ORIGINAL STUDY

Ассоциация генов *ITGB3* и *NOS3* с тяжестью течения ишемической болезни сердца при наличии и отсутствии сахарного диабета 2-го типа

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Сахарный диабет 2-го типа (СД2) является одним из ключевых предикторов ишемической болезни сердца (ИБС) и ее осложнений. Но в настоящее время, наряду с метаболическими факторами риска ИБС, особое внимание уделяется изучению генов-кандидатов, в числе которых рассматривают ген тромбоцитарного рецептора к фибриногену ITGB3 и ген эндотелиальной NO-синтазы 3 типа NOS3.

***Цель**. Оценить ассоциацию полиморфизмов T1565C гена ITGB3 и T-786C гена NOS3 при сочетанном развитии ИБС и СД2 с клиническим состоянием пациентов русской национальности, постоянно проживающих на территории Западно-Сибирского региона.*

***Материалы и методы**. Обследовано 237 больных ИБС, из которых 78 (32,9%) пациентов имели СД2. Амплификацию полиморфных участков выполнили методом аллель-специфичной ПЦР. Статистический анализ проводили с использованием теста Манна-Уитни или теста Крускала-Уоллиса для количественных данных и критерия χ^2 Пирсона или точного теста Фишера для дискретных величин.*

***Результаты**. В выборке ИБС+СД2 генотип 786CC гена NOS3 (p=0,039) и аллель 1565C гена ITGB3 (p=0,045) встречались реже, чем среди больных ИБС без СД2. Но в группе ИБС+СД2 среди носителей аллеля 1565C была выше частота ожирения, чем у гомозигот 1565TT (p=0,039), а носители аллеля 786C отличались наибольшей концентрацией глюкозы по сравнению с гомозиготами 786TT (p=0,018). Кроме того, в группе пациентов без СД2 обнаружена ассоциация аллеля 786C с ожирением (p=0,015).*

***Заключение**. Носительство аллеля 1565C гена ITGB3 и аллеля 786C гена NOS3 можно рассматривать в качестве предикторов неблагоприятного течения заболевания при сочетанном развитии ИБС и СД2.*

***Ключевые слова:** полиморфизмы; ITGB3; NOS3; сахарный диабет; ИБС*

The association of *ITGB3* gene and *NOS3* gene with the severity of coronary artery disease with and without type 2 diabetes

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Type 2 diabetes (T2DM) is a key predictor of coronary artery disease (CAD) and its complications. Currently, along with metabolic risk factors for CAD, much attention has been given to study candidate genes, including platelet fibrinogen receptor gene ITGB3 and NOS3 gene of endothelial NO-synthase type 3.

***Aim**. To estimate the association of T1565C ITGB3 and T-786C NOS3 polymorphisms with the clinical condition of Russian patients from West Siberian region with concomitant development of coronary artery disease and type 2 diabetes.*

***Materials and methods**. The study included 237 patients with CAD; 78 (32.9%) of them had T2DM. Genotyping was performed via allele-specific polymerase chain reaction. Comparison of the quantitative variables between groups with different genotypes was performed using Mann–Whitney U test or Kruskal–Wallis test. Comparison of discrete parameters was performed using Pearson's χ^2 test or Fisher's exact test.*

***Results**. Genotype 786CC (NOS3) (p = 0.039) and allele 1565C (ITGB3) (p = 0.045) were less common in the CAD + T2DM group than in the CAD only group. However, in the CAD + T2DM group, the incidence of obesity was higher among carriers of 1565C allele than in homozygous 1565TT (p = 0.039), and carriers of 786C allele had higher glucose levels compared with homozygous 786TT (p = 0.018). Furthermore, 786C allele was associated with obesity in the CAD only group (p = 0.015).*

***Conclusion**. Genotypes 1565C (ITGB3) and 786C (NOS3) alleles may be predictors of the adverse course of the disease at concomitant development of CAD and T2DM*

***Keywords:** polymorphisms; ITGB3; NOS3; diabetes mellitus; CAD*

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Background

Type 2 diabetes mellitus (T2DM) is one of the key predictors of coronary artery disease (CAD) and its complications [1]. The prevalence of hyperglycaemia and diabetes mellitus has been increasing in developed countries [2]. The risk of developing cardiovascular diseases, such as CAD, increases 2–4-fold in patients with T2DM compared with the general population. Furthermore, the combination of T2DM and CAD increases the risk of death by more than 4-fold [3, 4].

