
THE RELATIONSHIP BETWEEN INFLAMMATORY MARKERS AND METABOLIC SYNDROME AND CORONARY ATHEROSCLEROSIS AMONG INHABITANTS OF YAKUTIA: ETHNICITY AND GENDER FEATURES

A.N. Romanova, M.I. Voevoda, A.S. Golderova

The relationship of inflammatory markers (interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α), interferon- γ (INF- γ) and C-reactive protein (C-RP)) with metabolic syndrome (MS) and coronary atherosclerosis among inhabitants of Yakutia depending on ethnicity and gender was studied. The results of the survey of men and women at the age of 45-64 years with verified coronary atherosclerosis and without clinical signs of coronary heart disease (CHD) are analyzed. The results of the research showed that in patients with metabolic syndrome complicated by coronary atherosclerosis in comparison with persons without clinical signs of CHD the levels of the all studied inflammatory markers were higher. The significant ethnicity and gender differences are revealed. Ethnicity differences were characterized by elevated IL-6 levels among non-native people of Yakutia unlike native population. Gender differences were characterized by the increase of IL-6 levels in women, than in men. In native men with coronary atherosclerosis the INF- γ level in comparison with non-native was higher.

Keywords: inflammatory markers, metabolic syndrome, coronary atherosclerosis, native and non-native inhabitants of Yakutia.

INTRODUCTION

Atherosclerosis – chronic disease, the pathogenesis of which is associated with inflammatory processes at the level of the vascular wall [23]. In formation of atherosclerotic plaque the smooth muscle cells, monocytes (macrophages) and lymphocytes which collect in the vascular wall in response to the release of inflammatory mediators, are involved. The inflammation contributes to the deposition of lipids in the vascular wall, has essential value in the destabilization of atherosclerotic plaque and development of atherothrombotic complications [1, 8].

Scientific researches in the recent years showed that the adipose tissue is biologically active and plays the important role in the development of mechanisms of inflammation. The greatest contribution to the development of MS and atherosclerosis brings super secretion of visceral

adipocytokines such as IL-6, IT-8, INF- γ and TNF- α , which are directly involved in the formation of chronic latent subclinical inflammation at the MS and play the important role in the development of atherosclerosis and their complications [1, 3, 14, 19, 29]. System activation of cytokines is predictive marker of the severity of progressing of MS and atherosclerosis [18, 20, 21, 26]. The IL-6 promotes the growth and differentiation of T- and B-lymphocytes, stimulates the production of acute phase proteins. The IL-6 production by adipose tissue is increased in persons with overweight. The IL-6 has direct effect on the formation of insulin resistance at the level of hepatocytes, inhibits the metabolic effects of insulin by blocking of insulin-dependently activation of signal transducer, insulin - induced of glycogen synthesis. The high IL-6 levels are associated with suppression of hepatic glikogensyntetase, activation of glycogen-phosphorylase and lipolysis, increased production of triacylglycerols [18, 21, 28]. Standing out a bit later, than IL-1 β and TNF- α , the IL-6 inhibits their formation (they on the contrary stimulate its release) and therefore belongs to cytokines, development of inflammatory reaction [3, 10]. The IL-8 acts as inductor of acute inflammatory reaction, stimulating adhesive properties of neutrophils and hemotaxis of T-lymphocytes. Suppressing the expression of tissue inhibitor of metalloproteinases-1 in macrophages with subsequent amplification of metalloproteinase activity, IL-8 causes destabilization of atherosclerotic plaque. The increased IL-8 level is associated with risk to the development of unstable angina and myocardial infarction [8, 30]. The INF- γ is produced by T-lymphocytes and NK-cells and promotes the formation of cellular immunity, keeping of inflammatory process in the lesion, increasing the cytotoxic activity of cells, infiltrating the diseased tissue, increased the phagocytic, adhesive ability of macrophages. Interacting with proapoptogenic factors, the INF- γ increased death of cells by apoptosis. Metabolic effects of INF- γ aren't fully understood. The INF- γ activates cytokine production by macrophages, stimulates the immune cytotoxicity, involved in lipid metabolism, reduces the activity of lipoproteinlypase and synthesis of its matrix ribonucleic acid by adipose tissue and enhances of lipolysis in adipocytes [8]. The TNF- α is one of key mediators to the development of insulin resistance, mainly produced by monocytes / macrophages, endothelial cells and mast cells. In patients with obesity reveal increase of TNF- α level in blood serum. The main cause of reduced secretion of adiponectin at the obesity, possessing anti-atherogenic and anti-diabetic properties associated with ability to suppress of gene of TNF- α expression of adiponectin. The TNF- α has the multiple effect on different types of cells by modulation of genes expression of growth factors, cytokines, factors of transcription, cellular receptors, acute phase proteins [8, 12, 25]. The C-RP – protein of acute phase of inflammation, is generally synthesized in hepatocytes under influenced by cytokines (mainly IL-6, TNF- α and IL-1 β), is nonspecific marker of inflammation. The C-RP level in healthy people has the risk factor in the development of CHD and

