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L162v Polymorphism of Peroxisome Proliferator-activated Receptor-alpha Gene and Markers of Immune Inflammation in Patients with Coronary Artery Disease

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Abstract

New risk factors for coronary artery disease (CAD) have been identified recently – mediators of immune inflammation. Peroxisome proliferator-activated receptors alpha (PPAR-α) belong to nuclear receptors superfamily and regulate the activity of different genes coding the factors of immune inflammation.

The goal of this study is to determine the association of L162V polymorphism of PPAR-α gene with factors of immune inflammation and the risk of coronary artery disease development in Russian population.

The current study included 414 patients with coronary artery disease (349 men and 65 women) aged 33 to 80 years (mean age- 61,6 ± 0,48 years). The control group consisted of 220 people without CAD of comparable age (mean age- 60,09 ± 0,72 years, p = 0.081). Polymerase chain reaction and restriction analysis were performed. IL-6, interferon-gamma (IF-γ) and tumor necrosis factor-alpha (TNF-α) levels of blood plasma were tested by Elisa. The frequency of L162V genotype of PPAR-α gene in coronary artery disease patients was higher than in control group (14,0% and 6,4% respectively, p=0.004). No significant differences in L162L and L162V genotype distribution in CAD patients with or without arterial hypertension, abdominal obesity, diabetes type2, smoking factor, family history were revealed. In CAD patients with the debut of the disease at the age of 45 and younger the frequency of L162V genotype was higher than in the subgroup of patients with the disease progress at age 46-59 years and (OR=4,68; CI:2,3÷9,52). The level of interleukin 6 was significantly higher in patients with CAD - L162V genotype carriers compared to L162L genotype carriers (37,5 ± 8,3 pg/ml and 9,2 ± 3,5 pg/ml respectively, p = 0.0006). The levels of TNF—α and IF-γ were significantly higher in patients with CAD - L162V genotype carriers compared with L162L genotype carriers.

The study has demonstrated that 162V PPARα allelic variant influence the predisposition for CAD in human subjects, probably mediated by modulation of the proinflammatory cytokines profile. L162V genotype and V162 allele of PPAR-α gene was associated with the risk of coronary artery disease debut at the age 45 years and younger.

Keywords: Abdominal obesity; Arterial hypertension; Diabetes type2

Introduction

Secondary prophylaxis of atherosclerosis in patients with coronary artery disease is one of the most urgent problems of cardiology. New risk factors for coronary artery disease (CAD) have been identified recently – mediators of immune inflammation [1,2].

Peroxisome proliferator-activated receptors alpha (PPAR-α) belong to nuclear receptors superfamily and regulate the activity of different genes coding the factors of immune inflammation [3,4]. These receptors are present in metabolically active tissues with high energy consumption: in liver, myocardium, skeletal muscles and kidneys. The ligands of PPAR- α are ω3-polyunsaturated fat acids and fibrates [5].

PPAR-α activation contributes to the inhibition of different mechanisms of immune inflammation: proinflammatory cytokine production (IL-6, IL-8, VCAM-1, IL-1β), mononuclear cells adhesion and migration into the subendothelium, reduction of proinflammatory activity in endothelium [6-8]. The study of these mechanisms in clinical conditions appears scientifically significant, which is essential for primary and secondary atherosclerosis prevention [9,10].

It has been established in several studies that interleukin-6 (IL-6) level of blood plasma is an independent risk factor for CAD [11].

L162V polymorphism of PPAR-α gene has been shown to be associated with coronary atherosclerosis [11]. Current experimental studies have revealed pathogenetic value of PPAR-α molecular-biologic effects in relation to heart remodeling and myocardial dysfunction development [12,13].

Therefore it is essential to investigate association between L162V polymorphism of peroxisome proliferator-activated receptor-α gene and immune inflammatory factors in patients with coronary artery disease which seems to be significant for the selection of different regimens of secondary CAD prevention.

The goal of this study is to determine the association of L162V polymorphism of PPAR-α gene with factors of immune inflammation and the risk of coronary artery disease development.

