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PREVALENCE OF MAIN RISK FACTORS AND CYTOKINE PROFILE IN PATIENTS WITH ACUTE CORONARY SYNDROME AND DIFFERENT SERUM MYOSTATIN LEVELS

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РАСПРОСТРАНЕННОСТЬ ОСНОВНЫХ ФАКТОРОВ РИСКА И ЦИТОКИНОВЫЙ ПРОФИЛЬ У ПАЦИЕНТОВ С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ И РАЗНЫМ УРОВНЕМ МИОСТАТИНА СЫВОРОТКИ КРОВИ

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Objective. To study the prevalence of the main risk factors and the value of proinflammatory cytokines in patients with acute coronary syndrome (ACS) depending on the determined level of serum myostatin.
Materials and methods. 120 patients with ST elevation ACS (STE-ACS) and non-ST-segment elevation ACS (NSTE-ACS), hospitalized in the cardiology department of the regional vascular center were examined.

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In 86 patients, the level of serum myostatin and proinflammatory cytokines was determined on the 5th day of the development of acute coronary syndrome.

Results. Patients were divided into two subgroups depending on the level of serum myostatin which was determined: group 1 – with a lower level of myostatin, group 2 – with a higher level of myostatin. Group 1 (serum myostatin level from 0.038 to 0.084 ng/ml) consisted of 23 patients (16 males). Group 2 (serum myostatin level from 0.137 to 0.630 ng/ml) contained 21 patients (14 males). The main risk factors for cardiovascular diseases such as family history of early development of cardiovascular diseases, smoking, dyslipidemia, obesity, arterial hypertension and type 2 diabetes mellitus were assessed.

The levels of pro-inflammatory cytokines were determined. Tumor necrosis factor alpha (TNF-alpha) and interleukin 18 (IL-18) levels were significantly higher in patients with higher myostatin levels. Correlation analysis revealed a relationship between serum myostatin concentration and TNF-alpha level ($r = 0.34$; $p = 0.0016$).

Conclusions. No differences in the prevalence of risk factors in patients with ACS and different myostatin levels, except for smoking were revealed in the study, the frequency of smoking was higher in the group with higher myostatin levels. Greater activity of pro-inflammatory cytokines TNF-alpha and IL-18 was revealed in patients with higher levels of myostatin, as well as a significant correlation between the level of myostatin and TNF-alpha.

Keywords. Myostatin, proinflammatory cytokines, acute coronary syndrome.

Цель. Изучить распространенность основных факторов риска и значения провоспалительных цитокинов у пациентов с острым коронарным синдромом (ОКС) в зависимости от определяемого уровня сывороточного миостатина.

Материалы и методы. Обследовано 120 пациентов с ОКС с подъемом (ОКСпST) и без подъема сегмента ST (ОКСбпST), госпитализированных в отделение кардиологии на базе регионального сосудистого центра. У 86 пациентов из госпитализированных был определен уровень сывороточного миостатина и провоспалительных цитокинов на 5-е сутки развития острого коронарного синдрома.

Результаты. Пациентов разделили на две подгруппы в зависимости от определяемого уровня сывороточного миостатина: группу 1 – с более низким уровнем миостатина, группу 2 – с более высоким уровнем миостатина. Группу 1 (уровень сывороточного миостатина от 0,038 до 0,084 нг/мл) составили 23 пациента (из них 16 мужчин). Группу 2 (уровень сывороточного миостатина от 0,137 до 0,630 нг/мл) – 21 пациент (из них 14 мужчин). Были оценены основные факторы риска сердечно-сосудистых заболеваний: наследственная отягощенность по раннему развитию сердечно-сосудистых заболеваний, курение, дислипидемия, ожирение, артериальная гипертензия и сахарный диабет 2-го типа.

Определены уровни провоспалительных цитокинов. Уровни фактора некроза опухоли альфа (ФНО-α) и интерлейкина 18 (IL-18) были достоверно выше у пациентов с более высоким уровнем миостатина. По данным корреляционного анализа выявлена взаимосвязь между концентрацией миостатина сыворотки и уровнем ФНО-α ($r = 0,34$; $p = 0,0016$).

