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Adipokines and adipocytokines in men with coronary atherosclerosis and overweight

Aim	To study concentrations of adipokines and their associations with proinflammatory cytokines in overweight men with coronary atherosclerosis.
Material and Methods	This study included 79 men aged 45–60 years with atherosclerosis who had undergone coronary endarterectomy during a coronary bypass surgery, and were overweight (body weight index (BWI), 25.0–29.9 kg/m^2). Based on a histological analysis of plaques, the patients were divided into two subgroups: 43 men with stable atherosclerotic plaques and 36 men with unstable plaques in coronary arteries. The control group consisted of 40 age- and BWI-matched men without clinical manifestations of IHD. Blood concentrations of adipokines, including adiponectin, adipsin, lipocalin-2, resistin, and plasminogen 1 activator inhibitor were measured by a multiplex analysis with a MILLIPLEX MAP Human Adipokine Panel 1. Concentrations of proinflammatory cytokines, including tumor necrosis factor α (TNF- α), interleukin (IL) – 1β, IL-6, and C-reactive protein (CRP) were measured by enzyme immunoassay.
Results	The blood concentration of lipocalin –2 was higher in patients with coronary atherosclerosis and stable or unstable atherosclerotic plaques than in the control group ($p<0.01$). Both subgroups of men with coronary atherosclerosis were characterized by significant differences from the control group in concentrations of TNF-α ($p<0.05$), CRP, and IL-6 ($p<0.01$). The most significant direct correlations were found between adipokines and TNF-α, IL-6, and CRP ($p<0.01$). Results of a logistic regression analysis showed that relative odds for the presence of significant coronary stenoses increased with increasing blood concentrations of lipocalin-2 (OR=1.005, 95% CI: 1.002–1.008, p=0.011) and IL-6 (OR=1.582, 95% CI: 1.241–2.017, p=0.001).
Conclusion	The changes in blood concentrations of adipokines associated with higher levels of proinflammatory cytokines may represent a factor that increases the probability of clinically significant coronary stenosis in overweight men with coronary atherosclerosis.

Keywords	Coronary atherosclerosis; atherosclerotic plaque; adipokines; proinflammatory cytokines
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Introduction

Atherosclerosis is the leading cause of cardiovascular diseases (CVDs), which are the most common pathological conditions and have high morbidity and mortality rates [1]. Depending on the location and nature of vascular atherosclerosis, its clinical picture may vary significantly. Acute coronary syndrome (ACS) is one of the most clinically significant manifestations of coronary atherosclerosis [1, 2].

The latest data emphasize the importance of such factors as inflammation, dyslipidemia, oxidative stress and others in the development of atherosclerosis [3]. Researchers believe that inflammation markers may be the best predictors of atherosclerosis due to the strong correlation between atherosclerosis and inflammation. Pro-inflammatory cytokines, such as C-reactive protein (CRP), interleukins (IL), and many others, were shown to be nonspecific predictors of atherosclerosis by reflecting only the inflammatory state [4, 5]. Other markers, particularly adipose tissue cytokines (better known as adipokines), endothelial dysfunction, hypercoagulation, insulin resistance, as well as systemic inflammation, which in turn contributes to the development of atherosclerosis [6, 7]. It is worth noting that there few studies showing an independent association between various adipokines,

pro-inflammatory cytokines, and CVDs with a sufficient level of evidence, and their results are contradictory [8–12]. Therefore, our objective was to study the blood levels of adipokines and their correlation with pro-inflammatory cytokines in male patients with coronary atherosclerosis and overweight.

Material and methods

This is a cross-sectional observational study. It was conducted under joint research studies of Research Institute of Internal and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences (IIPM – Branch of IC&G SB RAS) and the National Medical Research Center named after Academician E. N. Meshalkin. The study was approved by the local ethics committees of both facilities. Data and biological samples were collected after obtaining written informed consent from all subjects.

General characteristics of the examined patients

At the preliminary stage, 120 male patients (mean age 55.48±7.33 years) with angiographically verified coronary atherosclerosis (Table 1), with stable exertional angina functional class II–III, without ACS, admitted to the hospital of the National Medical Research Center named after Academician E. N. Meshalkin for coronary artery bypass grafting surgery, were included in the study (2011–2021).