Materials and Methods

The current study included 414 patients with coronary artery disease (349 men and 65 women) aged 33 to 80 years (mean age- 61,6 ± 0,48 years). All the women at the time of inclusion in the study were postmenopausal for over 9 years. We enrolled 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 November 2009 and April 2014.

The control group consisted of 220 people without coronary artery disease of comparable age (mean age- 60,09 ± 0,72 years, p = 0.081).

Including criteria

men and women of age 30 - 80 years with clinically and angiographically verified diagnosis of coronary artery disease, which have signed the informed consent to participate in this study.

Exclusion criteria

- Chronic heart failure functional class IV,
- Uncontrolled arterial hypertension,
- Cancer and oncohematological diseases,
- Inflammatory diseases in the acute phase,
- Postponed infectious or viral diseases to the last 2 months,
- Viral hepatitis,
- Systemic vasculitis,
- Systemic connective tissue disease,
- Thyroid disease,
- Clinically significant pathology of the liver and kidneys,
- Severe chronic complications of diabetes (diabetic retinopathy, nephropathy, neuropathy),
- Severe concomitant diseases in the phase of the decompensation, adversely affecting prognosis.

Clinical characteristics of overall study population and according to the age of CAD incidence is presented in Table 1. Group of all CAD patients characterized by a mean age of 61,6 ± 0,48 years, the average age of developing coronary artery disease- 55,8 ± 0,45 years. The majority of CAD patients had a history of myocardial infarction- in 295 (70%) of all patients and in 47 (81%) patients with the debut of the disease at the age of 45 years or less (Table 1). The definition of myocardial infarction was performed according to the recommendations of Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. CAD debuted in the form of myocardial infarction in 165 (39%) of all patients, and the patients with the debut at the age of 45 years or less- in 31 (54%) people, aged from 46 to 59 years- 82 (40%) aged 60 years and older- 52 (34%) patients with coronary artery disease. Thus, coronary artery disease debut with myocardial infarction in patients with early onset of the disease, while CAD often debut with angina in patients 60 years of age and older.

Variables	Control group without CAD (n=220)	All CAD patients (n=424)	Debut of CAD at the age of 45 years and younger (n=56) (1)	Debut of CAD at the age of 46-59 years (n=205) (2)	Debut of CAD at the age of 60 years and older (n=153) (3)	P value
Age, mean ±SD, years	60,1 ± 0,72	61,5 ± 0,5	52,1 ± 0,8	58,5 ± 0,3	69,1 ± 0,4	0,08
Male, (%)	41	84	93	85	81	P1,2=0,079 P1,3=0,074 P2,3=0,06
Risc factors, %						
Smoker	58,6	64,6	67	69,1	57,4	P1,2=0,471 P1,3=0,083 P2,3=0,007
Non smoker	41,4	35,4	33	30,9	42,6	
Hypertension	31,8	95,4	87,9	96	97	P1,2,3>0,05
Hypercholesterolemia		63	80	58	62	P1,2=0,041 P1,3=0,06 P2,3=0,071
Diabetes mellitus	7,9	19,1	22,4	19,7	16,3	P1,2=0,375 P1,3=0,005 P2,3=0,0001
Obesity (BMI > 30)	16	33	47	36	24	P1,2=0,065 P1,3=0,011 P2,3=0,021
Previous history , n%						

CAD debut with MI		39	54	40	34	P1,2=0,018 P1,3=0,003 P2,3=0,042
CAD debut with angina pectoris		61	46	60	66	
AMI		70	81	70,6	63,6	P1,2=0,041 P1,3=0,002 P2,3=0,013
Previous PCI		40	35	45	35	P1,2=0,05 P1,3=0,129 P2,3=0,015
Previous CABG		28	30	23	39	P1,2=0,073 P1,3=0,079 P2,3=0,002
MI: Myocardial Infarction; PCI: Percutaneous Intervention; CABG: Coronary Artery Bypass Graft						

Table 1: Clinical characteristics of overall study population and according to the age of CAD incidence.