Выводы. В исследовании не выявлено различий по распространенности факторов риска у пациентов с ОКС и разным уровнем миостатина, за исключением курения, частота которого была выше в группе с более высоким уровнем миостатина. Зафиксирована большая активность провоспалительных цитокинов ФНО-α и IL-18 у пациентов с более высокими уровнями миостатина, а также достоверная корреляция между уровнем миостатина и ФНО-α.

Ключевые слова. Миостатин, провоспалительные цитокины, острый коронарный синдром.

INTRODUCTION

Myostatin (growth differentiation factor 8) is a member of the superfamily of the transforming growth factor-β whose primary target is myoblasts. It is secreted primarily by skeletal muscle, although small amounts of myostatin are also produced by the myocardium and adipose tissue [1]. It is secreted primarily by skeletal muscles, although small amounts of myostatin are also produced by the myocardium and adipose

tissue [1]. Myostatin inhibits skeletal muscle development and regulates fibroblast proliferation in skeletal muscle, i.e. the properties of the extracellular matrix [2], and also affects the structure and function of tendons [3]. The role of myostatin in influencing the cardiac muscle or myofibroblasts in coronary heart disease (CHD) and myocardial infarction (MI) is less clear. Recent studies in transgenic animals have shown that long-term overexpression of myostatin in the mouse heart reduces ejection fraction (EF) and stroke volume, increases end-systolic and diastolic volumes, induces the development of fibrosis and a decrease in heart weight, whereas the removal of myostatin has the opposite effect – it leads to myocardial hypertrophy [1]. In mice, Sarina Lim et al. found significant differences in outcomes between myostatin-null and wild-type mice after MI. The myostatin-null group had better EF recovery, less myocardial collagen deposition, and lower mortality. The researchers hypothesized that low myostatin levels are associated with better cardiac function after MI, possibly by limiting the extent of fibrosis [4].

There are isolated studies concerning the concentration of myostatin in the serum after myocardial infarction in humans. The study by Oliveira et al. [5] included 102 patients with MI and showed a decrease in the concentration of myostatin, compared to that in healthy people. Mortality among patients with lower concentrations of serum myostatin was higher than among patients with less reduced levels.

Thus, there are quite contradictory data on the direction of changes in myostatin concentration in the post-infarction period in the experiment and in clinical observations. Obviously, additional studies are needed to study the relationship between the myostatin level and the course of the disease in patients with acute coronary syndrome.

The aim of the study was to investigate the prevalence of major risk factors and the significance of proinflammatory cytokines in patients with acute coronary syndrome depending on the determined level of serum myostatin.

MATERIALS AND METHODS

A total of 120 patients with acute coronary syndrome with and without ST elevation were examined, hospitalized in the Cardiology Department at the Regional Vascular Center of the S.N. Grinberg City Clinical Hospital (RVC S.N. Grinberg City Clinical Hospital) from 2019 to 2021.

The inclusion criteria for the study were: diagnosis of acute coronary syndrome according to the clinical guidelines of the Russian Ministry of Health and the recommendations of the European Society of Cardiology[1]; age 30–90 years; voluntary informed consent of the patient to participate in the study. Exclusion criteria were non-coronary heart disease, malignant neoplasms, kidney and liver diseases with impaired function, blood diseases, acute infectious diseases, the presence of heart failure stage IIB–III and functional class III–IV before hospitalization.

Examination and treatment of patients was carried out in accordance with the Clinical Guidelines of the Russian Ministry of Health, Guidelines of the European Society of Cardiology[2], in force at the time of the study.

All patients underwent collection of clinical and anamnestic data; physical examination with measurement of blood pressure (BP), heart rate (HR), height and weight with calculation of body mass index (BMI), waist circumference (WC) and hip circumference (HC) with calculation of the WC / HC ratio.

Standard laboratory testing included a complete blood count; follow-up of biochemical markers of cardiocytolysis (Troponin I-high sensitive, creatine phosphokinase-MB (CPKMB)); urea content, blood creatinine with calculation of the glomerular filtration rate (cGFR); aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, glucose, blood lipids (total cholesterol (TC), low-density lipoprotein (LDL), very low-density lipoproteids (VRDL), high density lipoproteins (HDL), triglycerids (TG) with calculation of the atherogenic coefficient (AC) and non-high-density lipoprotein cholesterol).

