were counted. The number of adherent cells was accepted as a difference between initial number of cells in suspension and number of the precipitated cells in washing solution. Further vessels were fixed in 4% PFA and counterstained with DAPI. Uniformity of cell adhesion was assessed using fluorescence microscope by counting the number of ADMSC nuclei in the surface regions of the same area.

Results: The number of adherent cells was not significantly different in all 4 groups at the same cell concentration and was maximal at 3×10^6 cells/mL. At 4×10^6 cells/mL was not observed significant increase in the number of adherent cells. In group I cell adhesion occurred mainly on the lower wall of the vessel along its longitudinal axis in the form of a narrow stripe. Cell adhesion in groups II and III also occurred predominately axially on the lower graft wall, but the area of uniform cell distribution (width of the stripe) was greater and took up to 30% of the inner surface of the vessel. Adherent cells in the group IV were visualized on the entire inner vascular surface in the form of separate cells or their clusters without preferential localization on any of the walls.

Conclusions: Described recellularization procedures have been demonstrated to have identical efficiency concerning the number of adherent cells. Use of LSRP through spiral-oriented vascular circuit allows achieving more uniform adhesion cells and thereby improving efficiency of the graft recellularization.

Keywords: recellularization, decellularized human umbilical arteries, tissue-engineered vascular grafts, mesenchymal stem cells, reversible perfusion

Arginine residues of proteins and their role in binding of cholesterol

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In experiments on animals (rats, guinea pigs, rabbits) lipid-lowering effect of arginine and proteins contain arginine was shown. Cholesterol, triglyceride and atherogenic lipoproteins in the blood serum were reduced. At the same time the antiatherogenic high-density lipoproteins content increased. When administrated intravenously polyarginine to the rabbits the change in lipoprotein spectrum of blood was detected. The effect appeared within 10 minutes after administration, then it restored after 48 hours.

In vitro experiments showed that various proteins interact with cholesterol, depending on their content of arginine residues. If using equimolar amounts of arginine in proteins it was found out that all proteins are able to interact with cholesterol. When adding argininecontaining compounds to various lipoproteins it was shown that they interact with all lipoproteins.

Keywords: arginine residues, cholesterol, triglyceride, atherogenic lipoproteins, HDL

Hypercholesterolemia as heart failure morphological remodeling major factor (experimental atherosclerosis model)

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The aim of this work is to establish the role of hypercholesterolemia in development of heart contractile elements morphological remodeling in processes of heart failure (HF) in experimental atherosclerosis (EA).

Objects and Methods: The experiments were carried out on rabbits in which EA was produced (on 80 male rabbits weighing 2.5-3.0 kg, received a cholesterol -rich diet 0.3 g by kg weight) for study the ultrastructural-functional (UF) changes of the heart, aorta in the various stages of the development atherosclerosis(2 week, 1, 2, 3, 4 and 6 month). The animals were killed with i/v injection of 30 mg Thiopental sodium and the samples of organs after fixation and with corresponding treatment were cut on a Reichert OmU2-ultramicrotome. Section were stained and examined in a Tesla BS-500electron microscope.

Results and Conclusion: Comparative study of aorta wall and myocardial intracellular elements, microcirculatory network show that atherogenic process simultaneously damage those structures, begin of connective tissue elements and among them endothelium (En) UF changes. Microcirculatory elements disturbance provoke the cardiomyocytes alteration. In model of EA early stages (2 week, 1 month) has been pick-out the HF development mechanisms: energetical deficiency provokes mitochondrial structural disturbance- edema and destruction of external membrane. But compensatory mechanisms to restitution of heart homeostasis were revealed. Mitochondrial edema and volume increases provoke extension of cristae and followed energoproduction surface enforcement. After membranes destruction membrane's phospholipids transform to unesterified fatty acids as additional energetical substrates. The second mechanism is lysosomal number increasing. Their contact with mitochondria's membranes provoke its destruction. At this time lysosomal number correlates with mitochondrial division intensifies. It is known that after destruction of mitochondrial membranes its hereditary information goes out in cytoplasm and in condition of enforcement of proteins exchange novel mitochondria are created. Those three basic mechanisms support cardiomyocytes bioenergetic. Later, under hypercholesterolemia, despite mitochondrial hypertrophy and hyperplasia, insufficiently of myocardial energetic demands are revealed. Mitochondria and its cristae number decrease, progress of energy deficiency follows, part of myofibrils from the contractility are excluded and myocardial function commonly decreases. At the late stage of experimental atherosclerosis heterogeneity of contractile myocardium is increased: muscular cells atrophied and diameter of nuclei is sharply reduced. Collagen fibers substitute degenerated muscular fibers. The comparison of intercellular connective tissue dynamics, changes in En, cardiomyocytes with atherosclerotic damages of aorta and large arteries have shown that pathologic process effects arterial and capillary network supporting the opinion that atherosclerosis is systemic disease initiating in the En.

This suggestion may be used as basic mechanism for explication of developing the HF clinical reveals even in early stage of human atherosclerosis under hypercholesterolemia.

Keywords: Experimental atherosclerosis, heart failure, hypercholesterolemia

One century of cholesterol atherosclerosis model creation

Nina Solomonovna Parfenova (Institute of experimental medicine, St.-Petersburg, Russian Federation), ***Yuri Pavlovitch Golikov*** (Institute of experimental medicine, St.-Petersburg, Russian Federation), ***Anatoliy Nikolaevitch Klimov*** (Institute of experimental medicine, St.-Petersburg, Russian Federation)

At 1912 the world will mark by celebration one hundred anniversary since experimental cholesterol atherosclerosis model was created by N.N. Anitchkov and S.S. Chalатов.

Its appearance became an important stage in the development of atherosclerosis pathogenesis and determined the further Anitchkov investigations direction as well as others Russian and world researchers.