Genetic polymorphisms can also affect the development and severity of CAD. The precise combination of gene mutations and environmental factors introduce a high degree of variability in different pathophysiological conditions [5]. For example, *ITGB3*, the gene encoding the subunit of the platelet-specific fibrinogen GPIIb/IIIa receptor, and *NOS3*, the gene encoding endothelial nitric oxide (NO) synthase type III, are associated with CAD.

The T1565C polymorphism of *ITGB3* enhances the signalling activity of the GPIIb/IIIa complex, and this effect has been shown to increase ADP-induced platelet aggregation in vitro [6]. The 1565C allele is associated with a high risk of MI, rapid progression of atherothrombotic disease and high mortality rate [7, 8]. The T-786C polymorphism of *NOS3* inhibits the function of the eNOS enzyme, thereby reducing NO synthesis and increasing the risk of long-term coronary spasms [9]. Because NO inhibits platelet aggregation, leukocyte adhesion, smooth muscle cell proliferation and low-density lipoprotein (LDLP) oxidation, NO deficiency increases the risk of developing CAD [10, 11].

The clinical significance of genetic polymorphisms and their contribution to the pathogenesis of multifactorial diseases, including T2DM and CAD, largely depends on the demographic characteristics and lifestyle patterns of the patient population. Identifying the differential effects of allelic variants associated with different ethnicities and geographical regions can help assess the risk of various diseases in different regions [5]. Therefore, we evaluated the association of *ITGB3* and *NOS3* polymorphisms with CAD severity in the patients in West Siberia.

Goal

The aim of this study was to assess the association of the *ITGB3* T1565C and *NOS3* T-786C polymorphisms with the clinical characteristics of CAD and T2DM in ethnic Russian patients permanently residing in West Siberia.

Materials and methods

Clinical data was obtained from patients with cardiovascular disease who were treated at the department of rehabilitation at the Federal State Budgetary Scientific Institution Cardiology Research Institute from 2011 to 2014. The work was approved by the Committee on Biomedical Ethics of the Cardiology Research Institute. All of the patients provided informed consent to participate in the study.

Among the 237 unrelated patients evaluated, 198 were men and 39 were women. We evaluated their medical history and the results of their physical examination and laboratory diagnostics. All of the patients were diagnosed with CAD and were undergoing standard antianginal therapy in accordance with the recommendations of the Russian Society of Cardiology of 2013.

The patients were divided into two groups. One group (n = 159) included patients with CAD but without carbohydrate metabolism disorder (CAD group) and the other group (n = 78) included patients with both CAD and T2DM (CAD + T2DM group). The duration of T2DM in patients in the CAD + T2DM group was 1–3 years. Patients in this group were examined by an endocrinologist and were undergoing individualized antihyperglycemic therapy. Glycosylated haemoglobin (HbA1c) levels were determined using the Konelab 20XTi system (Thermo Scientific, USA). The mean HbA1c level in the CAD + T2DM group was 6.4% [interquartile range (IQR): 5.7–7.1]. Glucose levels were measured using the automated biochemical analyser Konelab 60i (Thermo Scientific, USA). The mean blood glucose level in the CAD + T2DM group was 6.4 (IQR: 5.9–7.3) mmol/L.

DNA was purified from blood samples using the Wizard Genomic DNA Purification Kit (Promega, USA). The genetic regions encompassing the polymorphisms of interest were amplified using polymerase chain reaction (PCR) with SNP-express kits (NPF LITEH, Russia). The PCR products were evaluated using gel electrophoresis with 3% agarose gel and TBE buffer (Sigma, USA) supplemented with ethidium bromide (Sigma, USA).

The results were statistically analysed using SPSS v.13.0 software (IBM Corporation, USA). The Mann–Whitney U test was used to evaluate independent variables, and the Kruskal–Wallis test used for multivariate analyses. The results are presented as the median and IQR. Pearson's chi-squared or two-sided Fisher's exact test was used to compare discrete values. Qualitative data are presented as the absolute value (n) and the relative frequency (%). $p < 0.05$ was considered statistically significant.

