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ORIGINAL ARTICLE

PON1 (PARAOXONASE 1) Q192R GENE POLYMORPHISM IN NORTH MACEDONIAN POPULATIONWITH CONFIRMED CORONARY ARTERY DISEASE

Krsteva Jakimovska K[1,*], Vavlukis M[1,2], Eftimov A[3], Topuzovska S[4]

[*]**Corresponding Author:** Katerina Krsteva Jakimovska, Faculty of Medicine, 50 Division Street, No 6, 1000 Skopje, North Macedonia, +38970350439, E mail_katekr@yahoo.com

ABSTRACT

Aim: This study aims to examine the association between the prevalence of Q192R polymorphism of PON1 gene and the occurrence of atherosclerosis and coronary artery disease in patients in Republic of North Macedonia.

Method: This cross-sectional study includes subjects undergoing percutaneous coronary angiography with or without stenting due to monitoring of stable angina or induced ischemia, divided into two groups. Q192R polymorphism and its genotypic variants were analysed. The Polymerase Chain Reaction technique was used as a method for determining the single nucleotide polymorphism.

Results: A total of 165 subjects (106 belonging to the coronary artery disease (CAD) group and 59 to non-CAD group were evaluated in terms of their biochemical parameters and genetic variants. Results of the PON1 SNP Q192R groups (QQ, QR and RR) association related to CAD and non-CAD groups, resulted in a non-significant association (p=0.0632, OR=0.511, CI: 0.25-0.595, χ^2=3.4508, df=1). In further analyses, to obtain a more precise association, we analysed the association between SNP Q192R groups and stenting patients (control vs. stenting group). Further analysis confirmed the association of QQ vs. QR and control vs. stenting (p=0.0418, OR=0.461, CI: 0.216-0.589, χ^2=4.1432, df=1).

Conclusion: Results support the concept that genetic variants may contribute to an increased risk of CAD, emphasizing the importance of combined biochemical and genetic testing for better stratification of cardiovascular risk and early confirmation of the predisposition to develop serious cardiovascular disease. Further studies with a larger sample size are needed before Q192R gene polymorphism can be considered as a genetic risk factor for CAD.

Keywords: coronary artery disease; HDL cholesterol; lipoproteins; single nucleotide polymorphism

INTRODUCTION

Paraoxonases are a group of different enzyme forms that are consisted of three non-similar isoforms, PON1, PON2 and PON3. The genes for these three enzyme isoforms are located next to each other on the long arm of chromosome 7.

The enzyme paraoxonase-1 (PON1) belongs to a family of three human serum paraoxonases that also includes the enzymes PON2 and PON3. However, the enzyme PON1 remains the most relevant and well-studied member of this enzyme family [1]. This is largely due to the studies conducted by Mackness et al. who described the role of the enzyme PON1 associated with high-density lipoprotein (HDL) in reducing the accumulation of lipid peroxides in low-density lipoprotein (LDL) [2,3,4]. High-density lipoprotein (HDL) has received increasing attention because it has been shown to slow the oxidation of LDL. In fact, the HDL-associated enzyme, paraoxonase 1 (PON1), is shown to be responsible for preventing accumulation of lipid peroxides in LDL [5,6,7,8].

The above highlighted the potential link between the PON1 enzyme, HDL, and the prevalence of coronary artery disease in patients, and stimulated research interest in the

[1] Faculty of Medicine, Ss. Cyril and Methodius University in Skopje

[2] University Clinic for Cardiology, Skopje, North Macedonia

[3] Institute of Pathology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, North Macedonia

[4] Institute of Medical and Experimental Biochemistry, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, North Macedonia

activity of PON1 as well as its genotypic variants. The studies were mainly directed to clarify the physiological mechanisms of the enzyme PON1 [9] and the influence of single nucleotide polymorphisms of the PON 1 gene on the activity of the enzyme more precisely [7].