The Anitchkov biography and the history of experimental cholesterol atherosclerosis model creation described in details.

The present conception concerning the nature of hypercholesterolemia (Watanabe genetic model), demonstrating the cell receptors importance in the homeostasis maintenance was formulated.

The contribution of N.N. Anitchkov in the atherosclerosis pathogenesis study is enormous.

The experimental cholesterol atherosclerosis model keeps being actual until now and thousands of investigations in different laboratories concerning atherosclerosis pathogenesis have being performed using this model.

Keywords: cholesterol, atherosclerosis, model

Atherosclerosis and antiphospholipid syndrome

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Accelerated atherosclerosis has been described in systemic lupus erythematosus (SLE), but in addition to antiphospholipid antibodies (aPL), medication and hyperlipidaemia are possible explanations for this finding. In the same time it is unclear whether the presence of aPL in non-SLE patients with myocardial infarction (MI) is implicated in the generation of atheroma or thrombus formation. Classical and nonclassical risk factors are presumed to contribute the atherosclerosis progression in rheumatic diseases. aPL may involve in atherosclerotic process.

Objective. To evaluate artery intima-media thickness (IMT) in patients (pts) with antiphospholipid syndrome (APS) and the relationship between the IMT, aPL, antibodies and traditional risk factors of atherosclerosis.

Methods. A total of 206 (57 M, 149 F) pts and 89 healthy controls were included. Mean age and mean disease duration were 35.0 [28.0; 44.0] years and 9.0 [3.8; 18.0] years respectively. Primary APS (PAPS) was diagnosed in 58 pts; 72/206 pts had systemic lupus erythematosus and APS (SLE+APS) and 76/206 pts were with SLE. IgG/M anticardiolipin antibodies (aCL), lipid profile of plasma, traditional risks factors of atherosclerosis and IMT were assessed in all pts. IgG/M anti-beta2-glycoprotein I antibodies and lupus anticoagulant was measured in 115/206 and 59/206 pts respectively.

Results: Thick IMT and atherosclerotic plaques (APs) were detected in 46 pts (9 PAPS, 23 SLE+APS and 14 SLE) and in 25 pts (5 PAPS, 10 SLE+APS and 10 SLE) respectively. None of these differences were significant. The frequency of APs strongly associated with the age, ranging from 1% among those who were younger than 30 years to 11% among those who were 40 years or older ($p=0,01$). 166 (81%)/206 pts had one or more risks factors of atherosclerosis. APs were associated with hypertriglyceridemia (OR 8.06 [95% IC 1.02; 63.52], $p=0,02$), smoking (OR 1.87 [95% IC 1.54; 2.28], $p=0.001$) and with arterial hypertension (OR 5.08 [95% IC 1.86; 18.25], $p=0.03$). MI and stroke were diagnosed at 15 (6 PAPS, 8 SLE+APS and 1 SLE) pts and at 47 (19 PAPS, 27 SLE+APS and 1 SLE) pts respectively and were associated with APs, $p<0.01$ in all cases. The IMT, plaque prevalence, frequency of myocardial infarction, smoking, hypertension and dyslipidaemia did not differ between the groups of patients and healthy controls. Elevated IMT and APs also associated with combined arterial and venous thromboses ($p<0,05$). After we excluded pts older than 40 years, high positive levels of aCL associated with normal IMT and with the absence of APs.

Conclusion: aPL were not associated with subclinical atherosclerosis, but associated with actual vascular complication. aCL can play atheroprotective role. Further investigations are needed.

Keywords: atherosclerosis, antiphospholipid, syndrome

Binding of Lewis Y to Leukocyte Thrombomodulin Mediates Leukocyte Adhesion via Activation of p38 MAPK and β 2-integrins

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In response to vascular injury, endothelial cell-expressed thrombomodulin (TM) modulates inflammation through thrombin and protein C-dependent pathways. However, the role of leukocyte-expressed TM remains largely unknown. We previously demonstrated that the lectin-like domain of TM can bind Lewis^y (Le^y), which is upregulated in endothelial cells upon vascular inflammation and mediates cell adhesion. In this study, we investigated the interaction of leukocyte TM and Le^y in facilitating the adhesion of leukocyte under inflammation. Our results showed that knockdown of TM or treatment with TM-specific antibody in human monocytic THP-1 cells decreased the adhesion of THP-1 cells to inflamed endothelium under shear flow. Blocking TM in THP-1 cells attenuated their binding and adhesion to Le^y, showing the involvement of TM/Le^y interaction in mediating adhesion. Intriguingly, TM polarization was observed in adherent THP-1 cells on activated endothelial cells and Le^y-immobilized flow chamber. Treatment of THP-1 suspension with Le^y triggered p38 mitogen-activated protein kinase (MAPK) phosphorylation via TM. Le^y-induced p38 MAPK phosphorylation enabled both THP-1 and neutrophils to adhere firmly to intercellular adhesion molecule (ICAM)-1 by activating β 2-integrins. In vivo, carotid artery ligation was performed to induce vascular injury in TM wild-type (TM^{flox/flox}) and myeloid-specific TM-deficient (LysMCre/TM^{flox/flox}) mice, in which TM was conditionally knocked out in macrophages and granulocytes. Reduced leukocyte recruitment and neointima formation following ligation were observed in LysMCre/TM^{flox/flox} mice compared with those in TM^{flox/flox} mice. In the presence of Le^y, neutrophils from TM^{flox/flox} were more adhesive than those from LysMCre/TM^{flox/flox} mice. These findings reveal that leukocyte TM facilitates adhesion by binding Le^y, which subsequently induces signals for leukocyte firm adhesion.