In 86 patients, the level of serum myostatin and proinflammatory cytokines was determined on the 5th day of development of acute coronary syndrome.

Blood sampling for the study was performed from the cubital vein on an empty stomach in the morning. Venous blood, obtained without anticoagulants in vacuum tubes with gel, was left to stand for 30 minutes at room temperature until a clot is formed. The tubes were then centrifuged for 10 min at 1500 rpm. The separated serum was transferred to clean Eppendorf tubes, frozen and stored at -30 °C.

The concentration of myostatin was determined by enzyme immunoassay using the ELISA Kit for Myostatin (MSTN), USA, catalog No: CEB653Hu.

Also, by the enzyme immunoassay method, interleukin 6 (IL-6) was determined using the Interleukin-6-IFA-BEST reagent kit (A-8768) from ZAO Vector-Best (Russia) (series 42), interleukin 18 (IL-18) using the Interleukin-18-IFA-BEST reagent kit (A-8770) from ZAO Vector-Best (Russia) (series 28), and tumor necrosis factor alpha (TNF-α) using the Alpha-TNF-IFA-BEST reagent kit (A-8756) from ZAO Vector-Best (Russia) (series 65).

Instrumental diagnostic studies included electrocardiography (ECG); Holter ECG monitoring (HM ECG); echocardiography (EchoCG); chest radiography; selective coronary angiography (CAG).

Electrocardiographic examination (Nihon Kohden Cardiofax C ECG-2150, Japan)

[2] ESC Guidelines for the Management of Patients with Acute Myocardial Infarction without ST Elevation 2015. Russian Journal of Cardiology 2016, 3 (131): 9-63. DOI: 10.15829/1560-4071-2016-3-9-63; ESC Guidelines for the Management of Patients with Acute Myocardial Infarction with ST Elevation 2017. Russian Journal of Cardiology 2018; 23 (5): 103-158. DOI: 10.15829/1560-4071-2018-5-103-158; Clinical Guidelines of the Ministry of Health of the Russian Federation. "Acute Myocardial Infarction without ST Elevation of Electrocardiogram". Russian Society of Cardiology in Conjunction with the Association of Cardiovascular Surgeons of Russia. M. 2020; Clinical Guidelines of the Ministry of Health of the Russian Federation. "Acute Myocardial Infarction with ST Elevation of the Electrocardiogram." Russian Society of Cardiology in Conjunction with the Association of Cardiovascular Surgeons of Russia. M. 2020.

was performed in 12 standard leads upon admission of patients to hospital and then daily. To identify rhythm and conduction disturbances, the presence and duration of myocardial ischemia episodes, Holter ECG monitoring was performed (Astrocard Holtersystem-2f, AO MEDITEK, Russia).

Selective coronary angiography (CAG) was performed by specialists from the Department of X-ray Surgical Diagnostic and Treatment Methods of the S.N. Grinberg Regional Vascular Centre of the City Clinical Hospital using standard techniques and radial access.

All patients with acute coronary syndrome with persistent ST elevations (STE-ACS) underwent emergency CAG with subsequent reperfusion of the infarct-related artery. The decision on the necessity and urgency of CAG with possible percutaneous coronary intervention in patients with NSTE-ACS was made after risk stratification according to the GRACE[3] Scale.

Patients received therapy in accordance with Clinical Guidelines[3]: dual antiplatelet therapy, anticoagulant therapy (low molecular weight heparins), beta-blockers, mineralocorticoid receptor antagonists, drugs from the group of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, statins.

Statistical processing of the obtained data was carried out using the Statistica 10.0 program (StatSoft, Inc., USA). The Kolmogorov-Smirnov criterion was used to determine the normality of the distribution of features. To describe quantitative characteristics, the median (Me) and quartiles (Q_1, Q_3) were used. When assessing the statistical significance of differences (d) in independent samples for quantitative characteristics, the Mann – Whitney *U*-test (*U*) was used. The reliability of differences for qualitative characteristics was assessed using the nonparametric XI table test (χ^2). The relationship between the quantitative characteristics under study was determined using the correlation coefficient (*r*). The correlation was considered statistically reliable at $p < 0.05$.