PON 1 enzyme identification, classification and structure

Abraham Mazur and Norman Aldridge played a key role in the identification and classification of the PON1 enzyme in the mid-1940s to early 1950s. Initially, the enzymes were designated as "A"-esterases but later became universally known as paraoxonases due to their ability to detoxify the organophosphate compound paraoxon, which is a toxic metabolite of parathion, commonly used as an agricultural insecticide [10,11,12].

PON1 is a calcium-dependent hydrolytic enzyme that can be found in various mammalian species. Structurally, it is a glycoprotein consisting of 354-355 amino acids with a molecular mass of 43-45 kDa [13]. This enzyme possesses three enzymatic activities: lactonase, arylesterase and paraoxonase activity [14]. Although PON1 shows its enzymatic activity on oxidized lipids, the exact physiological substrates for PON1 are still not well known [15]. The enzyme is mainly synthesized in the liver, where it is its first site of expression, and then after release into the circulation, it is mostly associated with HDL, and its function is related to antioxidant and antiatherosclerotic activity. PON1 is part of the enzymes that are associated with HDL, and this group of enzymes also includes lecithin-cholesterol acyltransferase and platelet activating factor acetyl-hydrolase, which are responsible for the antioxidant activity of HDL.

Genetics and polymorphisms

The genes for this family of enzymes are expressed in various mammalian tissues, with *PON1* and *PON3* primarily synthesized in the liver and commonly associated with HDL in plasma. The levels of the paraoxonase enzymes are genetically regulated. The human *PON1* gene is located on chromosome 7q21.3. *PON1* is encoded as a primary transcript of nine exons, using classical splice acceptor and donor sites. In any given individual, paraoxonase status can be largely determined by polymorphisms in the PON1 gene.

Many single-nucleotide polymorphisms (SNPs) have been identified for human *PON1*; eight have been identified in the promoter region and 176 within the gene sequence, some of which alter *PON1* levels and activity [16]. These polymorphisms may also influence the risk of development and severity of coronary artery disease [17]. Studies have identified two polymorphisms in the coding region (at positions 55 and 192) that have been shown to affect PON1 enzyme activity and concentration. The single-nucleotide polymorphism in the PON1 gene is the rs662 (c.575A>G) missense mutation, which results in a glutamine-to-arginine substitution at position 192 (p.Gln192Arg) [18]. The glutamine/arginine polymorphism at position 192 (Q192R) has been shown to affect PON1 activity, with the Q192 isoform being shown to hydrolyse paraoxon and metabolize oxidized LDL more efficiently than the R192 isoform [19]. The Q192R polymorphism is considered a major biomarker of oxidative status, with LDL oxidation being most inhibited in patients homozygous for QQ, and least in patients with RR [20,21]. A meta-analysis documented that the Q192R polymorphism is the only genetic variant in the *PON1* gene that confers a highly significant, albeit small (7% per R allele), risk for coronary artery disease [22] and another independent meta-analysis estimated a 10% higher risk for carriers of the R allele [23]. The R allele is also associated with low HDL levels [24,25,26].

These genetic variants are also associated with significant differences in PON1 enzyme activity and thus are implicitly involved in coronary artery disease status. Low PON1 activity has been shown to be associated with an increased risk of coronary artery disease, indicating PON1 as a physiologically important enzyme [19,27,28].

Data on the frequency distribution of *PON1* Q192R genotype variants and the risk of CAD have been studied in several populations worldwide [29]. However, no study has investigated this issue in the Macedonian population where CAD is highly prevalent and associated with very high mortality risk. Namely, Macedonia is one of the countries of the very high-risk region, with age- and sex- standardized WHO CVD mortality rate of 387.8 per 100 000 inhabitants.

The association between PON1 activity and cardiovascular risk remains controversial and since genes are transmitted randomly during gamete formation, genetic polymorphisms represent a valid approach to investigate the incidence and causality of human diseases. For this reason, we chose the strongest genetic biomarker of paraoxonase activity discovered so far, the missense mutation in the PON1 enzyme gene encoding the Q192R variant (rs662) i.e. A and G alleles encoding the amino acids glutamine (Q) and arginine (R). The *PON1* gene is one of the most studied genes in terms of predisposition to cardiovascular abnormalities based on atherosclerosis, for which reasons we analyse the relationship between enzyme activity, genotypic variants of the rs662 polymorphism and the risk of coronary artery disease in the Macedonian population.

