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Генетические предикторы неблагоприятного течения облитерирующего атеросклероза артерий нижних конечностей

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Цель. Определение влияния полиморфизма –250G>A в гене LIPC и –1607insG в гене MMP-1 на течение облитерирующего атеросклероза артерий нижних конечностей (ОААНК).

Материалы и методы. В исследовании приняли участие 76 человек. В I группу (n = 34) были включены пациенты с неблагоприятным (прогрессирующим) типом течения ОААНК, у которых развилась критическая ишемия нижних конечностей в течение 5 лет от начала заболевания. Во II группу (n = 34) включались пациенты с условно благоприятным (не прогрессирующим) типом течения, у которых в течение 5 лет от начала заболевания критическая ишемия нижних конечностей не развивалась, а степень хронической ишемии не прогрессировала. В качестве контрольной группы (n = 8) были включены здоровые добровольцы без признаков атеросклероза во всех сосудистых бассейнах. Пациентам проводилось генотипирование полиморфизмов LIPC-250G>A и MMP-1-1607insG. Оценивалось различие наблюдаемых и ожидаемых частот по критерию $\chi 2$ Пирсона с поправкой на правдоподобие.

Результаты. При исследовании полиморфизма –250G>A гена LIPC выявлены статистически значимые (p = 0,013) различия наблюдаемых и ожидаемых частот при сравнении групп пациентов с ОААНК и здоровых добровольцев. При оценке I и II группы также выявлены различия наблюдаемых и ожидаемых частот (p = 0,004). Гетерозиготное носительство (генотип GA) ассоциируется с повышенным риском развития неблагоприятного течения ОААНК. Отношение рисков = 2,133 с 95% доверительным интервалом 1,214–3,748. При анализе полиморфизма -1607insG гена MMP1 получены статистически незначимые данные как при сравнении I и II групп (p = 0,128), так и при сравнении групп пациентов с ОААНК со здоровыми добровольцами (p = 0,38).

Выводы. Гетерозиготное носительство LIPC –250G>A ассоциируется с повышенным риском развития неблагоприятного типа течения ОААНК. Исследование данного полиморфизма может быть использовано у пациентов с впервые выявленным атеросклерозом артерий нижних конечностей с целью определения прогноза течения заболевания, особенно у молодых пациентов с ранней манифестацией и у лиц с отягощенным наследственным анамнезом. Полиморфизм –1607insG гена MMP1 не продемонстрировал влияния на течение ОААНК.

Ключевые слова: *атеросклероз; критическая ишемия; прогнозирование течения заболевания; генетические предикторы; полиморфизм; LIPC-250G>A; MMP-1-1607insG*

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Genetic predictors of an unfavorable course of obliterating atherosclerosis of lower limb arteries

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AIM: This study aimed to determine the influence of –250G>A polymorphism in the LIPC gene and –1607insG in the MMP-1 gene on the course of obliterating atherosclerosis of lower limb arteries (OALLA).

MATERIALS AND METHODS: Seventy-six individuals were included in this study. In the first group (n = 34), patients with an unfavorable (progressive) course of OALLA and developed critical ischemia of the lower limbs within 5 years from the onset of the disease were included. In the second group (n = 34), patients with a conventionally favorable (non-progressive) course but did not develop critical ischemia of the lower limbs within 5 years from the onset of the disease and did not have a progressive degree of chronic ischemia. In the control group, healthy volunteers (n = 8) without signs of atherosclerosis in all vascular pools were included. In all the patients, LIPC-250G>A and MMP-1-1607insG were genotyped. The difference in the observed and expected frequencies was evaluated via a Pearson $\chi 2$ test with correction for likelihood.

RESULTS: Significant differences (p = 0.013) in the –250G>A polymorphism of the LIPC gene were found between the observed and expected frequencies compared with those in patients with OALLA and healthy volunteers. The assessment of the first and second groups revealed differences in the observed and expected frequencies (p = 0.004). Heterozygous carriage (GA genotype) was associated with an increased risk of the development of the unfavorable course of OALLA (hazard ratio = 2.133 with 95% confidence interval = 1.214–3.748). In the analysis of the –1607insG polymorphism of the MMP-1 gene, statistically insignificant data were obtained compared between the first and second groups (p = 0.128) and between the groups of patients with OALLA and healthy volunteers (p = 0.38).

CONCLUSIONS: The heterozygous carrier of LIPC –250G>A was associated with an increased risk of an unfavorable OALLA course. This research on this polymorphism could be applied to patients with the newly diagnosed atherosclerosis of the arteries of the lower extremities to determine the prognosis of the disease course, especially in young patients with early manifestation and individuals with a burdened hereditary history. The –1607insG polymorphism of the MMP-1 gene had no effect on the course of OALLA.

