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Levels of metalloproteinases and adipose tissue hormones in men with coronary atherosclerosis

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ABSTRACT

Aim. To study the effect of adipose tissue hormones on the level of metalloproteinases in men with verified coronary atherosclerosis and to assess associations between the studied biomarkers and abdominal obesity.

Materials and methods. The study included 96 men aged 58.9 ± 5.1 years: 80 men with angiographically verified atherosclerosis and class II–III angina pectoris and 16 men without atherosclerosis. Anthropometric parameters were measured in all patients, and their blood was taken on an empty stomach. The blood levels of adiponectin, leptin, resistin, adipsin, amylin, and metalloproteinases (MMPs) -1, -2, -3, -7, -9, -10, -12, -13 were determined by the multiplex analysis. Statistical processing of the results was carried out using the SPSS 13.0 software.

Results. In patients with severe atherosclerosis, lipocalin, MMP-1, MMP-7, and MMP-12 levels were higher than in the control group. The blood concentration of adiponectin in patients with atherosclerosis was reduced. Inverse correlations were revealed between waist circumference and concentrations of MMP-1 and MMP-12, as well as between body mass index and MMP-1. A moderate direct relationship was revealed between resistin and MMP-2 and MMP-3; between amylin and MMP-9; between adiponectin and MMP-12; between leptin and MMP-7.

Conclusion. The results obtained suggest a relationship between the level of damage markers and adipose tissue hormones, which lead to complications of cardiovascular diseases and explain the effect of obesity on atherosclerotic plaque destabilization.

Keywords: metalloproteinases, atherosclerosis, adipose tissue hormones

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to examination and personal data processing. The study was approved by the Ethics Committee at E.N.Meshalkin National Medical Research Center (Protocol No. 6 of 05.07.2017).

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Уровни металлопротеиназ и гормонов жировой ткани у мужчин с коронарным атеросклерозом

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РЕЗЮМЕ

Цель: изучить уровни гормонов жировой ткани и металлопротеиназ у пациентов с верифицированным коронарным атеросклерозом и оценить ассоциации изучаемых биомаркеров с абдоминальным ожирением.

Материалы и методы. В исследование включили 96 мужчин в возрасте 58,9 ± 5,1 лет: 80 мужчин с коронароангиографически верифицированным атеросклерозом и стабильной стенокардией напряжения II–III функционального класса и 16 мужчин без атеросклероза. У всех исследуемых проводилось измерение антропометрических показателей и забор крови натощак. Методом мультиплексного анализа в крови определяли уровень адипонектина, лептина, резистина, адипсина, амилина, металлопротеиназ (ММП) 1, -2, -3, -7, -9, -10, -12, -13. Статистическая обработка результатов проводилась в программе SPSS 13.0.

Результаты. У пациентов с выраженным атеросклерозом по сравнению с контрольной группой были выше уровни липокалина, ММП-1, ММП-7 и ММП-12. Концентрация в крови адипонектина у пациентов с атеросклерозом была снижена. Выявлены обратные ассоциации между окружностью талии и концентрациями ММП-1 и ММП-12, индекса массы тела с ММП-1; обнаружена прямая связь средней силы между уровнями резистина и ММП-2 и ММП-3; амилина с ММП-9; адипонектина с ММП-12; лептина с ММП-7.

Заключение. Полученные результаты позволяют говорить о связи между уровнем маркеров деструкции и гормонами жировой ткани, которые ведут к развитию осложнений сердечно-сосудистых заболеваний и объясняют влияние ожирения на дестабилизацию атеросклеротической бляшки.