MATERAL AND METHOD

Study population

The study included 106 patients with confirmed coronary artery disease (CAD), treated with percutaneous coronary intervention (PCI) with or without stenting, as indicated, due to inducible ischaemia and/or stable CAD. The control group consisted of 59 randomly selected patients during the same period, matched for gender and age, admitted to hospital due to chest pain, in whom absence of atherosclerotic CAD and/or other structural heart disease was confirmed during the patient's diagnostic workup.

All patients were treated at the University Clinic of Cardiology, "Mother Teresa" Clinical Centre, Skopje.

All patients were of Caucasian origin and were recruited from the same geographical region (Republic of North Macedonia), representing a population with a relatively similar genetic background despite belonging to two different ethnic groups.

Patients who had major cardiovascular events, acute coronary syndrome, renal failure (creatinine >3.0 mg/dL), and a history of malignant diseases in the previous 5 years were excluded. Also, exclusion criteria were acute inflammatory processes at inclusion (e.g., infections, autoimmune diseases).

The study was approved by the Ethics Committee of the Faculty of Medicine-Skopje. The patients participated in the study only after carefully reading, understanding and signing the written preapproved informed consent. The research is conducted in accordance with the principles stated in the Declaration of Helsinki.

Clinical characteristics of the study population

The study group is consisted of 165 patients in total, from which 106 were classified in te study group as CAD patients and 59 were classified as control group (non-CAD patients). The group in total of 165 patients had a mean age of 63.68 years. In the group male patients predominated, while female patients consisted only 27%. Diabetes mellitus was present in 40% of the study participants, and 70% of the participants were smokers. Demographically, 134 patients were Macedonian, while the rest of the patients were of Albanian ethnicity. Both ethnicities were distributed in the study and control group nearly equally as shown in Table 1.

The collected samples for analysis (blood) from the study group were analysed for the following biochemical parameters: HDL, LDL, total cholesterol (TC), Lp(a), ApoB, ApoA1, glucose, triglycerides (TG). The samples were measured immediately after blood collection using standard routine methods at the Clinical Centre "Mother Teresa" University Institute of Clinical Biochemistry-Skopje.

In addition, all patients from the CAD and non-CAD groups were genotyped for the rs662 polymorphism.

Samples Analysis

All blood samples were collected in the morning following an overnight fasting period. From the taken samples, serum was obtained using tubes that did not contain anticoagulant, after a 30-minute rest of the sample. Plasma was obtained using tubes that contained anticoagulant, sodium citrate, and then a centrifuge set at 3000 rpm was used for its separation, for 10 minutes at 4 ºC.

Genotyping the single nucleotide polymorphism Q192R PON1 (rs662)

Collected blood samples were used to isolate genomic DNA using MagCore ® Nucleic Acid Extractor Super, RBC Bioscience, USA. Patients were genotyped for the single nucleotide polymorphism (c.575A>G) in the *PON1* gene encoding the Q192R protein variant. This polymorphism, described under the identification number rs662, was investigated using real time PCR technique and previously designed TaqMan Universal Master Mix II and TaqMan assays from Applied Biosystems (Applied Biosystems, Foster City, CA, USA). Allelic discrimination was performed with a 7500 Real Time PCR machine, Applied Biosystems, CA, USA at the Institute of Pathology, Faculty of Medicine, Skopje.

The steps of the procedure were as follows:

DNA was isolated using MagCore ® Nucleic Acid Extractor Super, RBC Bioscience, USA Principle: First step is cell lysis where cells are broken open using a lysis buffer in order to release nucleic acids, then under specific chemical conditions (high salt concentration and specific Ph) DNA/RNA is bound to magnetic beads. The next step is washing, where the beads are hold in place by magnetic field and the impurities are removed (proteins, lipids and cellular debris), and the last step is the elution where nucleic acids are released from to beads in a clean elution buffer (low salt concentration, nuclease free). This method ensures efficient, consistent and contamination-free extraction.