In all patients were analyzed traditional CAD risk factors. Hypertension was present in 397 (95%) of CAD patients. Obesity and overweight were observed in 68.1% of patients, with a mean BMI of them was 29,46 ± 0,22 kg/m^2. A history of smoking at the time of the development of coronary artery disease was observed in 275 people (64,6%). Family history of coronary artery disease was present in 170 patients (42%), and only 41 (10%) surveyed heredity had burdened both paternal and maternal. Type 2 diabetes was observed in 81 (19.1%) patients, while fasting hyperglycemia was detected in 109 (39.6%) examinees. All patients with type 2 diabetes were on a diet or sulfonylurea monotherapy or biguanides.

The group of patients with coronary artery disease debut at the age of 45 years or less have an average BMI 28,67 ± 0,64 kg/m^2, aged 46 - 59 years old - 28,14 ± 0,32 kg/m^2, aged 60 years and age - 27,5 ± 0,33 kg/m^2.

Anthropometric method's evaluation

Produced anthropometric survey of patients, which includes 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/m^2, overweight- BMI of 25 to 29.9 kg/m^2, and obesity- a BMI over 30 kg/m^2.

Type of obesity was assessed by measuring waist circumference through the middle of the distance between the lower edge of the costal arch and iliac crest in the horizontal plane of axillaris medium line. Diagnosis of abdominal type of obesity was carried out in accordance with the criteria of the International Diabetes Federation (International Diabetes Federation, 2006), when the subjects waist circumference equal to or more than 94 cm in men and 80 cm for women.

The definition of T2DM

Diabetes mellitus was diagnosed on the basis of anamnestic data and in accordance with the recommendations of the International Diabetes Federation (IDF 2012, 2013, 2014), the American Diabetes Association (ADA, 2012, 2015), the American Association of Clinical Endocrinologists (AACE, 2015) of the Russian Association of Endocrinologists (RAE 2015) with an increase in the level of glucose in the morning on an empty stomach, before and more than 7.0 mmol/L and glycosylated hemoglobin up to or more than 6.5%.

Molecular-genetic examination

Peripheral venous blood was obtained the next day after the patients were diagnosed with CAD following an overnight fast and centrifuged at 4°C and 3360 g for 15 min. All of the samples were then stored at −70°C until analysis.

Molecular-genetic examination of patients with CHD and a control group of comparable age without CHD was performed. Deoxyribonucleic acid (DNA) extraction from venous blood leukocytes was carried out on the column "K-SORB-100" ("Syntol", Russian Federation).

The identification of polymorphic variants of L162V polymorphism of PPAR-α gene based on the method of polymerase chain reaction (PCR) followed by restriction analysis, as described previously in the literature [14]. Amplification of the fragment of the gene was performed on an automated thermocycler Tertsik (DNA Technology, Moscow) using the following oligonucleotide sequences (Beagle, Russian Federation):

- Forward primer: 5'GACTCAAGCTGGTGTATGACAAGT-3;
- Reverse primer: 5'CGTTGTGTGACATCCCGACAGAAT-3.

The next step was carried out restriction analysis. The reaction mix for restriction analysis included 18 mkl of the PCR product, 1 ml of restriction enzyme Hinf I (SibEnzyme, US LLC), buffer O. Incubation of mix produces at 37°C for 12 hours.

Restriction analysis was performed using a vertical electrophoresis in 8% polyacrylamide gel followed by staining with ethidium bromide and visualization in the ultraviolet. If L162V genotype of the PCR product was cleaved to fragments of 117 bp and 24 bp. In the case of L162L genotype remained undigested PCR product of 117 bp in length.

IL-6, interferon-gamma (IF-γ) and tumor necrosis factor-alpha (TNF-α) levels of blood plasma were tested by Elisa method with the help of a set of reagents from Bender Medsystems.