Last Minute Poster Presentations

Cardiology/Hypertension

Effects of High Dose Statin on Infarct Size Evaluated by Cardiac MRI in ST-segment Elevation Myocardial infarction Patients Underwent Primary Percutaneous Coronary Intervention

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Objectives: Lipid-lowering therapy with statin may reduce the risk of cardiovascular events. Our study aim was to assess a dose dependent statin effects by using a cardiac MRI for measurement of myocardial infarction size.

Method: We evaluated the cardiac MRI findings of 44 consecutive patients with acute myocardial infarction who underwent a percutaneous coronary intervention in Saint Carollo hospital. Initial and follow-up cardiac MRI was checked at 1 week and 12weeks after revascularization and high dose lipid-lowering therapy (Rosuvastatin 40mg, Group I, n=24) or low dose (Rosuvastatin 5mg, Group II, n=20). In MRI analysis, we evaluated the changes of microvascular obstruction (MVO, first-pass enhancement) and infarct size (delayed enhancement) that was expressed as a percentage of left ventricle area.

Results: There were no differences of baseline characteristics between groups. The mean follow-up periods of cardiac MRI was 12.9 ± 1.2 weeks. The changes of MVO in 2 groups showed a tendency of decreasing size, but there was no significant difference (-1.90 ± 1.49 vs. -1.52 ± 1.83 , $p=0.455$). However the changes of infarct size in Group II was larger than Group I (0.45 ± 2.4 vs 2.27 ± 3.24 , $p=0.013$).

Conclusions: Compared with a low dose, high dose treatment of rosuvastatin significantly suppressed the increasing of infarct size after revascularization in AMI.

Keywords: statin effects, myocardial infarction size, cardiac MRI

Roles of High Density Lipoprotein Cholesterol in Patients with Acute Myocardial infarction

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Many observational studies showed HDL-C is a strong inverse predictor of CV outcome. However, interventional studies to raise HDL-C have failed to show the protective role of HDL-C.

A total of 28,357 AMI patients were enrolled in the Korea Acute Myocardial Infarction Registry (KAMIR) which was a prospective, multi-center, nationwide, web-based database of AMI in Korea. From this registry, we evaluated 3,574 patients with AMI who have follow-up HDL-C level to investigate its association with clinical outcomes. The primary endpoint was the relationship between follow-up change in HDL-C and a 12-month composite of major adverse cardiac events (MACEs). Patients with initial HDL-C > 40 mg/dL showed significantly lower rates of 12-month MACEs, especially cardiac and all-cause mortalities ($p < 0.001$). When patients were stratified into 4 group according to the change of HDL-C, patients with decreasing HDL-C showed significantly higher rates of 12-month MACEs as comparable with patients with increasing HDL-C. A multivariate analysis indicated that HDL-C level was a significant predictor of CV events (hazard ratio, 1.38; 95% confidence interval, 1.12–1.71) after correcting for confounding variables.

The follow-up change in HDL-C level was significantly related with CV outcomes in patients with AMI.

Keywords: High-density Lipoprotein, Acute myocardial infarction, Prognosis

Coronary Atherosclerosis in Patients with Frequent Chronic Obstructive Pulmonary Disease Exacerbations

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Objective: To determine angiographic features of coronary atherosclerosis in patients with frequent chronic obstructive pulmonary disease (COPD) exacerbations

Methods: There was 110 patients with acute coronary syndrome and COPD included in observation, 24 of which (study group) had frequent COPD exacerbations (FE). Selection criteria were: COPD diagnosis; age ≥ 40 years; smoking history ≥ 10 pack-years; acute coronary syndrome at the presentation to hospital; ≥ 1 stent implantation; ≥ 2 COPD exacerbations during last year, diagnosed accordingly to GOLD criteria. Control group had < 2 COPD exacerbations per last year, other including criteria were the same. Based on the coronary angiogram CAG data right coronary artery, left anterior descending artery and left circumflex coronary artery were divide on 2 or 3 (depend on dominance coronary system) segments: proximal, medium and distal. Detail «segment by segment» analysis was used to describe all lesions. $\geq 50\%$ lesions were considered as major, and $< 50\%$ as minor.

Results: There was no significant difference between the groups in regards of age, gender, cholesterol levels, myocardial infarction history, left ventricular ejection fraction, such concomitant diseases as arterial hypertension, diabetic mellitus, chronic kidneys disease. Follow-up median was 19 months. We have found more severe atherosclerotic lesions in group with FE of COPD. The row of features in atherosclerotic lesion distribution and frequency were founded: 1) patient with FE of COPD had higher total number of lesions (6 [5; 7] vs 4 [3; 5] $p < 0,001$), major lesions (3 [2; 4] vs 2 [1; 3], $p < 0,001$) in main arteries and total occlusions in main and collateral arteries (2 [1; 3] vs 1 [1; 1], $p = 0,003$); 2) there was no statistically significant differences in frequency of total lesion number in left main artery, proximal, medium and distal segments in both groups, however the number of proximal (1 [1; 2] vs 1 [1; 1], $p = 0,031$) and distal major lesions (1 [0; 1] vs 0 [0; 1], $p = 0,012$) was significantly higher in group with FE of COPD; 4) extended (> 20 mm) stenosis (no depends of localisation) are more specific for the patients with FE of COPD ($p = 0,016$).

Conclusion: Comparing COPD and FE of COPD individuals, study group possess higher prevalence, extend, and severity of CAD. In some clinical cases such features as prolonged and distant lesions could make difficulties during PCI (needing for long and narrow stent), as well as CABG (needing endarterectomy).

Keywords: chronic obstructive pulmonary disease, coronary artery disease, exacerbations

Case Report

“You are as old as your arteries”! – A Case of Familial Hypercholesterolemia

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Subash Chandra V (Manipal Hospital, Bangalore, India)

Familial hypercholesterolemia (FH) is an autosomal dominant inheritance disease and leads to premature atherosclerotic vascular disease (ASCVD). It is usually underdiagnosed and undertreated. We report a case of FH, which ran a relentless course ending fatally.