Real-time PCR Amplification: Isolated genomic DNA was amplified using primer sets and TaqMan probes designed to detect the target polymorphism using predesigned commercial TaqMan SNP Genotyping Assay C__2548962_20 (Applied Biosystems. AB). (Cat. No.: 4362691). Each allele-specific TaqMan MGB probe has: a reporter dye at its 5' end. The target genomic sequence context surrounding the SNP, provided for reference and assay design is TAAACCCAAATACATCTCCCAGGAT[C/T] GTAAGTAGGGGTCAAGAA AATAGTG

PCR was performed in a thermal cycler under the following temperature conditions: denaturation at 95′ for

15 seconds, annealing and extension at 60′ for 1 min for 35 cycles. The products obtained from the PCR amplification were analyzed with the Thermo Scientific PikoReal PCR 2 Allelic Discrimination Software [Cat. No. 12076]. The system software records the results on a scatter plot of allele 1 (VIC® dye) versus allele 2 (FAM™ dye).

RESULTS

Table 1 showcase the demographic and clinical characteristics of the patients classified according to CAD, Q192R *PON1* genotype, presence of stent, restenosis, smoking status, and diabetes. In the patient group, only 2 patients (below 5%) carried the RR genotype, a number that is too small to provide statistically significant conclusions. Therefore, these patients were combined with the QR genotype group (QR+RR group) in the statistical processing of the data.

The statistical significance of the biochemical parameters was analysed using one-way ANOVA statistical method, in relation to different patient groups: according to CAD and non-CAD grouping and Q192R *PON1*allele (QQ, QR). The obtained results are shown in Table 2 and Table 3, respectively.

Statistical significance between the CAD patient group and the control (non-CAD) patients is indicated in bold

Table 1. Profile of the patient group in the study

	CAD	non-CAD
Gender (Male)	80 (72%)	31(28%)
Gender (Female)	26 (48%)	28 (52%)
Nationality (Macedonian)	87 (66%)	45 (34%)
Nationality (Albanians)	19 (58%)	14 (42%)
Smoking	31 (70%)	13 (30%)
Stent	36 (100%)	0 (0%)
Restenosis	46 (100%)	0 (0%)
Diabetes	36 (72%)	14 (28%)
Q192R(QQ)	22 (52%)	20 (48%)
Q192R(QR)	81 (67%)	39 (33%)
Q192R(RR)	2 (100%)	0 (0%)

Table 2. Biochemical parameters statistical relevance between CAD and non-CAD

	CAD	*nonCAD*	*All patients*	*Sample size*	*ANOVA*
	Mean (StDev)	*Mean (StDev)*	*Mean (StDev)*	*(CAD/non -CAD)*	*p*
Age	*64.72(±8.3)*	*61.83(±9.4)*	*63.68(±8.8)*	*106/59*	**0.0428**
Statins (mg/day)	*31.42(±17.9)*	*21.95(±17.7)*	*28.03(±18.3)*	*106/59*	**0.0013**
Glucose	*7.46(±3.3)*	*6.57(±2.1)*	*7.15(±2.8)*	*103/58*	*0.0508*
Lp(a)	*40.21(±50.2)*	*16.51(±15.2)*	*32.19(±43.2)*	*84/43*	***0.0031***
ApoB	*0.92(±0.3)*	*0.9(±0.2)*	*0.91(±0.3)*	*101/57*	*0.7213*
ApoA1	*1.23(±0.2)*	*1.36(±0.3)*	*1.28(±0.2)*	*99/57*	***0.001***
HDL	*1.12(±0.3)*	*1.28(±0.3)*	*1.17(±0.3)*	*103/53*	***0.0011***
LDL	*1.83(±0.9)*	*1.89(±0.8)*	*1.85(±0,9)*	*99/56*	*0.7001*
Total Cholesterol	*3.7(±1.3)*	*3.45(±0.8)*	*3.7(±1.1)*	*103/55*	*0.8718*
TG	*1.17(±0.7)*	*1.18(±0.7)*	*1.18(±0.7)*	*97/56*	*0.9699*
ACT	*22.7(±16.8)*	*22.29(±8.2)*	*22.56(±14.3)*	*104/58*	*0.8622*