Statistical analysis was performed using the statistical software package Statistica 10 (Stat Soft Inc., version 10.0.228.8, Oklahoma, USA). Analysis of the conformity of the type distribution characteristic normal distribution was carried out using the Shapiro-Wilk test. To evaluate the quantitative parameters of the normal distribution calculated following parameters: arithmetic mean (M), an error of the arithmetic mean (m), standard deviation (SD). In the absence of signs of a normal distribution statistical analysis was performed using non-parametric mathematical criteria. Analysis of qualitative binary signs held by means of Fisher's exact test. An analysis of the relationship of the two signs was performed using Spearman correlation analysis. Significant differences were considered when the probability of the null hypothesis (P) does not exceed a value of 0.05. The sample size calculation was based on formula: $n = f(\alpha/2, \beta) \times [p1 \times (100 - p1) + p2 \times (100 - p2)] / (p2 - p1)^2$

Results

L162V polymorphism of PPAR-alpha gene was identified in 414 coronary artery disease patients and in 220 healthy people of the same age. The frequency of L162V genotype of PPAR-α gene in coronary artery disease patients was higher than in control group (14,0% and 6,4% respectively, p=0.004) (Table 2). The frequency of V162 allele in patients with coronary artery disease was higher than in the control group (0.068 and 0.037 respectively, p=0.005). V162V genotype of PPAR-α gene in CAD patients and in healthy people was not revealed.

Groups	PPAR-α genotype		Allele frequency	
	L162L	L162V	L162	V162
CAD patients (n=414)	358 (86,0%)	56 (14,0%)	0,932	0,068
Control group without CAD (n=220)	206 (93,6%)	14 (6,4%)	0,963	0,037
p	0,004		<0,005	
OR	OR=2,13; CI:1,16÷3,9		OR=2,21; CI:1,21÷4,01	
Note- P-confidence probability when checking the homogeneity of the distribution of genotypes and alleles when compared of group of CAD patients and control group without CAD				

Table 2: L162L, L162V genotype distribution, and frequency of L162 alleles and V162 alleles of PPAR-α gene in patients with coronary artery disease and in control group of individuals without coronary artery disease.

Groups	PPAR-α genotype		Allele frequency	
	L162L	L162V	L162	V162
1. Debut of CAD at the age of 45 years and younger (n=56)	36 (64,2%)	20 (35,8%)	0,82	0,18
2. Debut of CAD at the age of 46-59 years (n=205)	183 (89,3%)	22 (10,7%)	0,95	0,05
3. Debut of CAD at the age of 60 years and older (n=153)	140 (90,9%)	14 (9,1%)	0,954	0,046
p(1,2) p(2,3)	0,00002 0,133		0,00005 0,13	
OR(1,2)	4,68; CI:2,3÷9,52, P < 0,0001		3,88; CI:2,02÷7,46, P < 0,0001	
Note- P-confidence probability when checking the homogeneity of the distribution of genotypes and alleles when compared of group of CAD patients and control group without CAD				

Table 3: L162L, L162V genotype distribution, and frequency of L162 alleles and V162 alleles of PPAR-α gene in patients with coronary artery disease according to the age of CAD incidence.

No significant differences in L162L and L162V genotype distribution in CAD patients with or without arterial hypertension, abdominal obesity, diabetes type2, smoking factor, family history were revealed. No significant differences in total cholesterol value in CAD patients – L162L and L162V genotype carriers of PPAR-alpha gene - was revealed (4,94 ± 0,07 mmol/l and 4,95 ± 0,2 mmol/l respectively). Previous percutaneus intervention (PCI) with angioplastic was performed in 168 patients (Table 1).

In CAD patients with the debut of the disease at the age of 45 and younger the frequency of L162V genotype was higher than in the subgroup of patients with the disease progress at age 46-59 years and

(Table 3), (OR=4,68; CI:2,3÷9,52, p< < 0,0001). The same tendencies were revealed in of V162 allele frequency: OR= 3,88; CI:2,02÷7,46, p<0,0001 (Table 3). Thus the presence of L162V genotype and V162 allele of PPAR-α gene was associated with the risk of coronary artery disease debut at the age 45 years and younger.

The level of interleukin 6 was significantly higher in patients with CAD - L162V genotype carriers compared to L162L genotype carriers (37,5 ± 8,3 pg / ml and 9,2 ± 3,5 pg / ml respectively, p = 0.0006). On Spearman correlation analysis, IL-6 negatively correlated with year of CAD incidence (r=-0,21, p<0.05), and positively with IF-γ (r=0.32, p<0.05) and TNF-α (r=0.25, p,0.05) plasma level. In the control group the IL-6 Level was the same in patients with different genotypes (p = 0.78, Table 4). The levels of TNF-α and IF-γ were significantly higher in patients with CAD - L162V genotype carriers compared with L162L genotype carriers (Table 4), but had no differences in patients without CAD– carriers of L162L and L162V genotypes of PPAR-alpha gene.

