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Levels of proprotein convertase subtilisin/kexin type 9 in patients with acute myocardial infarction

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Aim. To study the levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) in patients with acute myocardial infarction (MI).

Material and methods. The study included 74 patients with acute MI. PCSK9 was determined by enzyme-linked immunosorbent assay.

Results. The mean PCSK9 levels were 479,7±15,4 ng/ml. No significant correlation was found between PCSK9 and total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides. In the group of smokers, a significant inverse correlation was found between the levels of PCSK9 and HDL-C (-0,45; p=0,039). In the group of patients with body mass index <25 kg/m^2, a significant inverse correlation of PCSK9 levels with total cholesterol (-0,45, p=0,008), HDL-C (-0,42; p=0,029) and LDL-C (-0,47; p=0,003) was found.

Conclusion. In patients with MI, a correlation of PCSK9 levels with lipid profile was found in smokers, as well as in patients with a low body mass index.

Key words: proprotein convertase subtilisin/kexin type 9, myocardial infarction.

Relationships and Activities: not.

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Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a hydrolase enzyme that binds to the low-density lipoprotein receptor. This leads to its degradation in endosomes and lysosomes and increases the level of low-density lipoprotein cholesterol (LDL-C) in the blood serum. There are a number of studies on the correlation of PCSK9 levels and coronary artery disease (CAD). In a study of 4232 healthy men and women with 15-year follow-up, the authors revealed a significant direct relationship between the PCSK9 level and cardiovascular events [1]. In a study by Caselli C, et al. of 412 patients with stable CAD, PCSK9 plasma levels was an independent predictor of coronary atherosclerosis severity [2].

In a study by Dalgic Y, et al. of 168 patients with non-ST segment elevation acute coronary syndrome, PCSK9 levels was an independent predictor of a high SYNTAX score [3]. The use of PCSK9 inhibitors in the acute myocardial infarction (MI) is currently a debatable issue [4]. The aim of this study was to assess the PCSK9 levels in patients with MI.

Material and methods

The study included 74 patients with MI confirmed by generally accepted criteria: cardiac troponin I increase; typical clinical picture; characteristic electrocardiography (ECG) changes; coronary angiography data. There were following inclusion criteria: acute MI; age of patients 40-70 years, signed informed consent. The exclusion criteria were: age over 70 years; not signed informed consent; circulatory failure; cerebrovascular accident in last 6 months prior to inclusion; severe kidney (creatinine >160 μmol/L) and liver failure (transaminase levels ⩾3 times the normal range); any heart rhythm disorders requiring treatment; second- and third-degree atrioventricular block; bradycardia (⩽50 bpm); sinoatrial block; respiratory failure (⩾II degree); ineffective contraception in women of reproductive age; pregnancy and lactation; alcoholism and drug addiction; history of cancer.

Upon hospital admission, we determined levels of troponin I, brain natriuretic peptide, lipids and glucose. Complete blood count, ECG, body mass index (BMI), smoking profile and Gensini score estimated by coronary angiography were also assessed. Blood levels of PCSK9 were determined using the Human PCSK9 ELISA kit (BioVendor, Czech Republic); blood samples were frozen at -70° C.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The local medical ethics committee approved this study.

Statistical analysis methods. Normality of distribution was determined using the Shapiro-Wilk test. To describe normally distributed quantitative traits, the arithmetic mean (M) and the standard deviation (σ) were considered as M±σ. To describe the sampling distribution of non-normally distributed quantitative traits, we used the median (Me), lower (25%) and upper (75%) quartiles (Q1 and Q3) as Me [Q1; Q3]. The statistical significance of quantitative trait differences was evaluated by the nonparametric Mann-Whitney U test. To identify the association between the PCSK9 level and other quantitative variables, nonparametric Spearman's correlation analysis was used.

Table 1
Blood levels of PCSK9 in patients with MI

	PCSK9 levels (ng/ml) M±σ Me [Q_1; Q_3]	p (between subgroups of men and women)
General group (n=74)	479,7±15,4 466,0 [378,0-582,8]	
Men (n=59)	465,6±16,2 461 [375,5-556,5]	
Women (n=15)	534,9±38,9 515 [441,5-658,0]	0,122

Results

The study included 74 patients: 59 (79,7%) men aged 58 years (interquartile range: 52-64 years old), 15 (20,3%) women aged 63 years (interquartile range: 62-65 years old). Forty-three patients had Q-wave MI.