Keywords: *atherosclerosis; critical ischemia; disease course prediction; genetic predictors; polymorphism; LIPC-250G>A; MMP-1-1607insG*

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ECO•VECTOR

Obliterating atherosclerosis of the lower limb arteries (OALLA) is a severe multifactorial disease. In certain cases, it can have an unfavorable outcome — development of critical ischemia and subsequent amputation of the limb. In the majority of cases, improvements in reconstructive operations and advances in endovascular technologies permit to resolve ischemia. However, the problem of progression of atherosclerosis as a *systemic disease* remains unsolved [1].

The clinical course of OALLA is quite diverse. In some cases, the disease is asymptomatic, which significantly complicates its timely identification. *Intermittent claudication* is the most common manifestation of the disease that can be referred to as a conventionally favorable course of the disease. The development of *critical lower limb ischemia* (CLLI) is an unfavorable predictor, in terms of preservation of both the limb and life of the patient [2]. The risk of death in patients with CLLI is 25%, and the risk of amputation in the first year after CLLI development is 30%, despite adequate angiosurgical care [3]. The development of *acute arterial obstruction* with clinical presentation of acute limb ischemia is also considered an unfavorable course of OALLA.

Genetic studies are considered the most relevant in the long-term forecast of the course of any disease [4]. To date, great progress has been made in this area; however, test systems for predicting the course of OALLA are still unavailable.

Various studies showed the association of –250G>A polymorphism in hepatic lipase gene (LIPC) promoter with elevated levels of insulin, low-density lipoproteins, and very low-density lipoproteins, which is, in turn, a risk factor for the development and progression of atherosclerosis [5]. E.A. Vil'ms et al. (2012) registered disorders of lipid metabolism in men associated with the carriage of A allele of –250G>A polymorphism [6]. P. Valdivielso et al. (2007) noted that the presence of pathological A allele of –250G>A polymorphism in the LIPC gene is a predisposing factor for the development of OALLA in patients with diabetes mellitus [7].

The effect of matrix metalloproteinases (MMPs), belonging to the collagenase family, on the course of various diseases has been studied for a long time. Several publications are devoted to the effect of these enzymes on the state of connective tissues [8,9]. Evidences confirm the destructive effect of MMPs on the fibrous cap of atherosclerotic plaques, leading to its rupture and subsequent arterial thrombosis with the clinical picture of acute coronary syndrome [10]. Furthermore, an increase in the concentration of MMP-1 in unstable atherosclerotic plaques was determined in the study by D. E. Ivanoshchuk et al. (2018) [11]. The analysis of the literature showed that 1607insG polymorphism in the MMP-1 gene has not been studied in the context of OALLA.

This study **aimed** was to the effect of 250G>A polymorphism in the LIPC gene and 1607insG polymorphism in the MMP-1 gene on the course of OALLA.

MATERIALS AND METHODS

The study was carried out at the clinical bases under the Department of Cardiovascular, Roentgen-Endovascular, Operative Surgery and Topographic Anatomy, Ryazan State Medical University. The laboratory part of the study was performed based on the Central Scientific Research Laboratory of Ryazan State Medical University. The study is approved by the Local Ethics Committee of Ryazan State Medical University.

The study involved 76 individuals, categorized into three groups.

Group I (n = 34) included patients with *unfavorable (progressing) course* of OALLA with the development of critical ischemia of the lower limbs within 5 years from the onset of the disease.

Group II (n = 34) included patients with *conventionally favorable (non-progressing) course* of OALLA, in whom critical ischemia of the lower limbs did not develop within 5 years from the onset of the disease, and the degree of chronic ischemia did not progress.

The control group (n = 8) included healthy volunteers with no signs of atherosclerosis in any vascular pool.

The study patients were subjected to the following diagnostic examinations: ultrasound dopplerography with determination of the ankle–brachial index, duplex ultrasound of the lower limb arteries and brachiocephalic arteries, and angiography (on indications). The treatment of patients was conducted according to the national guidelines for the diagnosis and treatment of diseases of the arteries of the lower limbs, 2019 [12]. The characteristics of patients by the level of occlusive–stenotic lesions of the arteries of the lower limbs are presented in Table 1.

The statistical analysis of the obtained results was carried out using Statistica 13.0 software (Stat Soft Inc., USA). The difference between the observed and expected frequencies was estimated using Pearson chi-squared test with correction for likelihood, Cramer's V test, hazard ratio (HR), and 95% confidence interval (CI) of HR. The critical level of statistical significance for the difference in the compared parameters was assumed to be $p < 0.05$.