Variable		L162L genotype M ± σ	L162Vgenotype M ± σ	p
IL-6, pcg/ml	CAD patients	9,2 ± 3,5	37,5 ± 8,3	0,0006
	Control group	4,13 ± 1,92	3,14 ± 0,88	0,78
TNF-α, pcg/ml	CAD patients	7,4 ± 3,59	16,2 ± 9,66	0,0002
	Control group	1,57 ± 2,7	2,32 ± 2,17	0,64
IF-γ, pcg/ml	CAD patients	95,2 ± 30,9	174,8 ± 75,0	0,007
	Control group	9,82 ± 4,31	12,31 ± 2,1	0,56

Table 4: The content of serum IL-6, TNF-alpha, IFN-gamma, in patients with coronary artery disease and in patients from the control group without coronary artery disease - carriers L162L, L162V genotypes of PPAR-α gene.

Discussion

It is known that, in the Framingham study, the incidence of L162V genotype of PPAR-α gene in the general population was 6,9% [14,15]. Thus, the frequency L162V of genotype PPAR-α gene in CAD patients was twice as high (14%) than in the population of the Framingham study and in control group without CAD. Analysis of the traditional risk factors of coronary artery disease: hypertension, smoking, total cholesterol level and family history did not reveal statistically significant differences in the carriers L162L L162V genotypes of PPAR-α gene. In addition, no statistically significant differences in the occurrence of obesity and overweight in CAD patients carriers of different genotypes of studied polymorphism. This is consistent with studies Flavell et al. as well as Goini-Berthold et al. [16], who found no association between carriage L162V genotype and body mass index.

Carriage L162V genotype and 162V allele of PPARα gene was associated with an increased risk of CAD. These findings echo the results obtained by Skoczynska et al., which showed that the 162V allele was detected in patients with angiographically verified coronary atherosclerosis in four times more likely.

The results are consistent with two major clinical trials - Helsinki Heart Study and the Veterans Affairs High-Density Lipoprotein Intervention Trial-that proved the association of PPAR-α with the development of CAD. These studies have demonstrated the clinical significance of modulating the activity of PPAR-α using fenofibrate. Treatment with this drug reduced the risk of acute coronary syndrome by 34%.

L162V genotype gene PPAR-α was detected significantly more often in patients with CAD debut at age 45 years and younger. Similar results were obtained in a prospective study Northwick Park Heart Survey, in which the association was established between L162V genotype of PPAR-α and the early development of CAD in patients of the North-West region of Europe.

In the experimental trial by Rudkowska in 2009 it was reported that L162V genotype of PPAR-α gene was associated with low transcriptional activity [17]. This in turn leads to a reduction in receptor affinity to ligands and corresponding reduction of PPAR-α effect on immune inflammation factors.

PPAR-α are expressed in smooth muscle cells of the aorta and coronary arteries. PPAR-α regulate immune inflammation via the signaling pathway of the nuclear factor kappa beta (NF-kB). Apparently, the decrease in activity of PPAR-alpha in CAD patients-L162V genotype carriers is associated with increased production proinflammatorty cytokines- IL-6, TNF- α, IF-gamma, which was detected in this study. The patients with early debut of CAD had more active systemic inflammation, as measured by IL-6, TNF-α and IF-γ. The multifactorial regression analysis revealed the negative correlation between year of myocardial infarction incidence and L162V genotype carriage, body mass index and triglyceride level (r=-0.293, p=0.0004). It is known, that IL-6 may be the new target of CAD prevention, as well as modulation of PPAR-alpha activity. The data suggest, that in Russian population L162V polymorphism is associated with early debut of CAD and more active systemic inflammation.

Conclusion

L162V genotype and V162 allele of PPAR-α gene was associated with the risk of coronary artery disease debut at the age 45 years and younger.

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