Results

In the overall study population of patients with CAD, 219 patients (92.4%) were diagnosed with angina pectoris. Among the 219 patients, 47 (21.5 %) had been diagnosed with functional class (FC) I angina, 98 (44.7 %) had been diagnosed with FC II angina and 74

Table 1

Risk factors for CAD progression in patients with or without type 2 diabetes mellitus

Indicator	Patient group		*p
	CAD(n = 159)	CAD + T2DM (n = 78)	
**Age, years	56 (52–61)	62 (54–68)	**0.001**
**Glucose level, mmol/L	5.6 (5.3–6.0)	6.4 (5.9–7.3)	**<0.001**
Angina pectoris, FC I/II/III, n (%)	29 (19.9) 64 (43.8) 53 (36.3)	18 (24.6) 34 (46.6) 21 (28.8)	0.492
Arterial hypertension, n (%)	135 (84.9)	74 (94.9)	**0.026**
LV hypertrophy, n (%)	33 (20.8)	27 (34.6)	**0.021**
Obesity, n (%)	48 (30.2)	43 (55.1)	**<0.001**

*p-value reflects the difference between CAD and CAD + T2DM groups.
**The values represent the median (IQR).]

Table 2

Frequency of the *ITGB3* and *NOS3* genotypes in CAD and CAD + T2D groups

Indicator		Patient group		*p
		CAD	CAD + T2DM	
NOS3 Gene	Genotype frequency, n (%) TT/TC/CC	58 (36.5) 72 (45.3) 29 (18.2)	30 (38.5) 43 (55.1) 5 (6.4)	0.039
	Allele frequency T/C, %	59.1/40.9	66.0/34.0	0.177
ITGB3 Gene	Genotype frequency, n (%) TT/TC/CC	98 (61.6) 55 (34.6) 6 (3.8)	57 (73.1) 21 (26.9) 0	0.080
	Allele frequency T/C, %	78.9/21.1	86.5/13.5	0.045

*p-value reflects the difference between CAD and CAD + T2DM groups.

(33.8%) had been diagnosed with FC III angina. Arterial hypertension (AH) was diagnosed in 209 (88.2%) patients and 60 patients (25.3%) had been diagnosed with left ventricular (LV) hypertrophy. In addition, 91 patients (38.4%) were obese (body weight index > 30 kg/m^2).

Patients in the CAD + T2DM group were older, on an average, than those in the CAD group (p = 0.001). In addition, the prevalence of AH, obesity and LV hypertrophy was significantly greater in the CAD + T2DM group than in the CAD group (p = 0.026, p < 0.001 and p = 0.021, respectively) (Table 1). In contrast, the proportion of patients with FC I, II and III angina did not significantly differ between the two groups.

We also evaluated the frequency of the *ITGB3* and *NOS3* polymorphism in the overall study population. With respect to *ITGB3*, 155 patients (65.4%) were carriers of the 1565TT genotype and 76 patients (32.1%) were carriers of the 1565TC genotype. Only six patients (2.5%) were carriers of the 1565CC genotype. The frequencies of the 1565T and 1565C alleles were 81.4% and 18.6%, respectively. With respect to *NOS3*, the 786TT and 786CC genotypes were detected in 88 (37.1%) and 34 patients (14.3%), respectively. The 786TC allele was detected in 115 patients (48.5%). The frequencies of the 786T and 786C alleles were 61.4% and 38.6%, respectively. The distribution of the T1565C polymorphism of *ITGB3* and the T-786C polymorphism of *NOS3* in the overall study population confirmed to the Hardy-Weinberg equilibrium principle (p = 0.351 and p = 0.716, respectively).

Table 2 presents the results of the comparative analysis of the *ITGB3* and *NOS3* genotypes between CAD and CAD + T2DM groups. The frequency of the *NOS3* 786CC genotype was nearly 3-fold lower in the CAD + T2DM group than in the CAD group (p = 0.039). The frequency of the *ITGB3* 1565C allele was also significantly reduced in the CAD + T2DM group compared with that in the CAD group (p = 0.045).

The results of the analysis of the *ITGB3* genotypes in the two groups are presented in Table 3. In the CAD group, the prevalence of FC I, II and III angina as well as that of AH, LV hypertrophy and obesity was similar between patients with the 1565TT genotype and those carrying the 1565C allele (TC and CC genotypes). In

Table 3

Association of the T1565C polymorphism of *ITGB3* with risk factors for CAD progression in CAD and CAD + T2DM groups