Table 3. Statistical relevance of the biochemical parameters between QQ and QR+RR

	QQ	*QR*	*QR+RR*	*All patients*	*Sample size*	*ANOVA*
	Mean (StDev)	*Mean (StDev)*	*Mean (StDev)*	*Mean (StDev)*	*QQ/QR/ QR+RR*	*p*
Age	*62.73(±10.2)*	*64.18(±8.2)*	*64.2(±8.2)*	*63.92(±8.2)*	*45/120/122*	*0.2756*
Statins	*28.67(±19.7)*	*28.29(±17.7)*	*28 (±17.8)*	*27.97(±18.2)*	*45/120/122*	*0.9437*
Glucose	*7.71(±3.3)*	*6.93(±2.6)*	*6.95(±2.6)*	*7.14(±2.8)*	*41/117/120*	*0.1375*
Lp(a)	*32.81(±43)*	*30.73(±41.2)*	*31.98(±43.4)*	*32.19(±43.2)*	*32/92/95*	*0.9260*
ApoB	*0.9(±0.3)*	*0.89(±0.3)*	*0.9(±0.3)*	*0.91(±0.3)*	*40/115/118*	*0.2952*
ApoA1	*1.3(±0.3)*	*1.27(±0.2)*	*1.27(±0.2)*	*1.28(±0.2)*	*40/113/116*	*0.5834*
HDL	*1.23(±0.3)*	*1.16(±0.3)*	*1.16(±0.3)*	*1.17(±0.3)*	*38/115/118*	*0.1731*
LDL	*2(±0.8)*	*1.81(±0.9)*	*1.8(±0.9)*	*1.85(±0.9)*	*40/112/115*	*0.2129*
Total Chol.	*3.97(±1)*	*3.62(±1.1)*	*3.62(±1.1)*	*3.71(±1.1)*	*41/114/117*	*0.0729*
TG	*1.2(±0.7)*	*1.16(±0.7)*	*1.17(±0.7)*	*1.18(±0.7)*	*39/112/114*	*0.7881*
ACT	*20.9(±8.1)*	*23.1(±16)*	*23.12(±15.9)*	*22.56(±14.3)*	*41/118/121*	*0.3934*

Table 4. Association between QQ vs. QR and non-CAD vs. CAD

	non-CAD	*CAD*	*χ2*	*OR (95% CI)*	*p*
QQ	*20 (E=15.02)*	*22 (E=26.98)*	*3.4508*	*0.511[0.25-0.595]*	*0.0632*
QR+RR	*39 (E=43.98)*	*83 (E=79.02)*			

Table 5. Association between QQ vs. QR and non-CAD vs. stenting

	non-CAD	*Stenting*	*χ2*	*OR (95% CI)*	*p*
QQ	20 (E=14.75)	17 (E=22.25)	*4.1432*	*0.461[0.216-0.589]*	*0.0418*
QR+RR	39 (E=44.25)	72 (E=66.75)			

where patients in the CAD group had higher Lp(a) levels (40.21 ± 50.2 nmol/L, p=0.03) and lower ApoA1 levels (1.23 ± 0.2 mmol/L, p=0.001), HDL (1.12 ± 0.03 mmol/L, p=0.0011) compared to the non-CAD group (Table 2).

The analysed biochemical parameters have not shown statistical significance within the genotype groups (Table 3).

