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Association of BsmI and ApaI Polymorphisms of the Vitamin D Receptor Gene with Dyslipidemia in Patients with Coronary Artery Disease.

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Abstract

Purpose: The goals of the present study were to assess the genotypic and allelic distribution of Bsm-I (rs1544410) and Apa-I (rs7975232) polymorphisms of the vitamin D receptor (VDR) gene in coronary artery disease (CAD) patients in comparison to control patients of the same age without CAD and to determine whether these gene variants are associated with dyslipidemia.

Materials and Methods: Based on a case-control design, 302 hospitalized patients with CAD and 194 people of comparable age without CAD were enrolled in the study. The BsmI and ApaI polymorphisms of *VDR* gene were studied using polymerase chain reaction followed by restriction analysis. The allele digested by the restriction enzyme was denoted by a lower letter, whereas that not digested was indicated by a capital letter. Determination of the level of vitamin D and immunoreactive insulin in the blood serum was carried out using the immuno-enzyme method.

Results: The bb genotype of Bsm-I VDR gene polymorphism was detected more often in patients with CAD than in the comparison group with an increased risk of CAD by 1.52 times (p=0.006, OR=1.52(1.05÷2.2). The level of HDL cholesterol was higher in CAD patients – carriers of BB genotype compared to its level in Bb genotype carriers and bb genotype carriers (1,13±0,05 mmol/l, 1,01±0,03 mmol/l, 1,02±0,03 mmol/l respectively, p<0,05). The level of vitamin D was higher in patients with BB genotype compared to its level in bb genotype carriers (45.12±3.73 nmol / l and 34.16±1.95 nmol/l respectively, p=0.008). The occurrence of a allele of Apa-I VDR gene polymorphism was higher in patients with CAD than in the control group (p=0.02, OR=1.21(0.93÷1.57). HDL cholesterol level was higher in CAD patients - AA genotype carriers compared with carriers of Aa and aa genotypes (1.18±0.08 mmol / l, 1,02±0.02 mmol / l and 1.01±0.03 mmol/l respectively, p<0,05). Immunoreactive insulin level was significantly higher in CAD patients – aa genotype carriers. No differences in LDL cholesterol and triglycerides were found. Vitamin D level was lower in CAD patients - Aa and aa genotype carriers (33,8±33,9 nmol/l ,p=0,02 and 24,7±4,9 nmol/l, p=0,05 respectively in comparison to vitamin D level = 43,3 ±4,2 nmol/l in AA genotype carriers).

Conclusion: The bb genotype of Bsm-I VDR gene polymorphism is associated with an increased risk of CAD. A carriage of b allele in CAD patients is associated with lower level of vitamin D and HDL cholesterol. A carriage of a allele of Apa-I VDR gene polymorphism in CAD patients is associated with lower level of vitamin D and HDL cholesterol.

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Introduction

Coronary artery disease (CAD) is a polygenic, multifactorial pathology that occupies one of the leading places in the structure of morbidity and mortality of people of working age. More attention is paid to new genetic risk factors for CAD, since the use of exclusively traditional risk factors has limited opportunities to predict the development of the disease and its complications [1]. A complex risk assessment of CAD is required. E. Tikkanen and co-authors in 2013 developed a multi-locus genetic risk scale for cardiovascular disease and its complications. The authors found that additional genetic screening allows to reclassify the average risk of cardiovascular disease in 12 % of individuals per 10,000 people [2].

It has been established that vitamin D plays a key role not only in the prevention of osteoporosis, but also in the regulation of cell proliferation and differentiation and in the mechanisms of immune inflammation of the vascular wall. In recent years, vitamin D deficiency has been considered as one of the new risk factors for CAD [3, 4]. Studies on endothelial cell cultures have shown that vitamin D stimulates the production of nitric oxide by endothelial cells [5]. Apparently, vitamin D affects some mechanisms of atherosclerotic plaque stabilization. Angiogenesis contributes to the rupture of unstable atherosclerotic plaque. D. J. Manthell and co-authors found that vitamin D inhibits the production of vascular endothelial growth factor, endothelial growth, and angiogenesis [6].

M. Hewison in his review notes that vitamin D restores balance in the system of pro-and anti-inflammatory cytokines [7]. The activity of type 1 T-helpers that produce proinflammatory cytokines (interferon-gamma, TNF-alpha, IL-6, IL-12) decreases and the activity of type 2 T-helpers and the expression of anti-inflammatory cytokines (IL-5, IL-10, IL-13) increases.