The preliminary stage inclusion criteria were male sex; diagnosis of coronary artery disease (CAD); a history of myocardial infarction (MI) or episodes of stable exertional angina.

The preliminary stage exclusion criteria were female sex; a less than 6-month history of ACS before admission (unstable angina or MI); clinically significant severe concomitant pathology, acute or exacerbated (chronic diseases); known active cancer.

In this study, the presence of angiographically confirmed stenosis of >70% of the lumen was considered a significant coronary lesion [13].

At the stage of the final selection of patients, the necessary conditions were the performance of coronary artery endarterectomy and the collection of tissue samples containing the intima-media of the coronary arteries. The main study group comprised 79 male patients (mean age 54.75±3.29 years).

Histological evaluation of the samples was conducted in the pathomorphological laboratory of the National Medical Research Center named after Academician E. N. Meshalkin. After macroscopic description of the samples, the area of atherosclerotic plaque (plaque), the degree of coronary artery stenosis, hemorrhage in the plaque structures, calcification sites, and clots, were studied; each endarterectomy sample containing the intima-media of the coronary arteries was longitudinally and transversely symmetrically divided into 3–5 fragments for histological and biochemical

Table 1. Coronary angiographic characteristics of coronary artery involvement in patients with coronary atherosclerosis (n = 120)

Coronary artery involvement	Prevalence of coronary artery disease	
	Male patients, n (%)	%
Single-vessel disease	25	21
Two-vessel disease	41	34
Three-vessel disease	54	45
Left anterior descending artery	93	77.5
Right coronary artery	102	85
Left circumflex artery	57	47.5
Lumen occlusion degree:		
• Stenosis (25–50%)	51	42.5
• Subocclusion (60–80%)	42	35
• Occlusion (90–100%)	27	22.5
Preferential localization:		
• Proximal segments	34	28
• Middle segments	36	30
• Distal segments	19	16
• Total involvement	31	26

Table 2. Clinical and anamnestic characteristics of patients with coronary atherosclerosis

Parameter	Subgroup with stable plaques, n = 43	Subgroup with unstable plaques, n = 36	p
Mean age	54.57±3.61	55.01±2.90	0.707
HR, bpm	67.96±8.4	69.67±8.37	0.222
Systolic BP, mm Hg	133.53±14.28	135.44±11.77	0.524
Diastolic BP, mm Hg	82.23±8.48	82.5±8.68	0.891
BMI, kg/m^2	28.79±4.32	29.47±3.84	0.470
Waist circumference, cm	92.14±10.37	93.56±9.47	0.540
Overweight*	86.1%	91.6%	0.211
Obesity*	39.5%	41.6%	0.587
Abdominal obesity*	18.6%	19.4%	0.628
History of MI*	69.8%	71.3%	0.398
DM type 2*	22.2%	18.91%	0.218
Smoker*	76.19%	73.33%	0.851

* % of the absolute number (n). The data are expressed as means and standard deviations (M±SD).
BP, blood pressure; MI, myocardial infarction; BMI, body mass index; DM, diabetes mellitus; HR, heart rate.

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evaluation. Histological analysis of the intima-media fragments of the coronary arteries was performed using an Axiostar Plus binocular microscope after standard staining. The analysis of the intima-media fragments revealed the presence of plaques. An unstable plaque was differentiated by the following criteria: damaged plaque with a fibrous cap thickness<65 μm, infiltration by macrophages and T-lymphocytes (> 25 cells per power field of 0.3 mm), large lipid nucleus (>40%) [14]. Then, the main group was divided into two subgroups: Subgroup I included patients with stable plaques in the coronary arteries (43 male patients), Subgroup II comprised patients with at least one unstable plaque in the coronary arteries (36 male patients). Table 2 presents baseline patient characteristics depending of the plaque types (stable/unstable).

All patients with coronary atherosclerosis received high-intensity statin therapy at maximum tolerated doses (atorvastatin 40–80 mg, rosuvastatin 20–40 mg), and antihypertensive drugs until achieving the target values of blood pressure <140/90 mm Hg. The characteristics and doses of concomitant therapy were comparable in the subgroups.

The control group included 40 male patients (mean age 53.9±5.2 years) with comparable body mass index (BMI) and without clinical manifestations of diseases associated with atherosclerosis, such as CAD. The screening of the control group was carried out in IIPM – Branch of IC&G SB RAS.