acute myocardial infarction, in patients with cardiovascular disease – adverse prognostic sign [6, 8]. The majority of researchers considered C-RP as indicator of instability of atherosclerotic plaque. It is assumed that the mechanisms leading to destabilization of atherosclerotic plaque are induction of C-RP of the endothelial dysfunction, increased level of the production of adhesion molecules, stimulating of the formation of foam cells, activation of the complement system in the atherosclerotic plaque [9, 31].

Thus, existing data of the role of inflammatory markers in the development of MS and atherosclerosis give the opportunity to consider them as predictors of cardiovascular disease and their complications. Increase of morbidity and mortality from cardiovascular disease and their complications dictate the need for new approaches to atherosclerosis treatment. One of perspective approaches of treatment is creation of anti-atherogenous vaccines [4].

The **purpose of research** was studying of relationship of inflammatory markers, such as, IL-6, IL-8, FNO- α , INF- γ and C-RP, with metabolic syndrome and coronary atherosclerosis among inhabitants of Yakutia depending on ethnicity and gender.

MATERIAL AND METHODS

The study was conducted within the framework of a joint program of the Yakut Scientific Centre of Complex Medical Problems SB RAMS and Institute for Internal Medicine SB RAMS “Atherosclerosis: epidemiology, etiopathogenesis and development of measures of prevention, diagnosis and treatment among inhabitants of Far North by example of the population of Yakutia”. The research is approved by local committee on biomedical ethics of Yakut Scientific Centre of Complex Medical Problems SB RAMS (the protocol №13 of November 27, 2008). Results of survey of 396 men and 60 women are included in research at the age of 45-64 years with the verified coronary atherosclerosis according to selective coronaroangiography, being on stationary inspection in Cardiological branch of Republican hospital №1-Natsional center of medicine of Yakutsk which made the main groups. In forwarding conditions to areas of the Sakha Republic (Yakutia) by results of complex medical examination comparison groups of 212 men and 271 women without clinical signs of CHD at the age of 45-64 years are created. Research period: 2007-2010. For the comparative analysis the surveyed persons were subdivided into 4 groups: 1 – patients with the verified coronary atherosclerosis, representatives of native people of Yakutia ($n=217$), from them men – 189, middle age $54,34 \pm 0,44$ years, women – 28, middle age $53,39 \pm 1,28$ years; 2 – patients with the verified coronary atherosclerosis, representatives of non-native people of Yakutia ($n=239$), from them men – 207, middle age $54,76 \pm 0,43$ years, women – 32, middle age $55,81 \pm 1,01$ years; 3 – persons without clinical signs of CHD, representatives of native people ($n=253$), from them men – 108, middle age $51,28 \pm 0,57$ years, women – 145, middle age $51,19 \pm 0,43$ years;

4 – persons without clinical signs of CHD, representatives of non-native people (n=230), from them men – 104, middle age $51,09 \pm 0,52$ years, women – 126, middle age $51,37 \pm 0,47$ years. Yakuts are considered to be representatives of native nationality, non-native nationality – Russians, Ukrainians and the Belarusians living in Yakutia constantly.