RESULTS AND DISCUSSION

The distribution pattern of myostatin levels in patients differed from normal (Figure). The distribution median was 0.1131 ng/ml, the interquartile range (25–75 %) was 0.0835–0.134 ng/ml. To study the characteristics of patients with different levels of serum myostatin, two subgroups were taken for analysis: the 1st one included patients with low myostatin levels (1st quartile), the 2nd – with high (4th quartile).

[3] ESC Guidelines for the Management of Patients with Acute Coronary Syndrome without Persistent ST Elevation 2015. Russian Journal of Cardiology 2016, 3 (131): 9-63. DOI: 10.15829/1560-4071-2016-3-9-63; ESC Guidelines for the Management of Patients with Acute Myocardial Infarction with ST Elevation 2017. Russian Journal of Cardiology 2018; 23 (5): 103-158. DOI: 10.15829/1560-4071-2018-5-103-158; Clinical Guidelines of the Ministry of Health of the Russian Federation. "Acute Coronary Syndrome without ST Elevation of the Electrocardiogram." Russian Society of Cardiology with the Participation of the Association of Cardiovascular Surgeons of Russia. Russian Society of Cardiology in Conjunction with the Association of Cardiovascular Surgeons of Russia. M. 2020; Clinical Guidelines of the Ministry of Health of the Russian Federation. "Acute Myocardial Infarction with ST Elevation of Electrocardiogram". Russian Society of Cardiology with the Participation of the Association of Cardiovascular Surgeons of Russia. M. 2020.

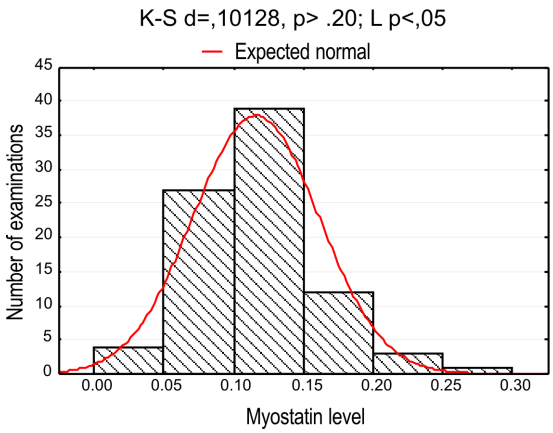

Fig. Histogram of Distribution of Myostatin Values in Patients with ACS

Group 1 (level of serum myostatin from 0.038 to 0.084 ng/ml) consisted of 23 patients (including 16 men). Group 2 (level of serum myostatin from 0.137 to 0.630 ng/ml) – 21 patients (including 14 men). The average age in Group 1 was 68 [58; 72] years, in Group 2 – 60 [51; 69] years. There were no statistically significant differences between the groups in terms of gender and age. The clinical characteristics of patients in both groups are presented in Table 1.

As can be seen from Table 1, the frequency of occurrence of the main risk factors for cardiovascular diseases (except smoking), concomitant diseases, and the history of coronary heart disease did not differ between the groups. Smokers were more common in the group with higher myostatin levels ($p = 0.011$). The smoking index did not differ and was 25.0 [14.0; 39.0] in group 2 versus 27.0 [19.5; 28.5] pack-years in group 1, respectively ($p = 0.876$). The groups were comparable in the structure of the final clinical diagnosis: 11 patients in each group were diagnosed with myocardial infarction, unstable cardiac angina was diagnosed in 12 people in group 1 and in 10 in group 2 ($p = 0.788$).

Table 2 presents the values of the studied proinflammatory cytokines. The levels of TNF-α and IL-18 were significantly higher in patients of the 2nd group. The values of IL-6 did not differ.

According to the correlation analysis, a relationship was found between the concentration of serum myostatin and the level of TNF-α ($r = 0.34$; $p = 0.0016$).

In recent decades, much new data has been obtained on various myokines and their local and systemic effects [6]. In particular, it has been shown that myostatin suppresses muscle tissue growth by reducing proliferation, myocyte differentiation, and protein synthesis [7; 8].