A 45 years old male patient was hospitalized for a scheduled transcatheter aortic valve replacement (TAVR). He was a case of FH, with his two brothers having high serum cholesterol levels with tendon xanthoma. He had undergone coronary bypass surgery (CABG) in 1994 at the age of 24 years, redo-CABG in 2007 and coronary artery stenting with a drug eluting stent to left anterior descending artery (LAD) in 2011. Two months earlier, he reported with effort angina and exertional dyspnea. He was found to have xanthelasma, a late peaking aortic stenosis murmur on auscultation, concentric left ventricular hypertrophy with strain on surface ECG, and severe valvular aortic stenosis and moderate LV dysfunction on echocardiography. Serum lipid profile showed a total cholesterol of 369 mg%, triglyceride of 123 mg%, HDL-C of 41 mg% and LDL-C of 304 mg%. Random blood sugar was 74 mg% and serum creatinine 1.7 mg% with a eGFR of 47.6 ml/min/1.73m².

CT aortogram as a preprocedural evaluation for TAVR showed extensive calcification of aortic root, arch and descending aorta, calcification of native coronary arteries, narrowing of intrarenal abdominal aorta and calcification of bilateral internal and external iliac arteries.

The day before he was due for TAVR, the patient had cardiac arrest. With institution of resuscitative measures including intubation and assisted ventilation, he was shifted to catheterization laboratory for emergency balloon aortic valvuloplasty (BAV). After balloon dilatation, the patient went into asystole requiring pacing. But subsequently he had recurrent VT and VF and could not be revived.

This patient of FH had undergone coronary revascularization – CABG twice and coronary stenting once, clearly indicating the very high risk of premature ASCVD in patients of FH. Only high intensity statin (rosuvastatin 40 mg daily) and ezetimibe could be offered to this patient. Newer lipid lowering agents – mipomersen, lomitapide, and PCSK9 inhibitors were not available as was apheresis. Therapeutic life style changes, rosuvastatin and ezetimibe could not achieve the LDL target – absolute or 50% reduction. With a history of two CABG's in the past, he was considered to be at a very high risk for surgical aortic valve replacement. Hence he was posted for TAVR. Unfortunately, the patient had sudden cardiac death and emergency BAV did not help.

A case of FH who had premature ASCVD and aortic stenosis died prematurely. With the recent emergence of PCSK9 inhibitors, the pharmacotherapy might bring some solace to such patients, and may alter the trajectory of the disease process. Early detection and early treatment are important.

Keywords: Familial hypercholesterolemia, Atherosclerotic vascular disease, Stain, PCSK9 inhibitor

Familial hypercholesterolemia

The time course of familial hypercholesterolemia according to a 10-year follow-up in patients with different gene mutations and other coronary heart disease risk factors in Saint-Petersburg (Russia)

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Familial hypercholesterolemia (FH) is one of the most common inherited diseases with a worldwide frequency of 1/500 in heterozygous and 1/1000000 in homozygous conditions. FH patients have significantly higher risk of coronary heart disease (CHD) and premature death than healthy individuals.

A total of 184 patients with FH according to the Dutch Lipid Clinic Network Score ≥ 8 have been screened in our clinic and followed-up of 10 years and more. This group included men and women aged 18-82 (mean age – 46 years) with 80 index patients and 104 – their close relatives.

CHD was diagnosed in 47% of FH patients (39% of males and 21% of females had previous myocardial infarction). The onset of the disease was, on average, 10 years later in females than in males besides of the same LDL-cholesterol level.

LDL receptor gene mutations were revealed in 45 probands, with original gene mutations found in 38 cases. Due to high heterogeneity of FH-causing mutations in Saint-Petersburg we failed to establish interrelations between type of LDL-receptor gene mutation and severity of atherosclerosis and CHD time course. We compared LDL/HDL ratio in 3 groups of FH patients: 1 – free of CHD, 2 – with stable CHD, 3 – with progressive and complicated CHD during the follow-up period. LDL/HDL ratio was found to be 5.2, 7.7, and 10.5, respectively ($p < 0,05$).

14% of the FH patients didn't take any hypolipidemic medications at the onset of the follow-up, whereas 61% took statins and 25% had statin + ezetimibe. Nevertheless, 26% of patients in the treated group didn't achieve the target LDL-cholesterol levels during the study. 40% of patients who didn't reach LDL goals were current smokers (compared with 5% in the group that reached LDL goals).

27 (14,7%) patients died during the study and there was only one death of cancer, with all other deaths having been of cardiovascular origin. It is important that 60% of FH patients who died during the prospective study had developed fatal myocardial infarction. Death rates in FH patients were strongly associated with age, male sex, LDL/HDL ratio, smoking, and effect of hypolipidemic treatment.

FH is strongly associated with high CHD risk; the time course of FH is much more favorable in females than in males besides of the same LDL-cholesterol levels. Type of gene mutation doesn't influence lipid levels and clinical manifestations of FH. Wide screenings are needed to reveal the disease at its early stages, especially in high risk populations.

Keywords: familial hypercholesterolemia, LDL-receptor gene mutations, the time course of familial hypercholesterolemia

Severe dyslipidemia and cardiovascular risk in the middle aged Lithuanian adults

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Objective: The aim of our study was to determine the prevalence of severe dyslipidemia in Lithuanian middle aged primary prevention population and investigate cardiovascular risk profile of these patients in compare with control group.

Material and methods: The group of 83376 people were examined in the Lithuanian High Cardiovascular Risk primary prevention program (LitHiR), during 2009-2015 years. This study recruited men aged 40-55 and women aged 50-65 without overt cardiovascular disease. The prevalence of cardiovascular risk factors was compared between severe dyslipidemia group and those without dyslipidemia, who were included in control group.