Blood levels of PCSK9 in all patients and depending on the gender are presented in Table 1. There was no statistically significant difference between the PCSK9 levels in men and women (p=0,122). The lowest PCSK9 level recorded in the group was 214 ng/ml, the highest — 786 ng/ml.

There was no statistically significant correlation of PCSK9 with levels of total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides. However, in the group of smokers (n=22), an inverse moderate correlation between PCSK9 and HDL-C was revealed (-0,45, p=0,039).

A significant correlation was found between PCSK9 levels and lipid metabolism parameters depending on BMI: in the group of patients with BMI <25 kg/m^2 (n=22), there was inverse correlation of PCSK9 with levels of total cholesterol (-0,45, p=0,008), HDL-C (-0,42, p=0,029) and LDL-C (-0,47, p=0,003).

Discussion

The study of PCSK9 is of great practical interest, since the effects of alirocumab and evolocumab on reducing its levels has been proved [5, 6].

In one study, the authors investigated the PCSK9 levels in men (44-73 years) in different population

subgroups, its relationship with cardiovascular risk factors and long-term 7-year unfavorable prognosis, where the mean level of PCSK9 was significantly lower [7] than in our study (131,1±4,2 ng/ml, median 119,8 ng/ml).

In another population-based study of men aged 25-45, the mean PCSK9 level was 325,9±141,97 ng/ml, the median and interquartile range — 300,19 ng/ml (240,20 ng/ml; 361,80 ng/ml); there were also higher variability (from 20,90 ng/ml to 1249,04 ng/ml) [8] than in our study.

High variability of PCSK9 levels was also observed in Dallas Heart Study: the minimum — 33 ng/ml, the maximum — 2988 ng/ml [9]. Perhaps this is due to the population specificity of the PCSK9 level.

Several researchers have identified differences in PCSK9 levels depending on gender and BMI. So, in the Dallas Heart Study, the PCSK9 level was higher in women than in men (517 ng/ml and 450 ng/ml, respectively) [8, 9], which was also noted in our study: 515 ng/ml in women, 461 ng/ml in men.

In a study by Zhu YM, et al., insulin, LDL-C, and triglycerides were independent predictors of high PCSK9 concentration, and BMI inversely correlated with PCSK9 level, which differs from our data [10].

In independent samples of young men without cardiovascular disease and with different smoking status, the authors found that the PCSK9 level was higher in smokers (339,49±139,86 ng/ml; 311,82 ng/ml (251,04; 369,78 ng/ml) than in the non-smokers (315,17±143,16 ng/ml; 286,16 ng/ml (229,91; 351,71 ng/ml) (p=0,011) [11]. In a study by Leander K, et al., it was demonstrated that smokers had higher PCSK9 levels in quartiles 3 and 4 than non-smokers [1]. In a population study by Ridker P, et al., association of PCSK9 protein with smoking status was not observed [12].

In the study of PCSK9 levels in patients with ST-segment elevation MI, the severity of atherosclerotic lesions was assessed using the Gensini, Jeopardy, and SYNTAX scores, and the authors determined that levels of PCSK9, total cholesterol, LDL-C, creatinine were independent predictors of high SYNTAX score [3]. In our study, the severity of coronary atherosclerotic lesions was assessed by Gensini score, and we did not find a relationship between the severity of coronary atherosclerosis and the PCSK9 levels. In the Swiss population of patients with acute coronary syndrome, PCSK9 levels reached 374±149 ng/ml [13].

The data obtained in our study characterize the levels of PCSK9, its distribution and relationship with other lipid metabolism parameters in patients with MI.

Conclusion

1. Patients with MI and BMI <25 kg/m^2 have a significant inverse correlation of PCSK9 values with levels of total cholesterol (-0,45, p=0,008), HDL-C (-0,42, p=0,029) and LDL-C (-0,47, p=0,003).

2. Smokers with MI have a significant inverse correlation between the levels of PCSK9 and HDL-C (-0,45, p=0,039, n=22).

Relationships and Activities: not.

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