Criteria of exception: anomalies of development of coronary arteries, intact coronary arteries, existence of unstable stenocardia, acute myocardial infarction in the anamnesis till 6 months for groups of patients; diagnosed of CHD for comparison groups; the acquired and congenital heart diseases, cardiomyopathy, worsening of any chronic diseases, age are more younger than 45 years and of 65 years and are more senior for all groups.

The survey was spent by standard techniques and included the following obligatory sections: standard poll under Rosers questionnaire (for comparison groups) and the questionnaire developed for estimation of objective condition; triple measurement of arterial pressure; anthropometrical survey with measurement of waist (WC) and hips (HC) circumferences and calculation of index WC/HC; electrocardiogram registration in rest; selective coronaroangiography (for patient groups); blood sampling from elbow vein in the morning on empty stomach with 12-one-hour break after meal for revealing of lipid (definition of total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) levels) and carbohydrate (blood glucose level) metabolisms, and also of immunological indicators (of interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α), interferon- γ (INF- γ) and C-reactive protein (C-RP) levels). Biochemical parameters were decided by enzymatic method for the automatic analyzer “Cobas mira plus” of La Roshe firm, Switzerland using of commercial sets of “Biocon”, Germany. For methods of immunofermental analysis used sets of firm ZAO “Vektor-Best”, Novosibirsk (definition of IL-6, IL-8, FNO- α and C-RP levels). The low-density lipoprotein (LDL) levels was calculation by the formula $LDL = TC - (HDL + TG / 2,18)$ mmol/l (Friedewald W.T. et al. 1972). The selective coronaroangiography was spent on angiographic installation “Axiom. Artis BA” (Siemens, Germany) by standard technique of Judkins. Degree of stenosis of coronary arteries was determined automatically by classification of American college of cardiology (ACC) and American cardiological association (ACA). For diagnosis of MS used the criteria of VNOK (2009). The MS was diagnosed in the presence of central obesity and two additional criteria. All researches are executed from the informed consent of examinees according to ethical standards of the Helsinki declaration (2000). Estimation of results spent on the standard classifications.

The statistical processing of data been conducted with the program SPSS (version 13). Tested for normal distribution of studied quantitative indices was performed by Kolmagorov-Smirnov's test. We've made correlation and multiple-factors analyses. Results are presented in the form of $M \pm$

to m , where M – average value, m – standard error of average value. Standard criteria for evaluating of statistical hypotheses: t -Student criterion, Mann-Whitney, χ^2 -Pearson were used. Distinctions were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The frequency of MS was significantly higher in both ethnicity and gender groups of patients with coronary atherosclerosis in comparison with persons without CHD (native: men – 52,9 vs 16,7%; women – 67,9 vs 20%; non-native: men – 67,1 vs 19,2%; women – 96,9 vs 25,4% accordingly, $p=0.000$). The frequency of MS was higher in non-native people of Yakutia, than in an indigenous people (patients: $p_m=0.004$; $p_w=0.003$, in comparison groups the distinction were traced at the level of tendency). The gender differences in group of patients with coronary atherosclerosis among non-native nationality were characterized by the higher frequency of MS in women in comparison with men ($p=0.001$).

The C-RP, FNO- α , IL-6 and IL-8 levels ($p=0.000$) (the INF- γ level in comparison groups wasn't defined) were significantly higher in patients with coronary atherosclerosis in both ethnicity and gender groups in comparison with persons without CHD, which coordinated with inflammatory cytokine's role in the development of MS, therefore, and atherosclerosis (tab. 1). According to the prospective research it was shown that the cardiovascular mortality linearly increased with increase in the IL-6 levels and C-RP [11]. The IL-6 level was the significant predictor of cardiovascular mortality in the model including the inflammatory markers and MS. The IL-6 and C-RP levels explained about 1/3 the MS associations with cardiovascular mortality. Strict linear dependence of cardiovascular mortality on the content of IL-6 independently of MS and the C-RP level was shown. On the contrary, the relationship of C-RP with cardiovascular mortality was not significant after the correlation of the IL-6 level. The C-RP level has high correlation with the IL-6 level, as IL-6 is the main stimulator of hepatic production of SRB [26]. In the research (R.M. Shakhnovich et al.) was shown that in patients with myocardial infarction the C-RP level was significantly higher than in persons without cardiovascular disease. In patients with myocardial infarction with wave Q increased the C-RP level (more than 2 mg/l) in month from the beginning of myocardial infarction was marker of the adverse prognosis. The association of C-RP level with volume of lesion was not revealed [6].