Results: Severe dyslipidemia was present in 13.5% (11265) of the subjects; 66.6% (7508) were females. Three or more risk factors more frequent had people with severe dyslipidemia in compare with people in control group (84.5% vs. 44.1%, $p < 0.001$). The subjects with severe dyslipidemia had significant higher rates of arterial hypertension (63.5% vs. 44.2%, $p < 0.001$), diabetes mellitus (16% vs. 8.1%, $p < 0.001$), abdominal obesity (51% vs. 30.3%, $p < 0.001$), body mass index (BMI) > 30 (kg/m²) (38.8 % vs. 24.1%, $p < 0.001$), metabolic syndrome (47.2 % vs. 9.2 %, $p < 0.001$), unbalanced diet (66.5% vs. 53.5%, $p < 0.001$), insufficient physical activity (56% vs. 44.2%, $p < 0.001$), anamnesis of CVD (29.7% vs. 22.7%, $p < 0.001$) in compare with control group. The subjects without dyslipidemia had significant higher rates of smoking (26.4% vs. 22.7%, $p < 0.001$). According to the abnormal lipid levels and family anamnesis, the prevalence of familial hypercholesterolemia was 0.1 %, familial hypertriglyceridemia – 0.2 % and familial mixed dyslipidemia – 0.1% of the subjects examined in the LitHiR programme.

Conclusions: Severe dyslipidemia is associated with higher frequency of other cardiovascular risk factors. According to the abnormal lipid levels and family anamnesis, the prevalence of familial hypercholesterolemia was 0.1 %, familial hypertriglyceridemia – 0.2 % and familial combined dyslipidemia – 0.1%. Our results suggest that dyslipidemia is likely to be a major contributor to the high cardiovascular mortality among Lithuanian middle aged population.

Keywords: severe dyslipidemia, primary prevention, cardiovascular risk factors

Amplicon extension allows finding more mutations in familial hypercholesterolemia

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We aimed to identify the majority of mutations causing familial hypercholesterolemia (FH) in Petrozavodsk sample. For this purpose we have studied low density lipoprotein (LDL) receptor gene sequence variation in FH patients with two sets of primers, either (1) amplifying all exon sequences or (2) allowing to analyze also the exon-intron boundaries. Most of mutations, namely c. 245G>C [*p.(Cys82Ser)*], c.1222G>A [*p.(Glu408Lys)*], c.1327 T>C [*p.(Trp443Arg)*], c.1859 G>C [*p.(Trp620Ser)*] were detected with both sets of primers, but only the second set was of use for identification of c.313+2T>G (IVS2+2T>G) mutation in the invariant donor splicing site sequence of the third intron. Out of the mutations reported in the current study, *p.(Trp443Arg)* was previously reported in Russian patient from Moscow, and the change *p.(Glu408Lys)* was characterized in different populations in the world, but unknown in Russia. Three other sequence variants were new, previously undescribed from other populations in the world and most probably causative for FH development. Our investigation demonstrates specific features of Karelian population in respect to LDL receptor gene mutation spectrum, and supports the opinion about the necessity of exon-intron boundaries analysis in the LDL receptor gene when studying genetic basis of FH.

The research was supported in part by RFBR grant 15-04-03513. Sequencing reactions were performed in St. Petersburg State University Resource Centre “Development of Molecular and Cell Technologies”.

Keywords: exon-intron boundaries, familial hypercholesterolemia, low density lipoprotein receptor, mutation, Petrozavodsk

Lomitapide in homozygous familial hypercholesterolemia – Clinical experiences

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Background: Lomitapide is a new class of drug for reducing LDL-cholesterol (LDL-C) significantly by inhibiting the microsomal transfer protein (MTP inhibitor). Inhibiting MTP reduces assembly of chylomicrons in the intestine and of VLDL in the liver and thus the amount of circulating LDL-C. Since this effect is independent of functionality of LDL-receptors Lomitapide might be a unique option for patients with homozygous familial hypercholesterolemia (hoFH) who are endangered by extremely high levels of LDL-C and subsequently early development of cardiovascular disease.

Methods: Nine patients with hoFH were started on Lomitapide in a clinical setting (named patient program). All patients were advised to reduce fat intake < 20 % of caloric intake and to refrain from alcohol; concomitant maximal lipid lowering medication was stable and the apheresis schedule (9 of 10) is adapted according to LDL-C levels.

Results: Three patients had no problems to follow diet instructions and to increase the dose, three have two started just recently, and three had unrelated medical conditions delaying regular treatment.

Weight is stable except in patient 1 who started exercising additionally and lost 25 kg. Pre apheresis LDL-C is reduced markedly in all patients. Patient 1: LDL-C -31% (5 mg), -42% (10 mg), -52% (20 mg); patient 2: -61% (10 mg); patient 3: -10% (5 mg), -37% (10 mg), -59% (20 mg). In patient 1 apheresis frequency was reduced from every week to every two weeks. Liver enzymes increased repeatedly in patient 1 due to alcohol intake and decreased with abstinence.

Conclusions: Even low dose Lomitapide reduced LDL-C markedly and treatment goals may be reached in the course of treatment for the first time in these patients who have extremely high LDL-C levels from birth on. Necessity for lipoprotein apheresis might be reduced in the future. Lomitapide proves to be well manageable and tolerable in clinical settings in most patients. Strict guidance and adherence to diet restrictions are very important to prevent or reduce possible side effects. Long term data will have to show safety as well as reduction of cardiovascular events in addition or comparison to lipoprotein apheresis.

Keywords: homozygous familial hypercholesterolemia, Lomitapide, MTP inhibitor, LDL-cholesterol

International comparison of primary care knowledge and practices of familial hypercholesterolaemia (FH)

Gerald F Watts (University of Western Australia, Perth, Australia)

Objectives: To determine primary care physicians (PCPs)' awareness, knowledge and practices regarding the care of FH.