The distribution of SNP Q192R in CAD and non-CAD groups was further analysed using the Chi-square test. The analyses resulted in a non-significant association between Q192R and CAD (QQ vs. QR+RR; Odds ratio: 0.511[95% CI: 0.25-0.595], χ^2=3.4508, df =1, p=0.0632) (Table 4). In further analyses, in order to obtain a more precise association, we analysed the association between SNP Q192R groups and stenting patients (control vs. stenting group). The analysis resulted in statistically significant association between SNR Q192R and stenting (QQ vs. QR+RR and control vs. stenting; odds ratio: 0.461[95% CI: 0.216-0.589], χ^2 =4.1432, df=1, p=0.0418), leading to rejection of the null hypothesis of no association (Table 5).

DISCUSSION

Atherosclerosis and related cardiovascular diseases are major causes of morbidity and mortality in developed countries. While the factors such as diabetes, hyperlipidaemia, obesity and smoking, are established as major risk factors for atherosclerosis [30], emerging studies suggest that the enzyme PON1 and its enzymatic activity associated with high-density lipoprotein (HDL) may play an atheroprotective role [31,32].

Previous studies have shown that measuring PON1 enzyme activity alone is insufficient to assess the risk of developing CAD, as this activity is potentially influenced by its polymorphisms such as the single nucleotide polymorphism Q192R *PON1*. This has prompted the idea that it is necessary to consider and determine both enzyme activity and genetic polymorphisms to determine the possible risk of developing CAD [33].

This study highlights the multifactorial nature of coronary artery disease by evaluating both biochemical parameters and genetic factors. The observed lower levels of HDL ApoA1 activity in the CAD group are consistent with the idea that reduced antioxidant capacity predisposes individuals to lipid peroxidation and subsequent atherosclerotic changes. The HDL-associated enzyme PON1, in particular, plays a key role in hydrolyzing oxidized lipids, thereby mitigating oxidative stress and preserving endothelial function.

Furthermore, it is important to consider the potential influence of external factors such as medication use and the presence of comorbidities. For example, the concomitant use of statins and oral antidiabetics, which was observed in the patient population, may affect PON1 and overall lipid metabolism. Future studies should incorporate stratified analyses that account for these factors to clarify their modulatory effects on the antioxidant system [34].

In addition, the genetic background of the Macedonian population, which in this study was Caucasian but included different ethnic subgroups, suggests that population-specific genetic factors may also modulate CAD risk. Therefore, further studies should aim to compare these findings with other ethnic groups to determine whether the observed associations are consistent across populations.

The study design, which integrates both biochemical and genetic analyses, provides a meaningful approach to assessing cardiovascular risk.

In our study group, there is non-significant association (p=0.0632) between PON1-192 QR allele and CAD risk as opposed to QQ allele. Additionally, there is significant association (p=0.0418) between QR allele and CAD patients with stents. This is in line with other studies that have established significant PON1-192 R allele and CAD risk in some populations: Asian Indians [35,36], North American Caucasians [37,38], Japanese population [39] and Pakistanis [40]. On the other hand, some studies have shown the opposite for some populations: Chinese [35], Korean [41], Spanish [42], Italian [43], British Caucasian [44,23], Polish [45] and Iranian [46] populations.

However, the limitations imposed on the population selection result in a relatively small number of individuals with the RR genotype variant. To confirm these assumptions, additional longitudinal studies are needed to assess

the predictive value of the Q192R single nucleotide polymorphism on CAD risk.

The observed lipid profile differences, characterized by elevated Lp(a) and reduced ApoA1 and HDL levels in CAD patients, support the established role of impaired reverse cholesterol transport and increased atherogenic burden in coronary artery disease. The absence of significant biochemical differences between Q192R genotype groups suggests that this polymorphism does not primarily influence circulating lipid concentrations but may instead affect functional properties of HDL and oxidative balance. Although no statistically significant association between Q192R polymorphism and CAD presence was detected, a trend toward association was observed, indicating a possible modest genetic contribution. Notably, a significant association between Q192R genotype and stenting requirement was identified, suggesting that this polymorphism may be more closely related to disease severity or vascular response rather than disease initiation. These findings support the hypothesis that PON1 genetic variability may modulate clinical expression of atherosclerosis through mechanisms related to oxidative stress and HDL functionality.

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Declaration of Interest.

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Ethics approval.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments of comparable ethical standards.

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