Genetic Polymorphisms of Paraoxonase 1 and Susceptibility to Atherogenesis

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SUMMARY
Introduction Paraoxonase 1 (PON1) is a multifunctional enzyme associated with high-density lipoprotein particles (HDL). It is a cellular antioxidant that hydrolyses oxidized macromolecules, especially low-density lipoproteins (ox-LDL). Because increased oxidative stress is believed to play a crucial role in the initiation and propagation of atherosclerosis, coding (Q192R and L55M) and promoter (C(-107)T) region polymorphisms of *pon1* gene, that are responsible for catalytic efficiency, activity and the level of the enzyme, have been of great interest as a potential markers of susceptibility for atherogenesis.
Objective The aim of the study was to assess possible association between these *pon1* gene variants and clinical manifestations of the atherosclerosis and oxidative stress.
Methods A total of 60 angiographically documented patients with manifested atherosclerotic disease and 100 control individuals were analyzed. Genomic DNA was isolated from the peripheral blood cells and genotyping was performed using polymerase chain reaction followed by the restriction fragment length polymorphism (PCR-RFLP) analysis.
Results No significant difference in allele and genotype frequencies of all three examined polymorphisms was found between the atherosclerotic patients and healthy controls. The obtained results could not support an association of *pon1* gene variants with the oxidative stress and atherogenesis.
Conclusion These polymorphisms cannot be considered risk factors of atherosclerosis in Serbian population. A larger study is required in order to establish possible contribution of *pon1* variants to atherosclerosis-related cardiovascular diseases.
Keywords: paraoxonase 1; gene polymorphisms; oxidative stress; atherogenesis

INTRODUCTION

According to World Health Organization (WHO) [1] data for 2010, 95% of mortality in Serbia is caused by chronic non-contagious diseases, wherefrom 58% is caused by cardiovascular diseases (CVD). Although patients with CVD commonly have at least one identifiable risk factor, many ischemic events occur in the absence of any of them [2]. Atherogenesis, one of the main risk factors of CVD, is initiated by oxidation of the low-density lipoprotein (LDL) and by impairment of the oxidative stress-antioxidant balance. For this reason, there has been a profound interest in discovering the additional markers of oxidative stress, including gene variants, which may have a role in predicting the risk of disease.

Paraoxonase 1 (PON1) is a calcium dependent high density lipoprotein (HDL)-associated esterase (with paraoxonase, arylesterase and lactonase activities). The enzyme was named “paraoxonase” according to its ability to hydrolyse paraoxon, the toxic metabolite of the organophosphate insecticide parathion and later it was shown that it exhibited a broad spectrum of activities and had diverse substrates. When Mackness and colleagues connected PON1 with cardiovascular diseases in 1991 and demonstrated that PON1 could prevent the accumulation of oxidized lipids in low-density lipoprotein (LDL) [3], this cellular antioxidant became one of the most studied molecules in cardiovascular medicine. Despite intensive research, the exact physiological role of PON1 and mechanism of action have been still unexplained.

PON1 is the product of *pon1* gene, a member of paraoxonase gene family (along with *pon2* and *pon3*) located on the long arm of the chromosome 7 in humans (7q21.3-22.1) [4]. PON1 mRNA expression is limited to the liver but it associates with HDL in the circulation. In the coding region, two of the most studied polymorphisms are: glutamine to arginine substitution at codon 192 (Q192R) and leucine to methionine substitution at position 55 (L55M) [5, 6]. At least five polymorphisms have been detected in the *pon1* gene promoter region [C(-107/-108)T, G(-126)C, G(-162)A, G(-832)A and G(-909)C], but only C(-107T) seems to be significant for enzyme function [7, 8].

Polymorphisms R192Q and M55L in the coding and C (-107)T in the promoter region

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have the greatest impact on PON1 activity and concentration. R192Q polymorphism has been, so far, the most investigated. It determines isoforms of the enzyme which differ highly in the rate of hydrolysis of certain substrates [9], and it has been shown that position 192 is involved in HDL binding, stability, lipolactonase activity, and macrophage cholesterol efflux [10]. L55 isoform is more stable and more resistant to proteolysis than the M55 form, consequently it is related to blood enzyme levels. The C(-107)T polymorphism has the strongest effect on PON1 expression with C allele being associated with two-fold higher level of enzyme as compared with T allele [7, 8].