Methods: A formal questionnaire was anonymously completed by physicians in 10 different countries (Australia, Japan, Malaysia, Vietnam, India, the Philippines, United Kingdom, China, South Africa and South Korea). The survey sought responses relating to general familiarity, awareness of management guidelines, identification (clinical characteristics and lipid profile), prevalence and inheritance, extent of elevation in risk of cardiovascular disease (CVD), and practice on screening and treatment.

Results: 1,433 physicians completed the questionnaire with only 33% considered themselves to be familiar with FH. 76% correctly defined FH and 65% identified the typical lipid profile, with a higher proportion of physicians from United Kingdom, China and Japan selected the correct FH definition and lipid profile compared with those from South Korea, India and Vietnam. However, less than half of the physician across the 10 countries were aware of national or international management guidelines (38%), or correctly defined the prevalence (27%), inheritance (41%), and CVD risk of FH (11%). 56% suggested PCPs as the most effective health professional to detect FH. The majority of the physicians also considered laboratory interpretative comments are useful (82%) and statin therapy is an appropriate cholesterol-lowering therapy (91%) for FH management.

Conclusions: The study identified substantial deficits in the awareness and knowledge of FH among physicians in the region. Implementation of country-specific guidelines and extensive work in FH education and awareness programs are imperative to improve the care of FH.

Keywords: Familial hypercholesterolaemia, Cardiovascular disease, Lipid management

International Comparison of Services and Facilities for the Care of Familial Hypercholesterolaemia (FH)

Gerald F Watts (*University of Western Australia, Perth, Australia*)

Aim: To describe existing health services, facilities and resources for the care of FH in countries in the Asia-Pacific region, South Africa, Brazil and United Kingdom.

Methods: A formal questionnaire that investigates the six key elements of a desirable FH model of care (availability of national guidelines and protocols, lipid clinic network, DNA testing facilities, paediatric and cardiovascular imaging services, and apheresis facilities) was completed by leading experts in FH from 15 countries (Australia, Brazil, China, Hong Kong, India, Japan, Malaysia, New Zealand, the Philippines, Singapore, South Africa, South Korea, Taiwan, United Kingdom and Vietnam).

Results: 94 leading experts in FH completed the questionnaires. Of the 15 countries or regions studied, 45% had established national guidelines and protocols for FH management. Only 30% had a network of lipid clinics. More than half of the countries provided genetic (53%) and paediatric services (66%) to FH patients. Formal LDL apheresis service was only available in 7 countries (45%). All 15 countries or regions had cardiovascular imaging facilities available for FH patients. Australia, United Kingdom and Japan are the three countries providing all six services and facilities to FH patients. In contrast, the care of FH in Vietnam and the Philippines is suboptimal with less than three services and facilities available in their countries.

Conclusions: This survey has identified important gaps in services and facilities for FH management. Further focus on implementation of national management guidelines, lipid clinic network and apheresis facilities are required, particularly in less developed countries.

Keywords: FH management

Genetics

Mitochondrial DNA mutations as promising biomarkers of predisposition to metabolic syndrome

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Several mutations of mitochondrial DNA (mtDNA) were shown to be associated with carotid atherosclerosis. Since metabolic syndrome (MS) shares many risk factors with atherosclerosis, we have studied possible association between MS and proatherogenic heteroplasmic mtDNA mutations.

The extent of carotid atherosclerosis was determined in 191 persons B-mode ultrasonography. The presence of MS was established by IDF 2009 criteria. The level of mtDNA heteroplasmy in leukocytes was determined by qPCR. The severity of MS was estimated by integral MS index derived from the data on waist circumference, triglycerides, systolic and diastolic blood pressure, HDL cholesterol and fasting glucose.

In 20% study participants MS was diagnosed. Among 10 mtDNA mutations known to be associated with carotid atherosclerosis, T3336C heteroplasmy level correlated with the severity of MS ($r=0.221$, $p=0.002$), obviously due to correlation with such MS components, as triglycerides ($r=0.290$, $p<0.001$) and fasting glucose ($r=0.180$, $p=0.013$). Other mtDNA mutations correlated with single components of MS only (e.g., del652G and G12315A with triglycerides; A1555G, C3256T and G15059A with SBP; A1555G with fasting glucose). As for association of MS and carotid atherosclerosis, we did not find statistically significant relationship between MS index and carotid intima-media thickness (correlation coefficient, 0.119, $p=0.1$).

Thus, known proatherogenic mtDNA mutations failed to explain variability of MS in general, except of its single components, thus allowing to consider that genetic mechanisms of mitochondrial dysfunction are rather different in metabolic syndrome and atherosclerosis.

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Keywords: metabolic syndrome, atherosclerosis, mitochondrial DNA, mutations, carotid intima-media thickness

Metabolic Syndrome (Diabetes, Obesity)

Clinical experience with Exenatide and Liraglutide in the internal medicine service two of hospitals in Valencia

Antonio Robles (Hospital of Requena, Valencia, Spain)

Background and objective: The upcoming new marketing presentations GLP1 analogues with a dosage more comfortable for the patient, we wanted to revise the two we currently have on the market. The target of this study is to determinate glicated hemoglobin (HbA1c) at 6 months of treatment, changes in weight, body mass index and tolerance.

Design and methods: Observational study that included 60 patients with diabetes mellitus type 2 (DM2) followed in the Internal Medicine Service of two hospitals in Valencia. The inclusion of patients was consecutive until achieve 30 patients with each of the treatments. Dose reached: Exenatide 10 mcg twice daily and Liraglutide 1.2 mg daily. Determinations baseline and 6 months of treatment.