The non-use of cardiovascular drug therapy was an inclusion criterion. The presence of CAD was excluded by results of full clinical examination.

Laboratory tests

The biological samples (blood) were taken from all patients. All tests were performed in the Laboratory of Clinical Biochemical and Hormone Tests of Therapeutic Diseases in IIPM – Branch of IC&G SB RAS. The levels of adipokines (adiponectin, adipsin, lipocalin-2, resistin and plasminogen activator inhibitor 1 (PAI-1)) were determined by multiplex analysis using the Human Adipokine Panel 1 (MILLIPLEX MAP, Germany) in a Luminex MAGPIX system. The levels of tumor necrosis factor-α (TNF-α), IL-1β, IL-6, and CRP were determined by enzyme-linked immunosorbent assay (ELISA) using standard test systems in the MultiscanEX ELISA analyzer (Finland).

Statistical analysis

The obtained results were statistically processed in SPSS 13.0. The Kolmogorov–Smirnov test was used to assess the nature of the attribute distribution. The comparative study of clinical and anamnestic characteristics was carried out in the groups using the Student's t-test. These characteristics of the attributes are presented as the arithmetic means (M) and their standard deviations (SD). The Mann–Whitney non-parametric U-test was used for non-normally distributed attributes. The obtained data are expressed as the medians (Me) and interquartile ranges (25th and 75th percentiles). The Spearman rank correlation coefficient (rs) was used to analyze the dependence of quantitative attributes of sample data from populations. Multivariate logistic regression analysis was used to assess the probability of the presence of clinically significant coronary artery stenosis. The results are presented as the odds ratios (OR) and respective 95% confidence intervals. The significance level was $p<0.05$.

Results

Unlike the control group, male patients with coronary atherosclerosis had changes in the levels of serum adipokines (Table 3).

It was found that the levels of lipocalin-2 is 1.65 times higher ($p<0.01$) in patients with coronary atherosclerosis and stable plaques than in the control group, and 1.45 times higher in male patients with unstable plaques ($p<0.05$). Analysis of adipokine levels between the subgroups of patients with coronary atherosclerosis did not show significant differences.

Among the inflammation markers studied, both subgroups of male patients with coronary atherosclerosis showed significant differences from the control group in the levels of TNF-α ($p<0.05$), CRP, and IL-6 ($p<0.01$) (Table 4). However, there was no statistically

Table 3. Adipokine levels in male patients with coronary atherosclerosis and the control group

Parameter	Control group	Patients with stable plaques	Patients with unstable plaques
Adiponectin, pg/mL	1.56 (0.01; 4.55)	2.65 (1.47; 4.42)	2.34 (1.31; 3.95)
Adipsin, pg/mL	9.82 (6.88; 14.64)	10.34 (8.17; 14.95)	10.77 (8.44; 13.96)
Lipocalin-2, ng/mL	196.64 (129.95; 253.75)	325.96 (185.53; 577.11) **	285.18 (189.38; 539.49) *
PAI-1, pg/mL	17.21 (11.7; 21.41)	17.97 (11.9; 26.55)	18.93 (12.74; 25.62)
Resistin, pg/mL	0.92 (0.49; 1.46)	0.98 (0.55; 1.45)	1.01 (0.39; 1.62)

* $p<0.05$, ** $p<0.001$ versus the control group.
The data are presented as the medians and interquartile ranges between the 25th and 75th percentiles (Me [25%; 75%]).
PAI-1, plasminogen activator inhibitor 1.

significant difference between patients with coronary atherosclerosis.

The pairwise correlation analysis showed that the most significant direct correlations were identified between lipocalin-2 content and inflammation markers: TNF-α (0.286; p<0.05), IL-6 (0.248; p<0.05), and CRP (0.338; p<0.01). PAI-1 was directly correlated with TNF-α (0.274; p<0.05) and CRP (0.332; p<0.01). A positive correlation was also established for resistin with IL-6 (0.299; p<0.05) and CRP (0.227; p<0.05). There were no correlations with adiponectin and adipsin.

The next step was to assess the probability of the presence of clinically significant coronary artery stenosis (>70%), depending on the levels of adipokines (Table 5) and pro-inflammatory cytokines (Table 6) in the multivariate logistic regression models.