OBJECTIVE

All three polymorphisms have been associated with a number of pathological conditions and the present study investigated the role of these *pon1* gene variants against the risk of clinical manifestations of atherosclerosis.

METHODS

A total of 60 patients with angiographically documented atherosclerosis (37 males and 23 females, age 30-80 years) treated at Dedinje Cardiovascular Institute and Zvezdara University Medical Center, Belgrade, Serbia from 2010-2011 were included in the study. The control group was composed of 100 healthy individuals, age and sex matched with cases. Participants were not related and originated from different parts of Serbia. The study was approved by the Ethics Board of Zvezdara University Medical Center.

Genomic DNA was extracted from peripheral blood cells by DNeasy Blood & Tissue Kit (Qiagen), and isolated DNA was stored at +4°C until further analysis.

Pon1 L55M, Q192R and C(-107)T genotyping was performed using the polymerase chain reaction-restriction fragment length polymorphism analysis (PCR-RFLP) as previously described [6, 11]. PCR mixture (total volume 20 μl) contained 2X PCR Master Mix (2X-concentrated solution containing *Taq* DNA polymerase, reaction buffer, $MgCl_2$, and dNTP, Fermentas Life Sciences), 0.5 μM of each primer (Metabion) and 0.2 μg of genomic DNA. The PCR reactions were carried out for each polymorphism separately. Digestion products were separated on 3 % agarose gel, stained with ethidium bromide (0.5 μg/ml) and visualised under UV light for genotype determination.

Statistical analysis was carried out using SPSS software (version 17). Allele and genotype frequencies in cases and controls were compared using the chi-square test and the risk was assessed by means of the logistic regression analysis. A p value <0.05 was considered significant.

RESULTS

Two polymorphisms in the coding (Q192R and L55M) and one in the promoter region (C-107T) of *pon1* gene were analyzed. The allele and genotype frequency distribution for the three analyzed polymorphisms in both patients and controls was given in Table 1.

There was no significant difference in allele and genotype frequencies for Q192R between the cases and controls. Frequencies of Q and R alleles and QQ, QR and RR genotypes were equal or almost equal in the two groups (Table 1).

The results of logistic regression analysis suggested that neither alleles nor genotypes of this polymorphism carried any risk of disease (Table 2).

No significant difference in the L55M polymorphism was found after comparing allele and genotype frequencies between the groups (p>0.05) (Table 1). Likewise, no association with disease risk could be observed for any of the alleles or genotypes.

Though C allele was more frequent in the patient group (57%) compared to the controls (43%) for the C(-107)T SNP, the difference, however, failed to reach statistical significance (Table 1). Similarly, none of the values obtained by the logistic regression analysis showed statistical significance indicating that this polymorphism could not be considered susceptibility factor (Table 2).

DISCUSSION

This is the first study dealing with the association between three polymorphisms in the *pon1* gene, namely Q192R, L55M and C(-107)T, and the development of atherosclerosis in Serbia.

It has been shown that paraoxonase 1 (PON1) has its role in atherogenesis: it protects LDL, HDL and macrophages against oxidative stress, as indicated by decreased macrophage intake of the oxidized LDL particles, inhibition of cholesterol synthesis and stimulation of HDL mediated cholesterol efflux within macrophages. These functions are related to lactonase activity of this enzyme [12, 13]. PON1 hydrolyses lipid peroxides and prevents their accumulation in LDL and HDL particles *in vitro* and *in vivo* [14]. Moreover, PON1 preserves the integrity of HDL and is responsible for its anti-oxidative and anti-inflammatory effects. Individuals with higher HDL and lower PON1 serum concentrations are more prone to atherosclerosis and coronary heart disease (CHD) than individuals with lower HDL and higher PON1 [15].