Ключевые слова: металлопротеиназы, атеросклероз, гормоны жировой ткани

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Recently, more and more studies have been aimed at investigating the effect of obesity on atherosclerosis and cardiovascular diseases (CVD). First of all, the presence of abdominal obesity is associated with atherosclerosis and an increased risk of adverse cardiovascular events. The data indicate that adipose tissue as an endocrine organ produces a large number of adipokines, such as leptin, resistin, adiponectin, and inflammatory cytokines that have both proatherogenic and antiatherogenic effects. Excessive accumulation of lipids in adipose tissue causes adipocyte dysfunction, as a result of which the secretion of proatherogenic

adipokines and inflammatory cytokines into the bloodstream increases. It leads to endothelial damage and formation of atherosclerotic plaques, which in the future, with an imbalance of metalloproteinases (MMP), can become unstable.

The pathophysiological processes underlying the effect of adipose tissue hormones on the level of MMPs, which may contribute to the pathogenesis of atherosclerosis, have not been sufficiently studied. Therefore, the aim of the study was to investigate the levels of adipose tissue hormones and metalloproteinases in the serum of patients with coronary atherosclerosis and to evaluate the association of the studied biomarkers with abdominal obesity.

MATERIALS AND METHODS

The collection of material for research was carried out in cooperation with E. Meshalkin National Medical Research Center. The ethical committees of the institutions approved the study, which included 96 men aged 58.9 ± 5.1 years. The main group encompassed 80 men who were hospitalized for coronary artery bypass grafting with coronary atherosclerosis verified by coronary angiography and class II–III angina pectoris. The control group included 16 men of the same age and with the same body mass index (BMI) without atherosclerosis recruited from a sample of Novosibirsk, the Research Institute of Internal and Preventive Medicine, a branch of the Institute of Cytology and Genetics SB RAS.

All patients signed an informed consent to participate in the study. Anthropometric data (height, weight, waist and hip circumference) were measured in all the subjects, and blood was taken on an empty stomach, 12 hours after the last meal. The group of patients with atherosclerosis was divided into subgroups depending on the presence / absence of abdominal obesity. The subgroup with abdominal obesity included men with a waist circumference (WC) ≥ 94 cm [1]. The blood levels of adiponectin, leptin, resistin, adipsin, amylin, and metalloproteinases (MMPs)- 1, -2, -3, -7, -9, -10, -12, -13 were determined by the multiplex assay on the Luminex MAGPIX flow fluorimetry system.

Statistical processing of the results was carried out using the SPSS 13.0 program. Biomarkers were tested for normality of distribution using the Kolmogorov – Smirnov test. Since most of the variables did not follow a normal distribution, the values in the tables were presented as the median and the interquartile range, *Me* [Q_{25}; Q_{75}]. The differences were evaluated using the Mann – Whitney test. Correlations were evaluated using the nonparametric Spearman's rank correlation coefficient. The differences were considered statistically significant at $p < 0.05$.

RESULTS

The results obtained during the study are presented in Table 1. In patients with atherosclerosis, the level of adiponectin was significantly lower (by 20%) compared to the control group. Significant differences between the main and control groups were also obtained for MMP-1, MMP-7, and MMP-12. The level of MMP-1 was higher in the main group by 67.9%; MMP-7 – by 30.6%, and MMP-12 – by 107.1% compared to the control group. No significant differences were obtained for the other parameters (Table 1).

The results obtained in patients with atherosclerosis, depending on the absence / presence of abdominal obesity, are presented in Table 2. The levels of MMP-1 and MMP-12 were 1.7 (p = 0.001) and 1.38 (p = 0.037) times higher in patients without abdominal obesity, respectively. For the other parameters, the level of statistical significance of the differences was greater than 0.05.