The limitation of $1,25(OH)_2D$/VDR signalling can cause increased renin/angiotensin activity with hypertension and cardiac hypertrophy, reduction in the bioavailability of the vasodilator nitric oxide with consequent impaired blood vessel relaxation, endothelial cell dysfunction, upregulation of proinflammatory cytokines [3,4].

The mechanisms of vitamin D influence on lipid metabolism have not been sufficiently studied. Y.Huang and co-authors in 2014 found that vitamin D level in blood plasma had a positive correlation with the concentration of lipoproteinlipase [8]. In population study S. Vogt and co-authors had concluded, that independently of abdominal obesity, higher 25(OH)D levels were associated with a metabolite profile characterized by lower concentrations of atherogenic lipids and a higher degree of fatty acid polyunsaturation [9].

The gene encoding the VDR is located on chromosome 12cen-ql2, contains 14 exons, and spans approximately 75 kilobases of genomic DNA. BsmI (rs1544410) and ApaI (rs7975232) restriction site polymorphisms occur in the intron separating exons VIII and IX. B allele of BsmI polymorphism and A allele of ApaI polymorphism show higher levels of mRNA expression in peripheral mononuclear cells than b and a alleles [10].

Polymorphism of the vitamin D receptor gene (VDR) was identified and analyzed mainly in the peoples of the Caucasus and to a lesser extent in other ethnic groups [11].

The goals of the present study were to assess the genotypic and allelic distribution of Bsm-I (rs1544410) and Apa-I (rs7975232) polymorphisms of the VDR gene in coronary artery disease patients in comparison to control patients of the same age without CAD and to determine whether these gene variants are associated with dyslipidemia.

Materials and Methods

This study included 302 patients with CAD (250 men and 52 women) aged 33 to 80 years (61.3±0.56 years). We included in this study the patients admitted to the Coronary Care Unit of First Saint-Petersburg State Medical university n.a. I.P. Pavlov with diagnosis of coronary artery disease, who underwent diagnostic coronary angiography between October 2011 and April 2016. The exclusion criteria were uncontrolled arterial hypertension, oncological diseases, inflammatory diseases in the acute phase, infectious or viral diseases transferred in the last 2 months, viral hepatitis, systemic vasculitis, systemic connective tissue diseases, thyroid pathology, clinically significant liver and kidney pathology, severe chronic complications of diabetes mellitus (diabetic retinopathy, nephropathy, polyneuropathy), severe concomitant diseases in the phase decompensation, negatively affecting the forecast. The limitation of the study was summer period to exclude the factor of insolation and concomitant therapy of drugs influencing on vitamin D level. This study was approved by the Ethics Committee of the FIRST St. Petersburg state medical University named after academician I. P. Pavlov. The comparison group consisted of 194 patients (134 men and 60 women) of comparable age without clinical signs of CAD.

Traditional risk factors for coronary artery disease were evaluated in all the examined patients. Hypertension was observed in 294 (95%) patients with CAD. At the time of CAD development, 204 people (66%) smoked. CAD-burdened heredity was detected in 113 patients (38%), while 35 (12%) patients were burdened with both maternal and paternal heredity. Anthropometric evaluation included measurement of height, weight, waist and hip circumferences. Calculated body mass index (BMI) = weight / height^2 (kg / m^2) (A. Quetelet formula). Normal body weight consistent with BMI values from 18.5 to 24.9 kg / m2, overweight - BMI of 25 to 29.9 kg / m2, and obesity - a BMI over 30 kg / m2.100 patients (33%) had obesity with body mass index ≥ 30 kg/m^2.

Molecular Genetic Examination of Patients with CAD was Carried out in Several Stages

1. Isolation of deoxyribonucleic acid from venous blood leukocytes;
2. Identification of ApaI and BsmI VDR gene polymorphisms was performed by polymerase chain reaction followed by restriction analysis.

Genomic DNA was amplified by PCR using specific primers: for ApaI polymorphism (A>C, rs7975232) - primer-1: 5′-GTATCACCGGTCAGCAGTCATAGA-3′; primer-2, 5′-AGAGAAGAAGGCACAGGAGCTCT-3′; for BsmI polymorphism (A>G, rs1544410)- primer-F: 5′-GAGCCCAGTTCACGCAAGAG-3′; primer-R: 5′-GGGGGGATTCTGAGGAACTAGATA-3′.

PCR products were amplified in a programmable thermal cycler "MG Research" (MG Research Inc). Recognition site for Pct-I restrictase is GCATTC (BsmI polymorphism). ApaI restriction endonuclease recognition site is GGGCCC.

The amplification reaction mixture with a volume of 10 µl per sample includes: 2 µl of sample (Sample-GS), 240 mM dNTP (AmpliSens, Moscow), 14 pM of each primer (NPF Litekh, Moscow), 2.5 units Taq polymerases (SibEnzyme, Novosibirsk) in a standard buffer (blue 5x AmpliSens, Moscow).