RESULTS AND DISCUSSION

In the analysis of 1607insG polymorphism in the MMP-1 gene, the differences between the observed and expected frequencies, according to the Pearson chi-squared test with correction for likelihood, were statistically insignificant when compared both between Groups I and II ($p = 0.128$), and between the Groups I

Table 1. Characteristics of Study Patients with Obliterating atherosclerosis of the lower limb arteries by the Level of Occlusive–Stenotic Lesions of the Lower Limb Arteries, n (share in the groups)

Level of Damage of Arterial Pool of the Lower Limbs	Aortoiliac Segment	Iliac–Femoral Segment	Femoral–Popliteal Segment
Group I (n = 34)	3 (0.09)	8 (0.24)	23 (0.68)
Group II (n = 34)	4 (0.12)	9 (0.26)	21 (0.62)
Total	7 (0.10)	17 (0.25)	44 (0.65)

and II taken together (n = 68) and healthy volunteers (p = 0.38, Table 2).

In the analysis of –250G>A polymorphism in the LIPC gene, statistically significant differences between the observed and expected frequencies were identified between the groups of patients with OALLA and healthy volunteers using the Pearson chi-squared test with likelihood correction (p = 0.013, Table 3). A positive relationship was observed according to the Cramer V test (+0.335). In the assessment of Groups I and II using Pearson chi-squared test, significant differences were obtained between the observed and expected frequencies (p = 0.004, Table 3). A positive relationship was observed by F-test (+0.354).

Table 2. Frequency of Distribution of –1607insG MMP-1 Genotypes in Study Groups, n (share in the groups)

Study Groups	Number of Patients in Groups with Genotypes			p
	1G/1G	1G/2G	2G/2G	
Group I (n = 34)	6 (0.18)	22 (0.65)	6 (0.18)	0.128[1]
Group II (n = 34)	12 (0.35)	14 (0.41)	8 (0.24)	
Control group (n = 8)	2 (0.25)	4 (0.50)	2 (0.25)	0.38[2]

Note: [1] statistically insignificant difference between Groups I and II, [2] statistically insignificant difference between Groups I and II taken together (n = 68) and healthy volunteers

Table 3. Frequency of Distribution of LIPC –250G>A Genotypes in Study Groups, n (share in the groups)

Study Groups	Number of Patients in Groups with Genotypes			p
	GG	GA	AA	
Group I (n = 34)	10 (0.29)	24 (0.71)	0	0.004[1,2]
Group II (n = 34)	22 (0.65)	12 (0.35)	0	
Control group (n = 8)	4 (0.50)	4 (0.50)	0	0.013[3]

Note: [1] HR = 2.133, 95% CI 1.214–3.748; [2] statistically significant difference between Groups I and II; [3] statistically significant difference between the Groups I and II taken together (n = 68) and healthy volunteers

According to the study by Y. Chahirou et al. (2018), lipase, which is a key enzyme for metabolism of high-density lipoproteins, was also found to be involved in the formation of a more atherogenic fraction—low-density lipoproteins [13]. Furthermore, various studies confirm the association between –250G>A polymorphism and the development of insulin resistance and elevated insulin levels, which is another important risk factor for the development and progression of atherosclerosis [6,14]. The study by W. Bakker et al. (2009), devoted to the determination of the role of hyperglycemia, insulin resistance, and obesity in the development of epithelial dysfunction, concluded that the reduction of the activity of hepatic lipase might lead to the progression of atherosclerotic process [15]. This fact confirms the results of our study, that is, the *prevalence of carriage*

of pathological A allele in –250G>A polymorphism in the LIPC gene in patients with unfavorable course of OALLA (Group I).

An earlier study on –250G>A polymorphism by P. Valdivielso et al. (2008) showed the reduction in the activity of hepatic lipase in patients with diabetes mellitus and with carriage of A allele; however, this fact was not studied in individuals without diabetes [7]. In the present study, heterozygous carriage (GA genotype) is found to be associated with an increased risk of unfavorable course of OALLA (HR = 2.133; 95% CI, 1.214–3.748).

In general, homozygote for the first allele (GG genotype) is normal. According to the results of our study, this genotype is reliably more common in patients with conventionally favorable course of OALLA (Group II).

CONCLUSIONS

The findings of this study conclude the following:

1) The heterozygous LIPC –250G>A carriage is associated with an increased risk of the development of unfavorable course of obliterating atherosclerosis of the lower limb arteries . Therefore, we suggest that study of this polymorphism may be used in patients with newly found atherosclerosis of the lower limb arteries to forecast the course of the disease, especially in young patients with early manifestation and in individuals with burdened heredity.

2) –1607insG polymorphism in the MMP-1 gene does not reliably produce any effect on the course of obliterating atherosclerosis of the lower limb arteries.

ADDITIONALLY

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Participation of authors. *R.E. Kalinin, I.A. Suchkov* — concept and design of research, editing, *A.A. Nikiforov, E.I. Shumskaya* — performing a genetic study and analyzing the results, *A.A. Chobanian* — analyzing literary sources, collecting and processing clinical data, statistical processing, writing a text.

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