Table 1

The levels of the studied biomarkers in the control group and in patients with coronary artery atherosclerosis, *Me* [Q_{25}; Q_{75}]

Parameter	Control group	Main group	*p*
Adiponectin, µg / ml	34.3 [16.4; 53.1]	24.4 [13.9; 38.5]	0.022
Adipsin, µg / ml	10.4 [7.0; 14.7]	9.6 [6.1; 13.1]	0.263
Resistin, ng / ml	21.7 [11.9; 49.1]	29.9 [11.4; 45.9]	0.716
Leptin, ng / ml	3.9 [1.2; 7.3]	4.6 [1.4; 8.2]	0.660
Amylin, pg / ml	6.2 [0.7; 16.2]	4.5 [1.6; 11.5]	0.790
MMP-1, ng / ml	5.3 [2.4; 8.9]	8.9 [5.7; 15.6]	0.002
MMP-2, ng / ml	111.7 [89.1; 126.9]	103.6 [78.3; 119.4]	0.253
MMP-3, ng / ml	47.1 [28.4; 66.5]	33.6 [21.3; 65.4]	0.202
MMP-7, ng / ml	8.5 [7.6; 11.9]	11.1 [9.4; 15.5]	0.012
MMP-9, ng / ml	236.0 [151.3; 307.6]	229.5 [131.0; 353.8]	0.611
MMP-10, ng / ml	0.62 [0.52; 0.82]	0.68 [0.52; 0.81]	0.722
MMP-12, ng / ml	0.14 [0.13; 0.17]	0.29 [0.18; 0.43]	0.000
MMP-13, pg / ml	30.4 [17.6; 71.9]	36.5 [18.5; 58.2]	0.701

Table 2

The level of adipose tissue hormones and metalloproteinases in patients with atherosclerosis, depending on the presence or absence of abdominal obesity, *Me* [Q_{25}; Q_{75}]

Parameter	Without AO	With AO	*p*
Adiponectin, µg / ml	28.3 [15.4; 41.9]	18.9 [11.7; 36.1]	0.188
Adipsin, µg / ml	10.9 [8.1; 13.6]	9.2 [5.5; 11.5]	0.07

Table 2 (continued)

Parameter	Without AO	With AO	*p*
Resistin, ng / ml	25.9 [8.2; 44.2]	16.6 [8.7; 34.7]	0.748
Leptin, ng / ml	4.0 [1.1; 7.9]	5.2 [2.1; 9.7]	0.347
Amylin, pg / ml	2.6 [1.6; 8.8]	4.5 [1.6; 10.5]	0.480
MMP-1, ng / ml	10.34 [7.1; 19.5]	6.1 [3.5; 10.0]	0.001
MMP-2, ng / ml	104.9 [82.3; 131.0]	93.7 [78.3; 112.9]	0.163
MMP-3, ng / ml	33.6 [23.6; 63.5]	35.9 [16.8; 65.8]	0.71
MMP-7, ng / ml	11.9 [9.4; 15.5]	10.2 [8.5; 14.3]	0.362
MMP-9, ng / ml	226.5 [122.1; 343.1]	205.5 [132.7; 325.9]	0.812
MMP-10, ng / ml	0.69 [0.55; 0.82]	0.68 [0.43; 0.82]	0.57
MMP-12, ng / ml	0.29 [0.17; 0.5]	0.21 [0.14; 0.33]	0.037
MMP-13, pg / ml	30.2 [17.8; 62.6]	43.15 [24.5; 58.4]	0.518

Note: AO – abdominal obesity.

In order to assess the effect of obesity on the level of metalloproteinases, we conducted a correlation analysis (using the Spearman's rank correlation coefficient). The relationship between the levels of MMP-1 (r = –0.531; p = 0.0001) and MMP-12 (r = –0.248; p = 0.032) with WC was revealed. The relationship with BMI was revealed only for MMP-1 (r = –0.264; p = 0.012). The association of MMP-2, MMP-3, MMP-7, MMP-9, and MMP-12 with adipose tissue hormones was revealed. Resistin was associated with concentrations of MMP-2 and MMP-3 (r = 0.321; p = 0.041 and r = 0.319; p = 0.002, respectively); leptin – with MMP-7 (r = 0.23; p = 0.035); adiponectin – with MMP-12 (r = 0.329; p = 0.008). The level of MMP-9 was associated with amylin (r = 0.568; p = 0.027).