Amplification program includes: DNA denaturation - 5 minutes at 95°C; 40 cycles: denaturation at 95°C during 20 sec., primer annealing - 30 sec., elongation at 72°C - 20 sec. The synthesis stage at 72 ° C during 10 min.

PCR products were digested with the restriction enzymes Apa I (SibEnzyme) according to the manufacturer's instructions (1 unit enzyme per 10 µl of amplification mixture for 16 hours at a temperature of 37 °C), and electrophoresed on 1.4% agarose gels. Restriction analysis was performed in vertical electrophoresis.

Levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) in serum were measured. To determine the parameters of

the blood lipid spectrum, venous blood was taken in the morning on an empty stomach (14 hours after the previous meal). Measurement of these indicators was performed on The unicel*C800(USA) using the standard enzymatic method, units of measurement mmol/l. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using Friedewald equation.

Determination of the level of vitamin D in the blood serum was carried out using the immuno-enzyme method using the Immuno Chem-2100 analyzer ((25 (OH)D ids) reagents). Statistical processing of the results was performed using the packages of specialized computer programs Statistica 10.0 (StatSoft Inc.) and SPSS 11.5 for Windows (SPSS Inc.).

Serum immunoreactive insulin level was revealed by ELISA. We used "DRG INSULIN ELISA KIT" (DRG Diagnostics, Germany). Incubation was performed in serum samples from micro well plate coated with specific antiserum to insulin. After fixation, the wells were detected by the AI binding a conjugate of anti-insulin and addition of the enzyme complex comprising horseradish peroxidase. Adding stop solution, which is a 0.5 M sulfuric acid increased the sensitivity. AI levels were determined by measuring the absorbance of the solution at 450 nm using a microplate reader.

The analysis of frequency differences in two or more independent groups was carried out using the method of conjugacy tables using the exact two-way Fisher test or the CHI-square test with Bonferroni correction. To determine the risks, the odds ratio (OR) was calculated. To compare independent variables t test was used. Nonparametric Spearman correlation was calculated.

One-factor variance analysis (ANOVA) and the Scheffe test for multiple comparisons were used to test the uniformity of quantitative characteristics in different groups.

Results

A comparative analysis of genotypes and alleles distribution of VDR gene BsmI polymorphism of the in CAD patients and in control group was performed (table 1).

The distribution in CAD patients: bb genotype - in 143 people out of 302 (47%), the sum of BB and Bb genotypes –in 159 people out of 302 (53%). In the control group without CAD, the distribution was as follows: bb genotype – in 72 people out of 194 (37%), the sum of BB and Bb genotypes – in 122 people out of 194 (63%). Thus, the bb genotype was detected more often in patients with CAD than in the comparison group with an increased risk of CAD by 1.52 times (p=0.006, OR=1.52 (1.05÷2.2), table 1). In the group of patients with CAD, the occurrence of B allele was 0.33, b allele - 0.67, while in the comparison group without CAD, the occurrence of B allele was 0.38, b allele-0.62, which was statistically significant without affecting the risks (p=0.014, OR=1.25(0.96÷1.63), table 1). The results indicate that the occurrence of the b allele was higher in the group of patients with CAD than in the control group without CAD.

Analysis of total cholesterol, TG, and LDL cholesterol and the immunoreactive insulin level in patients with CAD-carriers of the BB, Bb, and bb genotypes of the VDR gene did not reveal significant differences (p>0.05, table 2).

The level of HDL cholesterol in CAD patients with BB genotype was 1,13±0,05 mmol/l, with Bb genotype -1,01±0,03 mmol/l, with bb genotype -1,02±0,03 mmol/L. Thus, the HDL cholesterol level was higher in CAD patients – carriers of BB genotype compared to its level in Bb genotype carriers (p=0.022, table 2) and bb genotype carriers (p=0,05, table 2).

The vitamin D serum level in CAD patients - carriers of different genotypes of BsmI VDR gene polymorphism was determined. The vitamin D level in the group of CAD patients with BB genotype was 45.12±3.73 nmol / l, with Bb genotype-39.29±1.99 nmol/ l, with bb genotype -34.16±1.95 nmol l. Thus, the level of vitamin D was higher in patients with BB genotype compared to its level in bb genotype carriers (p=0.008, table 3). There were no significant differences in vitamin D levels in the control groups - BB, Bb, and bb genotypes carriers (p>0.05, table 3).

A comparative analysis of genotypes and allele distribution of ApoI VDR gene polymorphism in CAD patients and controls was performed (table 4).