J. Dong et al. demonstrated in an experiment an increase in fibroblast division under the influence of myostatin, which may result in muscle tissue fibrosis [9]. In the cardiac muscle, this process can influence the remodeling of cardiac sections in coronary heart disease and heart failure. Animal experiments have shown that in case of cardiac pathology the level of myostatin production in cardiac tissue increases several times [10]. In myocardial infarction, myostatin transcription increases in cardiomyocytes located around the damaged area [11], and the increase in concentration persists in animals after 8 weeks from the moment of MI [12]. In clinical studies, myostatin levels were found

Table 1

Clinical Performance of Patients

Characteristic Value	Group 1, $n = 23$	Group 2, $n = 21$	p
Sex (male / female), %	69.6/30.4	66.7/33.3	0.899
Age, years	68 [58; 72]	60 [51; 69]	0.693
BMI, kg/m^2	28.7 [24.8; 31.2]	29.1 [26.1; 32.5]	0.148
Waist circumference (WC), cm	92 [86; 96]	95 [89; 103]	0.111
Hip circumference Окружность бедер (HC), cm	96 [90; 100]	103 [99; 106]	0.001
WC/HC, relative units	0.96 [0.90; 0.98]	0.96 [0.87; 1.02]	0.925
Heart rate, bpm	74 [70; 74]	74 [68; 78]	0.239
SAP, mm Hg	130 [120; 140]	140 [130; 160]	0.205
DBP, mm Hg	80 [70; 90]	90 [80; 90]	0.307
Hereditary load for early development of cardiovascular diseases, abs./%	5/21.7	5/23.8	0.871
Smoking, abs./%	3/13	10/47.6	0.011
Dyslipidemia, abs./%	21/91.3	20/95.2	0.243
Obesity, abs./%	8/34.8	6/28.6	0.637
AH, abs./%	19/82.6	20/95.2	0.196
Type 2 diabetes, abs./%	6/26.1	8/36.4	0.626
CAD H/O, abs./%	14/60.9	16/76.2	0.550
PC H/O, abs./%	5/21.7	10/47.6	0.182

Notice: MAP – systolic arterial pressure. DBP – diastolic blood pressure. AH – arterial hypertension. Diabetes – diabetes mellitus.

Table 2

Serum Interleukin Levels in Patients with Different Serum Myostatin Levels (*Me* [Q_1; Q_3])

Characteristic Value	Group 1, $n = 23$	Group 2, $n = 21$	p
TNF-α, pg/ml	1.5 [1.1; 2.7]	3 [2.6; 3.4]	0.012
IL-18, pg/ml	175.4 [133.9; 264.2]	259.9 [187.9; 300.4]	0.043
IL-6, pg/ml	5.3 [1.6; 9.5]	3.6 [3.3; 7.3]	0.991

to be increased in left ventricular myocardial samples from patients suffering from ischemic or dilated cardiomyopathy (DCM) [13].

The main source of myostatin in the systemic circulation is skeletal muscle, but in cardiac pathology, cardiac myostatin also contributes to this indicator. This was shown in an experiment on mice [14].

It can be assumed that high production of myostatin in patients with acute coronary syndrome may lead to more pronounced fibrosis processes in the myocardium, systemic lipid metabolism disorders and atherogenesis, as well as sarcopenia [6].

This study revealed greater activity of proinflammatory cytokines TNF-α and IL-18

in patients with higher myostatin levels, as well as a significant correlation between myostatin levels and TNF-α. It can be assumed that elevated myostatin levels are associated with metabolic imbalance and systemic inflammatory response with hyperexpression of proinflammatory cytokines [4; 15]. Our data are supported by the results of experimental work, which showed that tumor necrosis factor-alpha (TNF-alpha) increases the expression of myostatin [12].

Study limitation

This study is limited by the sample size of patients, further research in this direction requires a larger sample size.

Conclusion

The study found no differences in the prevalence of major risk factors in patients with acute coronary syndrome and different levels of myostatin, with the exception of smoking, the frequency of which was higher in the group with higher levels of myostatin. Greater activity of proinflammatory cytokines TNF-α and IL-18 was found in patients with higher levels of myostatin, as well as a direct relationship between the level of myostatin and TNF-α.

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