Indicator	Patient group				*p; **p$_1$
	CAD		CAD + T2DM		
	TT (n = 98)	TC + CC (n = 61)	TT (n = 57)	TC + CC (n = 21)	
†Age, years	56 (51–61)	58 (53–62)	62 (56–69)	61 (53–67)	0.319; 0.414
†Glucose level, mmol/L	5.6 (5.4–6.0)	5.6 (5.3–6.0)	6.4(6.0–8.0)	6.3 (6.0–7.1)	0.381; 0.481
Effort angina, FC I/II/III, n (%)	17 (18.5) 43 (46.7) 32 (34.8)	12 (22.2) 21 (38.9) 21 (38.9)	16 (30.2) 22 (41.5) 15 (28.3)	2 (10,0) 12 (60.0) 6 (30.0)	0.645; 0.173
Arterial hypertension, n (%)	83 (84.7)	52 (85.2)	54 (94.7)	20 (95.2)	0.925; 1.0
LV hypertrophy, n (%)	21 (21.4)	12 (19.7)	17 (29.8)	10 (47.6)	0.791; 0.143
Obesity, n (%)	26 (26.5)	22 (36.1)	27 (47.4)	16 (76.2)	0.203; 0.039

*p-value reflects the difference between TT and TC + CC genotypes in the CAD group.
**p-value reflects the difference between TT and TC + CC genotypes in the CAD + T2DM group.
†The values represent the median (IQR).

Table 4

Association of the T-786C polymorphism of *NOS3* with risk factors for CAD progression in CAD and CAD + T2DM groups

Indicator	Patient group						*p; **p_1
	CAD			CAD + T2DM			
	TT (n = 58)	TC (n = 72)	CC (n = 29)	TT (n = 30)	TC (n = 43)	CC (n = 5)	
†Age, years	58 (54–62)	55 (51–61)	56 (52–61)	62 (53–68)	62 (54–68)	62 (61–64)	0.096; 0.810
†Glucose level, mmol/L	5.7 (5.3–5.9)	5.6 (5.3–6.0)	5.5 (5.4–6.0)	6.0 (5.6–7.0)	6.4 (6.1–7.3)	8.0 (7.2–8.6)	0.928; 0.018
Effort angina, FC I/II/III, n (%)	14 (26.9) 16 (30.8) 22 (42.3)	12 (17.9) 36 (53.7) 19 (28.4)	3 (11.1) 12 (44.4) 12 (44.4)	8 (29.6) 11 (40.8) 8 (29.6)	10 (24.4) 20 (48.8) 11 (26.8)	0 3 (60.0) 2 (40.0)	0.085; 0.759
Arterial hypertension, n (%)	48 (82.8)	62 (86.1)	25 (86.2)	28 (93.3)	41 (95.3)	5 (100)	0.840; 1.0
LV hypertrophy, n (%)	9 (15.5)	18 (25.0)	6 (20.7)	8 (26.7)	19 (44.2)	0	0.416; 0.083
Obesity, n (%)	12 (20.7)	23 (31.9)	13 (44.8)	17 (56.7)	24 (55.8)	2 (40.0)	0.063; 0.872

*p-value reflects the difference between carriers of the TT and TC + CC genotypes in the CAD group.
**p-value reflects the difference between carriers of the TT and TC + CC genotypes in the CAD + T2DM group.
†The values represent the median (IQR).

contrast, in the CAD + T2DM group, a significantly greater percentage of patients with the 1565C allele were obese than patients with the 1565TT genotype (p = 0.039).

The results of the analysis of the *ITGB3* genotypes in the two groups are presented in Table 3. In the CAD group, the prevalence of FC I, II and III angina as well as that of AH, LV hypertrophy and obesity was similar between patients with the 1565TT genotype and those carrying the 1565C allele (TC and CC genotypes). In contrast, in the CAD + T2DM group, a significantly greater percentage of patients with the 1565C allele were obese than patients with the 1565TT genotype (p = 0.039).

The results of the analysis of the association between the *NOS3* genotypes and risk factors for CAD progression are presented in Table 4. In the CAD group, the frequency of FC I angina was greater in patients with the 786TT genotype than in carriers of the 786C allele, but the difference was not statistically significant (p = 0.085). In contrast, no significant differences were observed in the prevalence of AH and LV hypertrophy. However, in the CAD + T2DM group, the 786C allele was significantly associated with obesity (p = 0.015; odds ratio: 1.82, 95% CI: 1.12–2.95). In addition, significantly lower glucose levels were associated with the 786TT genotype than with the 786TC and 786CC genotypes, indicating that the 786C allele may be directly associated with the severity of T2DM.