In the study (E.V. Panyugova et al.) it was revealed that the combination of clinical picture of coronary atherosclerosis and peripheral arteries disease was accompanied by increase the C-RP level [1]. It was shown that the C-RP level correlated with risk to the development of adverse events (death, myocardial infarction, stroke), with existence of the complicated stenosis in patients with



acute coronary syndrome more than with prevalence of coronary atherosclerosis [15, 16]. In the Dallas Heart Study (DHS) was shown that in patients with aortic atherosclerosis and high level of calcium index the concentration of C-RP was higher, than in patients without aortic atherosclerosis and with low level of calcium index. However when spent the multiple-factor analysis taking into account risk factors, such as body mass index, treatment with statins, the relationship between the C-RP levels and existence of aortic atherosclerosis wasn't significant and, therefore, the C-RP level wasn't significant predictor of the severity of atherosclerotic lesion [27]. According to the prospective research Mexico City Diabetes Study the C-RP level wasn't predictor to the development of MS within 6 years in men. At the same time in women the increased level of C-RP correlated with high risk to the development of diabetes and MS, regardless of abdominal obesity and insulin resistance [22]. In the Insulin Resistance Atherosclerosis Study (IRAS) the significant communication of C-RP with sensitivity indicators to insulin, fasting insulin and pro-insulin was revealed. Also was demonstrated the linear dependence of the C-RP level on number of the metabolic disorders included in the MS (dyslipidemia, abdominal obesity, insulin resistance, arterial hypertension) [13]. In the several researches was showed that in patients with CHD the IL-6 level was either independent or stronger factor, than C-RP [17, 24]. In the research spent in Novosibirsk was shown that in men with coronary atherosclerosis the IL-6 and IL-8 levels were increased [7].

In native men with coronary atherosclerosis the $\text{INF-}\gamma$ level ($p=0.035$) was higher than in non-native men. In non-native men ($p=0.002$) and women ($p=0.026$) the IL-6 levels was higher with comparison indigenous population of Yakutia that will be coordinated with data of other researchers [2, 5]. The comparative analysis of studied indicators in comparison groups also revealed ethnicity differences. So, among non-native people of Yakutia in men the C-RP ($p=0.000$), $\text{TNF-}\alpha$ (0.052), IL-6 ($p=0.037$) and IL-8 ($p=0.000$) levels and in women – the $\text{TNF-}\alpha$ (0.059) and IL-6 ($p=0.001$) levels were higher in comparison with indigenous people. The following significant gender differences are received. Among all men with coronary atherosclerosis ($p=0.003$; $p=0.008$), and without CHD ($p=0.000$) in both ethnicity groups the $\text{TNF-}\alpha$ levels were higher in comparison with women. In women from both ethnicity comparison groups the IL-6 levels ($p=0.000$) were higher than in men. The $\text{INF-}\gamma$ level was higher among urban men of native nationality in comparison with rural men ($p=0.044$). In other patient groups the significant differences in levels of inflammatory markers depending on the place of residence aren't revealed. In comparison groups among native rural women the $\text{TNF-}\alpha$ level ($p=0.000$) was higher than among urban residents. In urban women the IL-8 level ($p=0.000$) was higher. Among non-native people, living in city, in men the $\text{TNF-}\alpha$ ($p=0.004$) and IL-6 ($p=0.000$) levels and in women the $\text{TNF-}\alpha$ ($p=0.001$) and IL-8 ($p=0.000$) levels were higher in comparison with rural residents. The coronary atherosclerosis has positive

correlation with C-RP ($r=0.830$, $p < 0.01$), IL-6 ($r=0.805$, $p < 0.01$), IL-8 ($r=0.574$, $p < 0.01$) and TNF- α ($r=0.486$, $p < 0.01$) levels.