In our study, there are no statistically significant differences in the distribution of alleles and genotypes for the Q192R polymorphism between the cases and the controls, which is compatible with the results of some other studies [16, 17]. This means that none of the alleles or genotypes represent a risk factor of development of atherosclerosis in Serbian population. Apart from the fact that it is located within the active site of the enzyme and affects the substrate specificity of the enzyme [5, 6, 9], the position 192 in the protein is also included in the binding to HDL particles [10]. Even though the R isoform of the enzyme has been associated with the increased risk of the oxidative stress and the incidence of the clinical manifestations of

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Table 1. The allele and genotype frequencies of *pon1* gene polymorphisms Q192R, L55M and C(-107)T in patient and control groups

pon1		Polymorphism	Patients (n=60)	Controls (n=100)	χ^2	p
Q192R	Allele frequency (%)	Q (Gln)[a]	88 (73.0)	145 (72.5)		
		R (Arg)	32 (27.0)	55 (27.5)	0.03	0.86
	Genotype frequency (%)	QQ[a]	33 (55.0)	53 (53.0)		
		QR	22 (36.7)	39 (39.0)	0.08	0.78
		RR	5 (8.3)	8 (8.0)	0.00	1.00
L55M	Allele frequency (%)	L (Leu)[a]	76 (63.0)	136 (68.0)		
		M (Met)	44 (37.0)	64 (32.0)	0.73	0.39
	Genotype frequency (%)	LL[a]	20 (33.3)	45 (45.0)		
		LM	36 (60.0)	46 (46.0)	2.65	0.10
		MM	4 (6.7)	9 (9.0)	0.00	1.00
C(-107)T	Allele frequency (%)	C[a]	68 (57.0)	94 (47.0)		
		T	52 (43)	106 (53.0)	2.80	0.09
	Genotype frequency (%)	CC[a]	20 (33.3)	21 (21.0)		
		CT	28 (47.7)	52 (52.0)	2.15	0.14
		TT	12 (20.0)	27 (27.0)	2.70	0.10

[a] – reference allele and genotype; χ^2 – Chi-square test; p – probability

Table 2. The logistic regression analysis of *pon1* gene polymorphisms Q192R, L55M i C(-107)T distribution in patient and control groups

pon1		Polymorphism	Patients (n=60)	Controls (n=100)	OR	95%CI	p
Q192R	Allele frequency (%)	Q (Gln)	88 (73.0)	145 (72.5)	1.00	reference	
		R (Arg)	32 (27.0)	55 (27.5)	0.96	0.57–1.6	0.86
	Genotype frequency (%)	QQ	33 (55.0)	53 (53.0)	1.00	reference	
		QR	22 (36.7)	39 (39.0)	0.91	0.46–1.79	0.78
		RR	5 (8.3)	8 (8.0)	1.00	0.3–3.33	0.99
		QQ+QR vs RR	55/5	92/8	1.04	0.3–3.4	0.94
L55M	Allele frequency (%)	L (Leu)	76 (63.0)	136 (68.0)	1.00	reference	
		M (Met)	44 (37.0)	64 (32.0)	1.23	0.76–1.98	0.39
	Genotype frequency (%)	LL	20 (33.3)	45 (45.0)	1.00	reference	
		LM	36 (60.0)	46 (46.0)	1.76	0.89–3.49	0.10
		MM	4 (6.7)	9 (9.0)	1.00	0.27–3.63	1.00
		LL+LM vs MM	56/4	91/9	0.72	0.21–2.45	0.60
C(-107)T	Allele frequency (%)	C	68 (57.0)	94 (47.0)	1.00	reference	
		T	52 (43.0)	106 (53.0)	0.67	0.43–1.07	0.09
	Genotype frequency (%)	CC	20 (33.3)	21 (21.0)	1.00	reference	
		CT	28 (47.7)	52 (52.0)	0.56	0.26–1.21	0.14
		TT	12 (20.0)	27 (27.0)	0.46	0.18–1.10	0.10
		CC+CT vs TT	48/12	73/27	0.68	0.31–1.46	0.31

OR – odds ratio; 95%CI – 95% confidence interval

atherosclerosis, especially CHD, it appears that Q isozyme represents a less stable form with lower lipolactonase activity and, therefore, with lower antiatherogenic capacity [9, 10].