Discussion

In the present study, we found that obesity, AH and LV hypertrophy were more prevalent in patients with both CAD and T2DM than in patients with CAD in the absence of diabetes. These results are consistent with previous reports that insulin resistance is associated with AH, microvascular complications, obesity and chronic sub-inflammation [12].

In addition, the severity of angina was not significantly different in patients with CAD alone and patients with both CAD and T2DM. These results may reflect the differences in the distinct stages of comorbid diseases. In patients with CAD and T2DM, the increase in myocardial resistance to ischemia may represent an adaptive or cardioprotective mechanism, a notion that is consistent with long-term clinical studies [13] and animal experiments [14].

The distinct clinical characteristics of CAD in patients with diabetes mellitus may also be influenced by genetic polymorphisms. Consistent with this hypothesis, we identified differences in the distribution of *NOS3* and *ITGB3* allelic variants between patients with CAD alone and patients with both CAD and T2DM. The 786CC genotype of the *NOS3* gene was more frequently observed in patients with CAD alone than in patients with both CAD and T2DM. One possible explanation for this discrepancy is that the 786CC genotype is associated with fatal complications in patients with both CAD and T2DM and that these complications resulted in death prior to the initiation of the study. This hypothesis is consistent with the observation that the 786C allele of *NOS3* was associated with higher glucose levels in patients with both CAD and T2DM.

A previous report by C. Vecoli et al. (2012) demonstrated that the *NOS3* 786CC genotype is associated with an unfavourable prognosis [15]. The authors demonstrated that patients with LV systolic dysfunction who had the 786CC genotype presented with higher blood glucose and insulin levels than those with the 786TT genotype, and the 786CC genotype was an independent predictor of insulin resistance. Insulin resistance promotes an increase in free fatty acid levels, thereby disrupting the function of eNOS and inhibiting NO production. In addition, hyperglycaemia is accompanied by an increase in oxidative stress, and oxidative stress promotes CAD progression by inhibiting

vasodilation, anti-inflammatory mechanisms and NO-associated antiplatelet effects [2, 16].

We also found that the 1565C allele of the *ITGB3* gene was more prevalent in patients with CAD alone than in those with both CAD and T2DM. However, the 1565C allele was not significantly associated with glucose levels in either group. These findings are in contrast with those of a previous study, which reported that the 1565C allele was associated with elevated HbA1c levels in patients with diabetes mellitus and a higher risk of death risk in patients with impaired glucose tolerance (HbA1c: 5.5%–6.5%) [17]. However, obesity was more prevalent in patients with both CAD and T2DM who carried the 1565C allele than in those with the 1565TT genotype. Obesity is also a significant risk factor for the progression of both CAD and T2DM. In addition, previous reports have indicated that the 1565C allele of the *ITGB3* gene is associated with a low threshold for platelet activation and a consequent increase in platelet aggregation, both of which increase the risk of cardiovascular events [6, 8].

Conclusion

In the present study, the rates of AH, LV hypertrophy and obesity increased in patients with both CAD and T2DM compared with that in those with CAD alone. However, the severity of angina did not differ between the groups. The 786CC genotype of the *NOS3* gene and the 1565C allele of the *ITGB3* gene were less frequently observed in patients with both CAD and T2DM compared with patients with CAD alone. In addition, the 1565C allele of *ITGB3* was associated with a higher prevalence of obesity in patients with both CAD and T2DM. In patients with both CAD and T2DM, the 786CC allele of *NOS3* was associated with elevated glucose levels, suggesting that the allele is associated with more aggressive T2DM disease pathology. Together, these findings indicate that the 1565C allele of the *ITGB3* gene and the 786CC allele of the *NOS3* gene are predictors for an unfavourable prognosis in patients with both CAD and T2DM.

Further study of the association between the clinical significance of these polymorphisms and the progression of CAD progressing in patients with T2DM will help further our understanding of the pathophysiological and genetic mechanisms underlying these diseases.

Additional information

Information on conflict of interests and sponsorship

The work has been performed according to the open plan of the Cardiology Research Institute. The authors declare no potential conflict of interests related to the publication of the present paper.

Participation of the authors

Muslimova E.F.: genetic analysis, statistical analysis, interpretation of results and preparation of the article text; Rebrova T.Yu.: interpretation of results and checking critically important intellectual content; Afanasyev S.A.: conception and design of the study, checking critically important intellectual content and final approval for publication of the copy; Sergienko T.N.: formation of the study groups; and Repin A.N.: conception and design of the study and final approval for publication of the copy.

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