DISCUSSION

The differences in the levels of biomarkers between the control group and patients with atherosclerosis were obtained for adiponectin, lipocalin-2, MMP-1, MMP-7, and MMP-12.

Adiponectin can inhibit the formation of reactive oxygen species, the release of proinflammatory cytokines, the expression of adhesion molecules, and apoptosis of smooth muscle cells and promote the outflow of cholesterol from macrophages [2]. At the same time, data on the effect of adiponectin in coronary heart disease (CHD) are contradictory. According to the meta-analysis by L. Yang et al., elevated adiponectin levels were independently associated with a higher risk of cardiovascular diseases and all-cause mortality in patients with CHD [3]. Q. Li et al. showed that, on the contrary, the frequency of adverse cardiovascular events was higher in the group of patients with low adiponectin levels [4]. In our study, we found that the level of adiponectin was reduced in patients with atherosclerosis compared to the control group, which indicates the anti-atherogenic function of adiponectin.

The association of resistin with MMP-2 and MMP-3 shows that it may enhance endothelial dysfunction, induce proliferation of smooth muscle cells, and promote the entry of mononuclear leukocytes into the intima through exposure to MMP. The study by S. Niaz et al. [5] showed a progressive increase in serum resistin levels in patients with arterial hypertension and CHD compared to healthy subjects. In our study, the level of resistin was higher in patients with atherosclerosis, but the significance level was greater than 0.05, which may be due to the small sample size and requires further study.

MMP-1 is considered to be the main enzyme responsible for collagen degradation. In addition, MMP-1 can lead to platelet activation and promote plaque expansion, rupture, and hemorrhage through degradation of collagen inside the plaque. High levels of MMP-1 are associated with an increased risk of all-cause mortality in patients with verified or possible ischemic disease [6]. We obtained higher levels of MMP-1 in patients with atherosclerosis. We also obtained data on an inverse correlation between the level of MMP-1, BMI, and WC, which differs from the data of S. Boumiza et al. [7], who found a direct correlation. It may be due to the fact that only men participated in our study.

MMP-7 plays an important role in atherosclerotic plaque destabilization, as it is associated with apoptosis of vascular smooth muscle cells and with macrophages in the necrotic nucleus. An association was established between plasma levels of MMP-7 and all-cause mortality in patients with CHD. Our data on the elevated level of MMP-7 in patients with atherosclerosis are in line with the data of other researchers [8]. C. Chavey et al. [9] showed that MMP-7 significantly decreases with obesity. Our study revealed a decrease in its level, but the differences were not statistically significant.

It is known that the expression of MMP-12 is increased in obesity. It is produced by macrophages and is associated with the progression and instability of

plaques [10, 11]. An increase in the level of circulating MMP-12 has been reported in asymptomatic patients with high cardiovascular risk associated with carotid intima–media thickness and cerebrovascular events during follow-up [12], as well as with the presence of CHD [13]. In our study, MMP-12 was elevated in patients with atherosclerosis, which is in line with the results obtained by M. Marcos-Jubilar et al. [14].

CONCLUSION

The data obtained indicate a relationship between the level of damage markers and adipose tissue hormones, which lead to the development of complications of cardiovascular diseases and explain the effect of obesity on atherosclerotic plaque destabilization.

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Authors' contribution

Polonskaya Ya.V. – conception and design, analysis and interpretation of the data, drafting of the manuscript. Kashtanova E.V. – conception and design, justification of the manuscript. Stakhneva E.M., Shramko V.S., Sadovsky E.V., Ledovskikh S.R. – analysis and interpretation of the data. Garbuzova E.V. – analysis and interpretation of the data, drafting of the manuscript in English. Kurguzov A.V., Murashov I.S. – obtaining biomaterial, analysis and interpretation of the data. Ragino Yu.I. – final approval of the manuscript for publication.

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