Table 1

The comparative analysis the inflammatory markers levels in the investigated groups of men and women, $M \pm m$

Group			C-RP	TNF- α	IL-6	IL-8	INF- γ
1 Group with CHD, native	men (n=189)	urban	6.70 $\pm$ 0.59	5.37 $\pm$ 0.41	7.34 $\pm$ 0.93	10.40 $\pm$ 2.07	34.49 $\pm$ 5.32
		rural	5.64 $\pm$ 0.50	4.95 $\pm$ 0.33	6.06 $\pm$ 0.44	10.77 $\pm$ 2.06	22.13 $\pm$ 2.74
		total	6.13 $\pm$ 0.38	5.15 $\pm$ 0.26	6.64 $\pm$ 0.49	10.60 $\pm$ 1.45	27.99 $\pm$ 2.96
		p	$p_{1-3}=0.000$	$p_{1-3}=0.000$ $p_{m-w}=0.003$	$p_{1-3}=0.000$	$p_{1-3}=0.000$	$p_{1-2}=0.035$ $p_{c-v}=0.044$
	women (n=28)	urban	6.70 $\pm$ 0.88	3.84 $\pm$ 1.28	4.54 $\pm$ 0.66	11.29 $\pm$ 2.62	18.39 $\pm$ 5.42
		rural	5.37 $\pm$ 0.57	3.43 $\pm$ 0.44	4.83 $\pm$ 0.56	7.62 $\pm$ 1.33	18.48 $\pm$ 2.26
		total	5.81 $\pm$ 0.48	3.57 $\pm$ 0.52	4.73 $\pm$ 0.43	8.93 $\pm$ 1.28	18.45 $\pm$ 2.39
		p	$p_{1-3}=0.000$	$p_{1-3}=0.000$	$p_{1-3}=0.000$	$p_{1-3}=0.000$	
2 Group with CHD, non-native	men (n=207)	urban	7.34 $\pm$ 0.49	5.52 $\pm$ 0.41	8.60 $\pm$ 0.75	9.75 $\pm$ 2.29	25.37 $\pm$ 4.02
		rural	6.07 $\pm$ 0.33	5.56 $\pm$ 0.39	8.56 $\pm$ 0.66	10.73 $\pm$ 3.29	18.38 $\pm$ 2.15
		total	6.63 $\pm$ 0.29	5.54 $\pm$ 0.28	8.58 $\pm$ 0.49	10.24 $\pm$ 1.99	21.77 $\pm$ 2.26
		p	$p_{2-4}=0.000$	$p_{2-4}=0.000$ $p_{m-w}=0.008$	$p_{2-4}=0.000$ $p_{1-2}=0.002$ $p_{m-w}=0.071$	$p_{2-4}=0.000$	
	women (n=32)	urban	5.29 $\pm$ 0.45	3.51 $\pm$ 0.50	5.31 $\pm$ 0.50	6.46 $\pm$ 2.59	21.25 $\pm$ 4.38
		rural	7.34 $\pm$ 0.74	4.30 $\pm$ 0.69	6.71 $\pm$ 0.49	10.63 $\pm$ 4.30	15.09 $\pm$ 2.68
		total	6.12 $\pm$ 0.43	3.83 $\pm$ 0.41	5.88 $\pm$ 0.37	8.40 $\pm$ 2.41	18.75 $\pm$ 2.83
		p	$p_{2-4}=0.000$ $p_{c-v}=0.020$	$p_{2-4}=0.000$	$p_{2-4}=0.000$ $p_{1-2}=0.026$ $p_{c-v}=0.044$	$p_{2-4}=0.000$	
3 Group without CHD, native	men (n=108)	urban	0.51 $\pm$ 0.05	2.88 $\pm$ 0.34	0.37 $\pm$ 0.12	0.12 $\pm$ 0.04	-
		rural	0.59 $\pm$ 0.05	2.24 $\pm$ 0.25	0.19 $\pm$ 0.07	1.16 $\pm$ 0.26	-
		total	0.55 $\pm$ 0.04	2.56 $\pm$ 0.21	0.28 $\pm$ 0.07	0.64 $\pm$ 0.14	-
		p		$p_{m-w}=0.000$			
	women (n=145)	city	0.60 $\pm$ 0.06	0.11 $\pm$ 0.07	1.28 $\pm$ 0.26	5.06 $\pm$ 0.46	-
		village	0.86 $\pm$ 0.14	3.08 $\pm$ 0.27	0.80 $\pm$ 0.19	1.93 $\pm$ 0.56	-
		total	0.72 $\pm$ 0.07	1.53 $\pm$ 0.22	1.04 $\pm$ 0.16	3.56 $\pm$ 0.40	-
		p	$p_{m-w}=0.027$	$p_{c-v}=0.000$	$p_{m-w}=0.000$	$p_{3-4}=0.022$ $p_{m-w}=0.000$ $p_{c-v}=0.000$	
4 Group without CHD, non-native	men (n=104)	urban	0.75 $\pm$ 0.10	4.12 $\pm$ 0.45	1.07 $\pm$ 0.34	2.12 $\pm$ 0.34	-
		rural	0.98 $\pm$ 0.09	2.38 $\pm$ 0.24	0.33 $\pm$ 0.16	1.59 $\pm$ 0.24	-
		total	0.87 $\pm$ 0.07	3.24 $\pm$ 0.27	0.69 $\pm$ 0.19	1.86 $\pm$ 0.21	-
		p	$p_{3-4}=0.000$ $p_{c-v}=0.060$	$p_{3-4}=0.052$ $p_{m-w}=0.000$ $p_{c-v}=0.004$	$p_{3-4}=0.037$ $p_{c-v}=0.000$	$p_{3-4}=0.000$	
	women (n=126)	urban	0.71 $\pm$ 0.08	2.61 $\pm$ 0.40	1.41 $\pm$ 0.17	2.44 $\pm$ 1.85	-
		rural	0.93 $\pm$ 0.14	0.98 $\pm$ 0.16	1.37 $\pm$ 0.21	1.57 $\pm$ 0.35	-
		total	0.82 $\pm$ 0.08	1.80 $\pm$ 0.24	1.39 $\pm$ 0.13	2.00 $\pm$ 0.24	-
		p		$p_{3-4}=0.059$ $p_{c-v}=0.001$	$p_{3-4}=0.001$ $p_{m-w}=0.000$	$p_{c-v}=0.000$	