There were no significant differences of above mentioned genotypes distribution in CAD patients and

Table 1. The distribution of BsmI VDR gene polymorphism genotypes in CAD patients and in control group

Group	BsmI VDR gene polymorphism genotypes					Allele frequency	
	BB	Bb	bb	BB+Bb	bb	B	b
CAD patients (n=302)	39 (13%)	120 (40%)	143 (47%)	159 (53%)	143 (47%)	0,33	0,67
Control group (n=194)	25 (13%)	97 (50%)	72 (37%)	122 (63%)	72 (37%)	0,38	0,62
p	0,06			0,006		0,014	
OR				1,52(1,05÷2,2)		1,25(0,96÷1,63)	

p – confidence level of probability when checking the homogeneity of genotype distribution and allele occurrence when comparing a group of patients with CAD and in a comparison group without CAD

Table 2. Blood serum lipids levels in patients with coronary artery disease-carriers of BB, Bb and bb genotypes of the vitamin D receptor gene BsmI polymorphism (M±m)

VDR gene genotype (BsmI polymorphism)	Blood serum lipids levels, mmol / l				
	TC	TG	LDL-C	HDL-C	Immunoreeactive Insulin mcU/ml
BB (n=35)	5,35±0,27	1,72±0,14	3,35±0,25	1,13±0,05	15,3±2,6
Bb (n=107)	4,86±0,12	1,88±0,11	3±0,13	1,01±0,03	19,5±3,4
bb (n=129)	4,95±0,11	1,81±0,09	3,06±0,11	1,02±0,03	20,6±2,6
P (BB vs Bb)	0,056	0,411	0,185	0,022	0,42
P (BB vs bb)	0,108	0,626	0,224	0,054	0,28
P(Bb vs bb)	0,615	0,578	0,712	0,59	0,78

p – confidence level of probability when checking the homogeneity of genotype distribution and allele occurrence when comparing a group of patients with CAD and in a comparison group without CAD

Table 3. The level of vitamin D in the blood serum of patients with coronary artery disease and in the control group without CAD-carriers of BB, Bb and bb genotypes of BsmI polymorphism VDR gene, (M±m)

Group	Vitamin D level, nmol/l			P		
	BB genotype	Bb genotype	Bb genotype	BB vs Bb	BB vs bb	Bb vs bb
CAD patients (n=117)	45,12±3,73	39,29±1,99	34,16±1,95	0,128	0,008	0,081
Control group (n=117)	21,97±5,53	30,52±4,67	37,07±5,11	0,297	0,059	0,35

Table 4. Distribution of AA, AA and AA genotypes and occurrence of A and a alleles of the vitamin D receptor ApaI gene polymorphism in patients with coronary artery disease and in the comparison group without CAD

Group	ApaI VDR gene polymorphism genotypes					Allele frequency	
	AA	Aa	aa	AA+Aa	aa	A	a
CAD patients (n=282)	39 (14%)	157 (56%)	86 (30%)	196 (70%)	86 (30%)	0,42	0,58
Control group (n=194)	27 (14%)	115 (59%)	52 (27%)	142 (73%)	52 (27%)	0,44	0,56
p	0,356			0,06		0,02	
OR						1,21(0,93÷1,57)	

p – confidence level of probability when checking the homogeneity of genotype distribution and allele occurrence when comparing a group of patients with CAD and in a comparison group without CAD

controls. (p>0.05, table 4). The frequency of A allele in CAD patients was 0.42, a allele - 0.58, in the control group - 0.44 and 0.56, respectively. The frequency of a allele was higher in patients with CAD than in the control group (p=0.02, OR=1.21(0.93÷1.57), table 4).

Analysis of vitamin D serum concentration revealed differences in patients – carriers of AA, Aa and aa genotypes of ApaI VDR gene polymorphism. The vitamin D level was higher in patients - AA genotype carriers – 43,3 ±4,2 nmol/l. In comparison, vitamin D level was lower in CAD patients - Aa and aa genotype carriers (33,8±33,9 nmol/l, p=0,02 and 24,7±4,9 nmol/l, p=0,05 respectively).

Analysis of total cholesterol, triglycerides, and low-density lipoprotein cholesterol did not reveal significant differences in CAD patients with AA, Aa, and aa genotypes of ApaI VDR gene polymorphism (p>0.05, table 5). Immunoreactive insulin level was significantly higher in CAD patients – aa genotype carriers – Table 5.