The results showed that the odds ratio of the presence of significant coronary artery stenosis increased with higher blood levels of lipocalin-2 and IL-6 (p<0.01).

Table 4. Inflammation markers in male patients with coronary atherosclerosis and the control group

Parameter	Control group	Patients with stable plaques	Patients with unstable plaques
CRP, μg/mL	1.98 (0.51; 4.13)	6.4 (1.67; 16.97)**	7.61 (2.18; 21.47)**
TNFα, pg/mL	3.49 (2.54; 4.94)	4.74 (2.64; 6.5)*	4.89 (3.24; 6.42)*
IL-1β, pg/mL	1.21 (0.51; 1.77)	1.35 (0.76; 1.93)	1.37 (0.84; 1.95)
IL-6, pg/mL	0.84 (0.66; 1.52)	4.97 (1.9; 12.32)**	5.45 (2.36; 12.46)**

* p<0.05, ** p<0.001 versus the control group.
The data are presented as the medians and interquartile ranges between the 25th and 75th percentiles (Me [25%; 75%]).
IL, interleukin; CRP, C-reactive protein;
TNF-α, tumor necrosis factor alpha.

Table 5. Logistic regression analysis of the probability of significant coronary artery stenosis depending on the levels of adipokines

Parameter	Model 1	Model 2 (including age)	Model 3 (including waist circumference)
Adiponectin	0.965 (0.830–1.122). p=0.606	0.949 (0.763–1.181). p=0.638	0.962 (0.822–1.126). p=0.630
Adipsin	1.030 (0.960–1.105). p=0.410	1.002 (0.860–1.168). p=0.981	0.995 (0.920–1.076). p=0.897
Lipocalin-2	1.005 (1.002–1.008). p=0.011	1.006 (1.001–1.010). p=0.013	1.004 (1.001–1.007). p=0.004
PAI-1	0.991 (0.945–1.040). p=0.722	0.938 (0.842–1.045). p=0.244	0.997 (0.949–1.046). p=0.891
Resistin	1.011 (0.998–1.004). p=0.379	1.003 (0.997–1.009). p=0.303	1.001 (0.998–1.005). p=0.371

PAI-1, plasminogen activator inhibitor 1.

Discussion

The adipokines and adipocytokines are key factors in the inflammation process, as most of them increase in obesity and contribute to the indolent inflammatory state associated with obesity [15]. At the same time, it has been established that an increase in human BMI by one point above normal weight causes a ten percent increase in the risk of atherosclerosis and CAD [16]. In our study, mean BMI was 29.13 kg/m^2 and the waist circumference was 92.85 cm in male patients with coronary atherosclerosis, which is a critical threshold for obesity, including abdominal obesity. At the same time, the blood levels of adipokines are elevated and they are positively correlated with increased levels of adipocytokines. Our findings show that overweight individuals have an increased risk of developing CVDs as well as obesity.

The lipocalin-2 is a secreted glycoprotein that was originally identified as a product of neutrophils [17]. In conditions of inflammation, lipocalin-2 may function as an inflammation mediator. Moreover, it can form a complex with matrix metalloproteinase-9, thus preventing its inhibition by tissue metalloproteinase inhibitor 1 [18]. Expression of lipocalin-2 by adipocytes is induced by various pro-inflammatory cytokines known to be involved in the development of obesity, including TNF-α, IL-1β, and IL-6 [19]. For example, serum levels

Table 6. Logistic regression analysis of the probability of significant coronary artery stenosis depending on the levels of proinflammatory cytokines

Parameter	Model 1	Model 2 (including age)	Model 3 (including waist circumference)
CRP	1.458 (0.841–2.526); p=0.179	1.425 (0.679–2.991); p=0.350	1.307 (0.732–2.333); p=0.365
TNF-α	1.044 (0.836–1.302); p=0.705	1.180 (0.816–1.706); p=0.380	0.942 (0.752–1.180); p=0.601
IL-1β	1.002 (0.997–1.007); p=0.456	1.001 (0.991–1.010); p=0.960	1.003 (0.995–1.007); p=0.518
IL-6	1.582 (1.241–2.017); p=0.001	1.281 (1.496–2.035); p=0.010	1.622 (1.253–2.098); p=0.002

IL, interleukin; CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha.