L55M polymorphism, which is located in the N-terminal part of PON1, plays a role in binding of the enzyme to HDL, and thus may alter the ability of PON1 to form a complex with HDL [10, 18]. The allele L and genotype LL are associated with higher level of enzyme and with higher antioxidative protection as well [10, 11]. In addition, the polymorphism L55M affects the level of PON1, since the M isoform (MM genotype) is more susceptible to proteolysis than other isoforms [18]. In our study, the frequency of L allele was higher within the control group compared to the subjects, as expected, while the frequency of M alleles was higher in the patients group although without statistical significance. Djurić et al. [19] analyzed the frequency of L55M polymorphism in Parkinson's disease patients from Serbia, another disease related to oxidative stress, and their results support the assumption that MM genotype is a risk factor of disease progression. It is evident that the allele M is more frequent among patients compared to the controls in both studies from our region, though the results of our study are not statistically significant. The study of Taşkiran and coworkers showed association between the L55M polymorphisms and coronary artery disease (CAD) but not between Q192R polymorphism, in Turkish population [20].

The third polymorphism analyzed in the present study is the SNP C(-107)T in the promoter region of *pon1* which also strongly affects gene expression as well as PON1 serum levels. Recorded frequency of the C allele is higher within the case group compared to the controls, while the allele T is less frequent in comparison with the controls.

High frequency of T allele (53%) in the control group coincides with the frequency of this allele in Spanish population [21], which has the highest T allele frequency (54%) among European nations so far examined [21-24]. No association between "low expressor" genotype TT and atherosclerosis has been found in the present study. James and collaborators have analyzed C(-107)T in patients who suffer from type 2 diabetes with or without ischemic heart disease and patients who suffer from coronary artery disease, and determined that TT represents a risk factor of these diseases [18, 25].

A meta-analysis dealing with L55M, Q192R and C-107T polymorphisms in relation to CHD demonstrated only a weak positive overall association between Q192R polymorphism and CHD, while the remaining L55M and C(-107)T polymorphisms had no relevance [27]. Considerable variations from one population to another in allele and genotype frequencies have been found, especially in the promoter region C(-107)T and the coding region Q192R. Accordingly, the results of studies dealing with the association of *pon1* polymorphisms and cardiovascular disease risk in various populations proved to be heterogeneous and showed that each polymorphism separately affected only weakly complex disease such as atherosclerosis.

CONCLUSION

Our study evaluated PON1 polymorphisms distribution within Serbian population of the atherosclerotic patients and healthy controls. No significant differences in the examined *pon1* gene variants were found between the controls and patients, indicating that these polymorphisms are not risk factors of atherosclerosis in Serbian population. A larger cohort is required in order to establish accurately the possible contribution of the examined polymorphisms to atherosclerosis-related cardiovascular diseases.

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Генетички полиморфизми параоксоназе 1 и подложност атерогенези

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КРАТАК САДРЖАЈ

Увод Параоксоназа 1 (*PON1*) је мултифункционални ензим који је везан за липопротеине високе густине (*HDL*). То је ћелијски антиоксиданс који хидролизује оксидоване макромолекуле, нарочито оксидоване липопротеине ниске густине (*ox-LDL*). Сматра се да повишени оксидативни стрес игра кључну улогу у иницијацији и пропагацији атеросклерозе, па су полиморфизми у кодирајућем (*Q192R* и *L55M*) и промоторском (*C(-107)T*) региону гена *pon1*, који су одговорни за каталитичку ефикасност, активност и ниво ензима, од великог интереса као потенцијални маркери осетљивости на атерогенезу.

Циљ рада Циљ ове студије је био да се испита могућа повезаност варијанти гена *pon1* и клиничких манифестација атеросклерозе и оксидативног стреса.

Методе рада Анализирано је 60 болесника с ангиографски документованим манифестацијама атеросклерозе и 100 здравих испитаника. Геномска ДНК је изолована из ћелија периферне крви, а генотипизација је урађена применом реакције ланчане полимеразе, после које је урађена анализа дужине рестрикционих фрагмената (тзв. *PCR-RFLP* анализа).

Резултати Учесталости алела и генотипова три испитивана полиморфизма нису показале значајне разлике између испитаника оболелих од атеросклерозе и здравих особа. Добијени резултати не указују на повезаност анализираних варијанти гена *pon1* и оксидативног стреса и атерогенезе.

Закључак Ови полиморфизми се не могу сматрати факторима ризика за развој атеросклерозе у српској популацији. Потребна је студија са већим бројем испитаника, како би се утврдио могући допринос варијанти гена *pon1* на настанак кардиоваскуларних обољења у чијој основи је атеросклероза.

Кључне речи: параоксоназа 1; генетички полиморфизми; оксидативни стрес; атерогенеза

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