CONCLUSION

Results of the our research showed that the levels of the all studied inflammatory markers were higher in patients with metabolic syndrome complicated by coronary atherosclerosis in comparison with persons without clinical signs of CHD. Significant ethnicity and gender differences are received. In non-native people of Yakutia the IL-6 level in comparison with aboriginals was higher. Also the IL-6 level was higher in women, than in men. In native men with coronary atherosclerosis the INF- γ level in comparison with non-native men was higher, that is possible, connected with intensity of immune system in aboriginals.

References

- Panyugova E. V. Aleksandrova E. N. Nasonov E. L. Karpov U. A. Ateroskleroticheskoe porazhenie sosudov u bol'nyh so stabil'nym techeniem ishemicheskoy bolezni serdca : svjaz' s S - reaktivnym belkom [Atherosclerotic lesion of the vessels in patients with stable coronary artery disease: relations with concentration of C-reactive protein] Zh Kardiologiya [J Cardiology], № 4, Moscow, 2009, pp. 40 – 45.
- Vasilkova T. N. Klinicheskie i gigienicheskie aspekty formirovaniya metabolicheskogo sindroma u naseleniya Krajnego Severa [The clinical and hygienic aspects of the formation of metabolic syndrome in population of Far North] Avtoref. dis. ... d – ra med. nauk [Abstract Diss. ... Doctor. Med. Science]. Tyumen, 2009, 45 p.
- Gitel E. P. Gusev D. E. Rol' interlejkinov v patogeneze ateroskleroza [The role of interleukins in the pathogenesis of atherosclerosis] Zh Klinicheskaja medicina [J Clinical medicine], 2006, № 6, pp. 10 – 15.
- Kozlov V. A. Dushkin M. I. Verechagin E. I. Vakciny protiv ateroskleroza : sostojanie problemy i perspektivy ee razvitija [Vaccines against atherosclerosis : the state of the problem and perspectives] Citokiny i vospalenie [Cytokines and inflammation], 2008, № 1, pp. 8 – 14.
- Makharova N. V. Kliniko - instrumental'naja harakteristika koronarnogo ateroskleroza v Respublike Saha (Jakutija) [The clinical and instrumental characteristics of coronary atherosclerosis in Republic Sakha of Yakutia]: Avtoref. dis. ... d – ra med. nauk [Abstract Diss. ... Doctor. Med. Science]. Novosibirsk, 2010, 40 p.
- Shakhnovich P. M. Sukhinina T. S. Barsova R. M. [et al.] Polimorfizm S1444T gena CRP i koncentracija S - reaktivnogo belka v syvorotke krovi pri infarkte miokarda [Polymorphism