Results:

- After 6 months of treatment with exenatide, the weight loss was 2.99 ± 5.12 kg ($p < 0.01$), Body Mass Index (BMI) reduction 1.36 ± 1.18 kg/m² ($p < 0.0001$), of HbA1c $0.84\% \pm 2.06$ ($p < 0.05$) and of fasting glucose 23.63 ± 59.12 mg/dl ($p = 0.09$).
- After 6 months of treatment with Liraglutide, the weight loss was 3.18 ± 3 kg ($p < 0.05$), BMI reduction 1.18 ± 1.67 kg/m² ($p < 0.05$), of HbA1c $0.9\% \pm 1.9$ ($p < 0.05$) and of fasting glucose 27.31 ± 73.18 mg/dl ($p < 0.05$).
- Further reduction of BMI (0.18 ± 0.77 kg/m²) in the group treated with Exenatide ($p > 0.05$).
- Greater weight loss (0.19 ± 2.18 kg), greater reduction fasting glucose (21.18 ± 3.68 mg/dl) and a HbA1c greater reduction ($0.06\% \pm 0.610$) in the group treated with Liraglutide ($p > 0.05$).
- 10 patients (33.3%) had gastrointestinal intolerance in the group treated with Exenatide and 4 (13.33%) in the group treated with Liraglutide (3 gastrointestinal intolerance and 1 dizziness).
- 5 dropouts in the group of Exenatide (3 gastrointestinal intolerance, 2 insufficient metabolic control) and 3 in the Liraglutide group (2 gastrointestinal intolerance, 1 insufficient metabolic control).

BASELINE DATA	Exenatide	Liraglutide
Weight (Kgr)	102.61 (13.45 SD)	105.73 (24.19 SD)
BMI	38.19 (6.15 SD)	41.35 (7,11 SD)
Fasting glucose (mgr/dl)	189.56 (71.25 SD)	183.35 (SD)
HBA1c (%)	8,9 \pm 0.6	8,8 \pm 0,8

Discussion: Both drugs have comparable results to its pivotal trials. Although our study objectives were achieved by Liraglutide Exenatide in reducing excess weight, fasting glucose and HbA1c, these variations do not show statistical significance. Neither the difference in favor of Exenatide in BMI reduction target.

Liraglutide has the advantage of being administered 1 time daily, which involves a better quality of life for the patient. In our study, we found no statistically significant differences between Exenatide and Liraglutide.

Conclusions: Both drugs have very interesting clinical results in both efficiency (comparable to DPP4) and scarce secondary events. Notably Liraglutide currently offers an additional advantage for their a daily dosing.

Keywords: liraglutide, exenatide, diabetes mellitus, body weight

Combination therapy in diabetic patients with insulin glargine and exenatide in the internal medicine services of two hospitals in Valencia

Antonio Robles (Hospital of Requena, Valencia, Spain)

Background and objective: Combination therapy in diabetic patients is seeking better clinical outcomes by acting on different targets in the pathophysiology of the disease.

Insulin glargine provides excellent glycemic control, especially in the fasting glucose control, in spite of an increasing in weight, compared with exenatide which is more effective in controlling postprandial glycemic and in reducing insulin resistance, plus a reducing effect on the weight.

Design and methods:

- Men/Women: 12/18, age 67.36 ± 4.4 years, duration of diabetes 19.6 ± 4.7 years.
- Baseline Data: weight 106.51 ± 7.24 kg, body mass index (BMI) 41.25 ± 3.1258 kg/m², glicated hemoglobin (HbA1c) 8.8 ± 0.61 , $64.97 \pm$ insulin dose 18.64 UI.
- Changes in insulin requirements UI/Kg: Baseline 0.61 ± 0.18 , at 3-6 months 0.39 ± 0.06 and 0.23 ± 0.36 at 9-12 months. Significant reduction in insulin dose: 35.65% at 3-6 months and 48.65% at 9-12 months. Insulin was removed in 5 patients.
- Changes in weight: All patients lost weight: 4.6 ± 2.73 kg at 3-6 months and 8.4 ± 6.23 kg at 9-12 months.
- HbA1c evolution: Reduced by 83.2% at 3-6 months and 85.3% at 9-12 months. The mean reduction in HbA1c was 0.9 ± 1.03 at 3-6 months and $1.3 \pm 1.22\%$ at 9-12 months.
- Tolerance: Withdrawal for Exenatide in 4 patients (13.3%): 2 gastrointestinal intolerance and another 2 by insufficient metabolic control.

Conclusions: The combined use of insulin glargine and exenatide improves glycemic control and in many cases allows the reduction of insulin dose, obtaining further reduction in weight, which makes this partnership a first-choice treatment in of patients with type 2 diabetes and BMI over 30 Kg/m².

Keywords: diabetes mellitus, glargine, exenatide

Varia

Does atherosclerosis affect microcirculatory function?

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Objective: The purpose of this study was to determine, whether atherosclerosis affect microcirculatory function.

Materials and methods: This study enrolled 26 patients with established coronary artery disease (CAD) (55.8 ± 5.3 years; 24 males) and 21 healthy subjects (49.1 ± 5.6 years; 15 males). Patients with hypertension and diabetes were excluded. Microcirculation was assessed using laser Doppler flowmetry (LDF) at rest and with the vasoconstrictor (respiratory, cold and venous occlusion) and vasodilator (heating, electrostimulation and arterial occlusion) tests on the ulnar part of the forearm. Basal skin perfusion and the maximum relative increase/decrease in skin blood flow to each stimulus were determined.

Results: No significant differences were observed between two groups in basal skin perfusion. However, patients with CAD showed significantly increased vasoconstrictor response in cold test ($p < 0.05$) with no difference in respiratory and venous occlusion test. Additionally, vasodilator response to local heating and arterial occlusion was significantly reduced in patients with CAD compared with healthy subjects (both $p < 0.05$). Vasodilator response to electrostimulation was similar between two groups.