Statistically significant differences in the HDL cholesterol level in CAD patients - carriers of different genotypes of ApaI VDR gene polymorphism were revealed. The level of HDL cholesterol in CAD patients with AA genotype was 1.18±0.08 mmol / l, with Aa genotype -1,02±0.02 mmol / l, with aa genotype -1.01±0.03 mmol/l. Thus, the HDL cholesterol level was higher in CAD patients - AA genotype carriers compared with carriers of Aa and aa genotypes (p=0.012 and p=0.015, respectively, table 5).

Discussion

High-density lipoprotein (HDL) cholesterol is an independent predictor of coronary risk with protective effect. HDL is a main effector of reverse cholesterol transport from the peripheral tissues. Vitamin D deficiency has been associated with low levels of high-density lipoprotein (HDL) cholesterol [12]. Higher 25[OH]D levels are associated with large HDL particles. Theoretically, vitamin D may protect against cardiovascular risk by promoting formation of large HDL particles, activating reverse cholesterol transport.

High-density lipoproteins (HDL) are synthesized in the liver and initially do not contain cholesterol. Transporter A1 (ASCTA1), which, when combined with apoprotein A-I (APO A-I), leads to the formation of immature HDL. Then the free cholesterol of such HDL is esterified by the action of the enzyme lecithin-cholesterol acyltransferase (LHAT) and mature HDL is formed. HDL levels to some extent reflect the activity of reverse cholesterol transport from cells to the liver. HDL-cholesterol in CAD patients included in the study had negative correlation with body mass index – r=-271, p<0,05. There was no correlation between vitamin D level and body mass index.

Table 5. Blood serum lipids and immunoreactive insulin levels in patients with coronary artery disease-carriers of AA, Aa and aa genotypes of the vitamin D receptor gene ApaI polymorphism (M±m)

VDR gene genotype (ApaI polymorphism)	Indicators of the lipid spectrum of blood serum, mmol / l				
	TC	TG	LDL-C	HDL-C	Immunoreeactive Insulin mcU/ml
AA (n=26)	5,21±0,26	1,76±0,27	3,35±0,34	1,18±0,08	16,8±3,7
Aa (n=151)	4,88±0,11	1,79±0,08	3,01±0,11	1,02±0,02	16,9±1,4
aa (n=77)	4,99±0,15	1,9±0,12	2,98±0,13	1,01±0,03	25,1±3,2
P (Aa vs Aa) P (AA vs aa) P(Aa vs aa)	0,225 0,47 0,551	0,921 0,598 0,41	0,26 0,221 0,851	0,012 0,015 0,768	0,99 0,04 0,03

Activation of liver macrophage VDR by vitamin D ameliorates liver inflammation and improve the hepatocyte function . [13]. Initially, this process may be associated with better HDL synthesis. As a result, the synthesis of HDL by hepatocytes may be activated. The present research has revealed that the CAD patients – BB genotype carriers (BsmI VDR gene polymorphism) had higher level of vitamin D and higher HDL serum concentration. It is known that carriage of big B allele of Bsm-I VDR gene polymorphism is associated with better mRNA stability [10] and, apparently, with better vitamin D biotransformation and affinity to VDR. On the contrary, the CAD patients – bb genotype carriers had lower level of vitamin D and lower HDL serum concentration. It was revealed that the bb genotype of Bsm-I VDR gene polymorphism was associated with an increased risk of CAD.

In CAD patients carriage of a allele of Apa-I VDR gene polymorphism was associated with decreased serum level of vitamin D and HDL-cholesterol, the association with other lipid parameters was not found. CAD patients – aa genotype carriers had significantly higher levels of immunoreactive insulin. Vitamin D deficit is associated with insulinoresistance and reactive hyperinsulinemia. Limitation of vitamin D signaling worsen the activation of nuclear factor-κB, which plays a regulatory role for genes of cytokines of pro-inflammation implied in resistance to insulin[14].

The study of Alkhatatbeh M.G and co-authors (2019) has revealed positive association between serum 25-hydroxyvitamin D and HDL-C levels in subjects with non-cardiac chest pain [15]. In contrast, the authors did not found any significant association between vitamin D level and either TGs or LDL-C levels. The same results were achieved in the present study in CAD patients.

The clinical-genetic associations may be significant in personalized vitamin D deficit prevention in CAD patients. Correction of vitamin D deficit and insulin resistance may be useful in control of dyslipidemia with low HDL serum level in CAD patients.

Conclusion

The bb genotype of Bsm-I VDR gene polymorphism is associated with an increased risk of CAD. A carriage of b allele in CAD patients is associated with lower level of vitamin D and HDL cholesterol. A carriage of a allele of Apa-I VDR gene polymorphism in CAD patients is associated with lower level of vitamin D and HDL cholesterol.

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