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of lipocalin-2 were shown to correlate with CRP and predict serious adverse cardiac events and all-cause mortality in patients with CVD [20]. Recent studies suggest that elevated serum lipocalin-2 increases in CAD [21, 22], which is may be associated with the severity of the atherosclerotic process. Şahinarslan et al. [23] demonstrated higher levels of lipocalin-2 in patients with ACS than in patients with stable CAD.

In our study, significantly higher levels of lipocalin-2 were found in patients with coronary atherosclerosis compared to the control group. However, no difference was found between patients with stable and unstable plaques. The increased levels of lipocalin-2 significantly correlated in our study with inflammation markers, which is may be due to its effects on both metabolic and inflammatory processes. The obtained results suggest that lipocalin-2 can be used as a biomarker for diseases of inflammatory origin and an increased risk of coronary atherosclerosis.

Resistin is a part of the family of resistin-like molecules [24]. Its inflammatory role is mediated by intracellular activation of the transcription factor, which causes the secretion of various cytokines. These cytokines initiate multiple intracellular inflammatory cascades, which in turn can lead to atherothrombosis [25]. Elevated levels of resistin may predict coronary atherosclerosis, re-stenosis after coronary artery stenting, and serious adverse cardiovascular events in patients with CAD. Moreover, resistin correlates with inflammatory and fibrinolytic markers such as CRP, TNF-α, and IL-6 in the general population and patients with coronary atherosclerosis, diabetes mellitus (DM) type 2, chronic kidney disease, rheumatoid arthritis [26]. Despite the fact that, in our study, there was no significant difference in the levels of resistin between patients with coronary atherosclerosis and patients without CAD, we established direct correlations of resistin with CRP and IL-6, which may point to the severity of CAD.

Plasminogen activator inhibitor (PAI-1) is a major antagonist of tissue plasminogen activator. It is classified as an acute phase reagent in the literature [27]. Inflammatory cytokines, such as IL-1, IL-6, and TNF-α, can stimulate its endothelial production [28]. Elevated levels of PAI-1 have a negative impact on the formation of plaques in atherosclerosis. Elevated PAI-1 was found to be a predictor of adverse cardiovascular events, such as MI, thrombosis, and stent restenosis in patients with a history of percutaneous coronary intervention [29]. However, the initial values of PAI-1 do not always increase before surgery [30]. We collected tissue samples before coronary artery bypass graft surgery, and a history of acute coronary events, such as unstable angina or MI, was more than 6 months before admission to the hospital. No increase in PAI-1 levels was observed consequently in patients with coronary atherosclerosis. The established correlations between PAI-1, TNF-α and CRP demonstrate the interaction of oxidative and inflammatory mechanisms and are likely to be associated with an increased cardiovascular risk.

IL-6 is not only a pro-inflammatory biomolecule, but also an adipocytokine produced by visceral adipose tissue [31, 32]. Due to the fact that IL-6 has many functions, including endothelial cell activation, stimulating the production of acute phase proteins in the liver, enhancing coagulation and stimulating lymphocyte proliferation and differentiation [33], it can influence the development, progression, and complications of atherosclerosis-related diseases [34]. Zamani et al. [35] showed that IL-6 can contribute to the plaque formation and rupture thereby accelerating the progression of atherosclerosis. Moreover, high serum levels of IL-6 in overweight patients may point to high cardiovascular risk and the need for an invasive treatment [36]. In our study, the blood levels of IL-6 was 6.5 times higher male patients with unstable plaques and 5.9 times higher in the subgroup of male patients with stable plaques than in male patients without CAD. In addition, the logistic regression analysis showed that odds of significant coronary artery stenosis increases with a 2.5-fold increase in IL-6. Thus, IL-6 may be an adipocytokine that reflects an inflammatory reaction [37] and may also be a candidate biomarker for the prognosis of CVD risk.

Limitations

This study is a pilot study limited to a small sample of patients. Which is why, it will continue in a larger format, which should give a fuller picture of changes in the adipokine-cytokine profile in patients with verified coronary atherosclerosis.

Conclusion

Changes in the blood levels of adipokines associated with the elevation of pro-inflammatory cytokine levels may be a factor increasing the likelihood of clinically significant coronary artery stenosis (> 70%) in male patients with coronary atherosclerosis and overweight.

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