Conclusion: The results of cold test in patients with CAD are suggestive of enhanced constrictor response to sympathetic (noradrenergic) stimulation. Decreased vasodilator reserve in heating test indirectly indicates vasomotor dysfunction of microvascular endothelium in patients with CAD. Decreased response to arterial occlusion test in patients with CAD suggests impaired microvessel sensitivity to products of ischemic metabolism and possible regulatory effect of prostanoid metabolites.

Keywords: atherosclerosis, microcirculation, laser Doppler flowmetry

Loosening of apoA-I C-domain structure may facilitate ABCA1-dependent cholesterol efflux

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Site Directed Mutator (SDM) web-server was used in the present study to obtain stability score $\Delta\Delta G$ as an analog to the free energy difference between a wild type and mutant protein. The positive and negative $\Delta\Delta G$ values correspond to stabilizing and destabilizing stability changes, respectively, and $\Delta\Delta G$ absolute values exceeding 2 kcal/mol have been suggested as a threshold for protein malfunction. The functional mutations without gross stability change may influence the specific allosteric and binding sites in the protein structure. The changes in structure stability induced by missense mutations in C-domain of free apoA-I were analyzed in relation to mutation-induced changes in apoA-I ability to perform as cholesterol acceptor in cholesterol efflux assay. The crystal structure of free apoA-I truncated at N-end by 43 residues (PDB 1AV1) was used as structure template along with the gathered data on basal and cAMP-stimulated (ABCA1-dependent) cholesterol efflux for mutants compared to wild type apoA-I. We found significant negative correlation between apolipoprotein stability and the efficiency of cAMP-stimulated efflux, while correlation with basal efflux was insignificant. Importantly, the $\Delta\Delta G$ changes due to the mutations were neither accompanied by the change in helix content nor in resistance of the secondary structure to chemical denaturation, probably, due to the contribution of tertiary structure to stability score by SDM. The ability to mediate cAMP-stimulated efflux was lost completely in apoA-I mutants with an increase in stability higher than 2.4 kcal/mol. That coincides with the border between functional and structural mutations. Thus we conclude that (1) apoA-I C-domain is likely essential for cholesterol efflux, and (2) structure-destabilizing changes may significantly contribute to ABCA1-dependent cholesterol efflux mediated by free apoA-I.

Keywords: apoA-I, protein stability, protein structure, cholesterol efflux

Atherosclerosis as hidden target organ damage in patients infected by HIV.

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Introduction: Cardiovascular disease among HIV-infected patients is more frequent than in the general population. However, the prevalence of clinically atherosclerosis in HIV patients is lower. Therefore diagnose in its subclinical phase is very important because we are in a potentially reversible stage.

Background: The prevalence of subclinical atherosclerosis by pulse wave velocity (PWV) seen in the Internal Medicine doctor's office of two Spanish hospitals. We also studied other risk factors involved in cardiovascular risk, such as smoking, diabetes, dyslipidemia, hypertension, antiretroviral treatment (ART) or hepatitis C virus (HCV) coinfection, in addition to their calculated risk score and its correlation with PWV.

Material and Methods: A cross-sectional study where there were including 70 HIV positive patients visited from January to June 2015. We excluded patients already diagnosed with vascular disease. We performed PWV measurement using Mobil-O-Graph® © (pathological ≥ 12 m/seg). Patients were divided into 2 groups with the cutoff at age 50 and performed laboratory tests and urine.

Results: The mean age of patients was 49.8 ± 9.6 years and 79% were male. The mean duration of illness was 15.8 years. More than a third (34.9%) had already been diagnosed of AIDS. Cardiovascular risk factors more prevalent were: smoking (74%), dyslipidemia 58%, type 2 diabetes mellitus 12%, hypertension 9%, albuminuria 7.2%, and mean body mass index was 25.7. A 18.57% (13/70) of patients had a \geq VOP 12m/seg, and in multivariate analysis only HCV coinfection and the group over 50 years showed statistical significance.

Conclusions: The prevalence of subclinical atherosclerosis in our population of HIV is similar to other studies of international medical literature. Only patients coinfecting with HCV and those who aged were over 50 years, appear to have a direct relationship with the onset of this. These results may depend on the low average age of HIV patients studied.

Keywords: Atherosclerosis, Human Immunodeficiency Virus, Cardiovascular risk

Incidence of perioperative myocardial infarction following coronary artery bypass grafting (CABG)

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Introduction: Myocardial infarction after coronary artery bypass grafting is a serious complication and one of the most common causes of perioperative morbidity and mortality. **Aim of the study:** To determine the incidence of perioperative myocardial infarction and to detect predictors in hospital and 30 days clinical outcome related to perioperative myocardial infarction by using hs-TnI and evaluated the utility of adding to the troponin criteria new Q-waves or imaging evidence of new wall motion abnormality as suggested in the Universal Definition of MI. **Methods:** The study enrolled 250 consecutive patients undergone isolated CABG at the National Heart Institute, Cairo, Egypt and Benha University hospital, Benha, Egypt in the period from November 2013 to May 2014 (6 months). Threshold of 700 ng/l (10-times 99th percentile upper reference limit) of hs-TnI was prescribed plus ECG and or Echoardiographic evidence of new wall motion abnormality. **Results:** Perioperative MI was reported in 11% of patients after CABG with worse in hospital and 30 days clinical outcome. The study showed that, Body mass index, prior heart failure, EuroScore, Left main coronary artery stenosis > 50%, lesion type, % diameter stenosis and length, Aortic cross clamping time and Extracorporeal circulatory time were significant independent predictor of perioperative MI, $p < 0.05$. Perioperative MI was associated with increased risk of arrhythmias, heart failure and death. **Conclusion:** perioperative myocardial infarction is an important adverse event with worse clinical outcome after CABG.

Keywords: Coronary artery bypass surgery, high-sensitivity troponin, myocardial infarction, heart failure

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