C1444T of CRP gene and C-reactive protein concentration in blood serum of healthy people and patients with myocardial infarction] Zh Kardiologiya [J Cardiology], 2010, № 8, pp. 4 – 12.

Ragino Yu. I. Chernyavsky A. M. Tikhonov A. V. [et al.] Urovni lipidnyh i nelipidnyh biomarkerov v krovi u muzhchin s koronarnym aterosklerozom v Novosibirske [Blood lipid and non-lipid biomarkers in Novosibirsk men with coronary atherosclerosis] Ross. kardiolog. Zhurnal [Russian Journal of Cardiology], 2009, № 2, pp. 31 – 35.

Ragino Yu. I. Chernyavsky A. M. Volkov A. M. Voevoda M. I. Faktory i mehanizmy nestabil'nosti ateroskleroticheskoy bljashki [The factors and mechanisms of the instability of atherosclerotic plaques]. Novosibirsk : Nauka , 2008, 88 p.

A self – fulfilling prophecy : C - reactive protein attenuates nitric oxide production and inhibits angiogenesis / S. Verma, C. H. Wang, S. H. Li [et al.] // Circulation. – 2002. – Vol. 106. – P. 913 – 919.

Blankenberg S. Cytomegalovirus infection with interleukin - 6 response predicts cardiac mortality in patients with coronary disease // S. Blankenberg, H. J. Rupprecht // Circulation. – 2001. – Vol. 103. – P. 2915 – 2921.

Cardiovascular death and the metabolic syndrome : role of adiposity -signaling hormones and inflammatory markers / C. Langenberg, J. Bergstrom, C. Scheidt - Nave [et al.] // Diabetes Care. – 2006. – Vol. 29. – P. 1363 – 1369.

Cesaretti, M. L. Experimental models of insulin resistance and obesity : lessons learned / M. L. Cesaretti, O. Jr. Kohlmann // Arq. Bras. Endocrinol. Metab. – 2006. – Vol. 50. – P. 190 – 197.

Chronic subclinical inflammation as the part of the insulin resistance syndrome : The Insulin Resistance Atherosclerosis Study (IRAS) / A. Festa, R. Jr. D'Agostino, G. Howard [et al.] // Circulation. – 2000. – Vol. 102. – P. 42 – 47.

Coppack, S. W. Pro - inflammatory cytokines and adipose tissue / S. W. Coppack // Proc. Nutr. Soc. – 2001. – Vol. 60. – P. 349 – 356.

C – reactive protein and angiographic coronary artery disease : independent and additive predictors of risk in subjects with angina / J. S. Zebrack, Muhlestein J. B., Horne B. D. [et al.] // J. Am. Coll. Cardiol. – 2002. – Vol. 39. – P. 632 – 637.

C – reactive protein elevation and disease activity in patients with coronary artery disease / R. Arroyo-Espliguero, P. Avanzas, J. Cosin-Sales [et al.] // Eur. Heart J. – 2004. – Vol. 25. – P. 401 – 408.

C – reactive protein, interleukin - 6, and fibrinogen as predictors of coronary heart disease : the PRIME Study / G. Luc, J. M. Bard, I. Juhan - Vague [et al.] // Arterioscler. Thromb. Vasc. Biol. – 2003. – Vol. 23. – P. 1255 – 1261.

De Orazio, N. Obesity and immune function / N. De Orazio // Ann. Ital. Chir. – 2005. – Vol. 76 (5). – P. 413 – 416.

Early cerebrovascular disease in a 2 – year – old with extreme obesity and complete metabolic syndrome due to feeding of excessively high amounts of energy / D. Weghuber, D. Zaknun, C. Nasel [et al.] // Eur. J. Pediatr. – 2007. – Vol. 166. – P. 37 – 41.

Fasshauer, M. Regulation of adipocytokines and insulin resistance / M. Fasshauer, R. Paschke // Diabetologia. – 2003. – Vol. 46. – P. 1594 – 1603.

Garg, A. Regional adiposity and insulin resistance / A. Garg // J. Clin. Endocrinol. Metab. – 2004. – Vol. 89 (9). – P. 4206 – 4210.

Han, T. S. Prospective study of C - reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study / T. S. Han, N. Sttar, K. Williams // Diabetes Care. – 2002. – Vol. 25 (11). – P. 2016 – 2021.

Hansson, G. K. Inflammation, atherosclerosis, and coronary artery disease / G. K. Hansson // N. Engl. J. Med. – 2005. – Vol. 352. – P. 1685 – 1695.

Inflammatory markers and onset of cardiovascular events : results from the Health ABC study / M. Cesari, B. W. Penninx, A. B. Newman [et al.] // Circulation. – 2003. – Vol. 108. – P. 2317 – 2322.

Lang, C. H. Tumor necrosis factor impairs insulin action on peripheral glucose disposal and hepatic glucose output / C. H. Lang, C. Dobrescu, G. J. Bagby // Endocrinology. – 1992. – Vol. 130. – P. 43 – 52.

Metabolic syndrome and C-reactive protein in the general population (JMS Cohort Study) / S. I. Ishikawa, K. Kayaba, T. Gotoh [et al.] // Circ. Res. – 2007. – Vol. 27. – P. 26 – 31.

Relationship Between C – reactive Protein and Subclinical Atherosclerosis / A. Khera, J. A. de



Lemos, R. M. Peshock [et al] // Circulation. – 2006. – Vol. 113. – P. 38 – 43.

The differential effects of metformin on markers of endothelial activation and inflammation in subjects with impaired glucose tolerance : a placebo-controlled, randomized clinical trial / A. E. Caballero, A. Delgado, C. A. Aguilar - Salinas et al. // J. Clin. Endocrinol. Metab. – 2004. – Vol. 89 (8). – P. 3943 – 3948.

Wisse, B. E. The inflammatory syndrome : the role of adipose tissue cytokines in metabolic disorders linked to obesity / B. E. Wisse // J. Am. Soc. Nephrol. – 2004. – Vol. 15. – P. 2792 – 2780.

Zhou, R. H. Changes in serum interleukin - 8 and interleukin - 12 levels in patients with ischemic heart disease in a Chinese population / R. H. Zhou, Q. Shi // J. Atheroscler. Thromb. – 2001. – Vol. 8. – P. 30 – 32.

Zwaka, T. P. C - reactive protein - mediated low density lipoprotein uptake by macrophages : implications for atherosclerosis / T. P. Zwaka, V. Hombach, J. Torzewski // Circulation. – 2001. – Vol. 103. – P. 1194 – 1197.

The authors

Romanova A. N. – doctor of medical sciences, chief researcher of Department of epidemiology of chronic non-communicable diseases of Yakut Scientific Centre of complex medical problems SB RAMS, 677010, Sergelyakhskoe highway, 4km, Yakutsk, the Russian Federation , e-mail: ranik@mail.ru;

Voevoda M. I. – corresponding member of RAMS, doctor of medical sciences, professor, director of Institute for Internal Medicine SB RAMS; 630089, Boris Bogatkov str., 175/1 Novosibirsk, the Russian Federation;

Golderova A.S. – candidate of medical sciences, chief researcher of department of adaptation mechanisms investigation of Yakut Scientific Centre of complex medical problems SB RAMS 677010, Sergelyakhskoe highway, 4km, Yakutsk, the Russian Federation, e-mail: hoto68@mail.ru.