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Association between Q192R polymorphism in the PON1 gene and statin responses in cardiac patients

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ABSTRACT

Introduction: Paraoxonases are a group of different forms enzymes that consist of three non-similar isoforms, *PON1, PON2 and PON3*, which are located near to each other on the long arm of chromosome7. This study aims to investigate the association of a Q192R polymorphism of PON1 gene and statin response in patients with ischemic heart disease with dyslipidemia.

Methods: The studied population included three hundred patients with coronary artery disease with dyslipidemia who were prescribed statins. Total lipid profile was measured in these patients both before and after approximately 6 months of treatment. Q192R polymorphism of *PON1* gene was assessed by real-time PCR.

Results: There were no significant differences in baseline lipid levels according to different genotypes in all studied casesof Q192R (rs662) polymorphism. HDL-C goals were attained less often in patients with RR homozygosity than in Q allele carriers. Analysis by univariate logistic regression confirmed that QQ/QR carriers had an increased chance of attaining HDL-C goals.

Conclusion: This study shows that the Q192R polymorphism of *PON1*gene has important role in interindividual variety in accomplishment of HDL-C goals in response to statins.

1. Introduction

Coronary artery disease and other cardiovascular diseases (CVD) are the leading causes of morbidity and mortality in various areas of the world [1]. Risk factors include high blood pressure, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor diet, and excessive alcohol intake [2]. The underlying mechanism involves atherosclerosis of the arteries of the heart [3]. With respect to hereditary impacts on coronary illness advancement, there is prove showing that progressions in paraoxonase family (PON) qualities add to CVD pathogenesis [4]. Studies have demonstrated that the paraoxonase1 (PON1) chemical is related with the restraint of lipid peroxidation of high-thickness lipoprotein cholesterol (HDL-C), decreased oxidative alteration of low-thickness lipoprotein cholesterol (LDL-C) [5], and protection of HDL-C and LDL-C work [6]. Human paraoxonases are a group of polymorphic enzymes that consist of three different genes, *PON1, PON2* and *PON3*, which are located near each other on the long arm of chromosome7 (between q21.3 and q22.1) in humans [7]. The Q192R (rs662) polymorphism is more widely recognised than other polymorphisms and is a missense substitution that changes a glutamine (Q) to an arginine (R) [8]. Statins are a class of lipid-lowering medications that function by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is involved in the rate-limiting step in the production of cholesterol. Although statins are usually highly effective and are generally well tolerated, interindividual variety in viability has been watched [9].

The TaqMan test utilizes a single-stranded oligonucleotide containing a fluorophore and quencher placed 10–30 bases apart. Hydrolysis occurs during the amplification due to the 5′- 3 ′double-strand-particular exonuclease action of the Taq polymerase that isolates the fluorophore from the quencher, bringing about fluorescence increment. This study expects to examine the relationship of Q192R Polymorphism of *PON1* gene and statin response in patients with ischemic heart disease with dyslipidemia.

2. Subjects & methods

Subjects: This prospective study was conducted on three hundreds

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patients with ischemic heart disease (angiographically diagnosed with at least one major coronary artery showing > 70% of stenosis) with dyslipidemia who were on statin treatment during the period from April 2016 until February 2017. The cases were chosen from patients attending the cardiology department of Benha University Hospital. This study was approved by an Ethical Committee according to World Medical Association Declaration of Helsinki (UIN: researchregistry3565). All patients gave written informed consents.

2.1. Inclusion criteria

All patients are aged > 20 years old using statins for approximately 6 months, they were naive before this period. Most patients were hypertensive or had cardiovascular disease. Other prescribed medications were continued throughout the study.

2.2. Exclusion criteria

- Patients less than 35 years old.
- Triglyceride concentration more than 400 mg/dl (4.52 mmol/L).
- Hepatic or renal function disorders.
- unstable or uncontrolled disease that influences lipid metabolism

3. Methods

All patients were subjected to the following:

1 Full history taking including age, sex, IHD, smoking, treatment period, medications including (calcium channel blockers, diuretics, antithrombotic drugs, beta – blockers and ACE inhibitors) and family history of CVD.
2 Laboratory investigations:

Sampling: Five milliliters of venous blood from each patient were collected under aseptic precautions after 10–12 hrs fasting, and distributed as follows:

a Two milliliters whole blood was put in EDTA vacutainer (violet cap) and mixed up & down gently which was used to measure *PON1* polymorphism.
b Three plain test tubes without anticoagulant. The plain test tubes were left until coagulation. After coagulation, samples were centrifuged (at 1500 rpm for 15 min). The separated serum was used for the assay of the lipid profile and glucose.

4. Routine laboratory investigations

(1) Total cholesterol by an enzymatic method using Spin Reactreagent:
(2) Triglyceride by an enzymatic method using Spin Reactreagent: Biosystem A15 auto-analyzer applying using conventional enzymatic methods
(3) HDL-C was determined using a selective immune separation-homogenous assay, followed by colorimetric determination.
(4) LDL-C.

Low-denisty Lipoprotein Cholesterol was calculated according to "Friedwald's equation": LDL-C = Total cholesterol-(HDL-C + TG/2.2).

5. Specific laboratory investigations

Determination of *PON1* genotype:(Rs662 SNP is located on chromosome 7, at *PON1* gene. Change in alleles CTA to CCA leads to change of glutamine to arginine)

All subjects were genotyped for Q192R polymorphism of *PON1* gene by real-time PCR TaqMan Universal Master Mix II and TaqMan assays by the following steps:

1 DNA was extracted by Thermo Scientific Gene JET Genomic DNA Purification Kits **(50 preps), (Invitrogen by Thermo Scientific Cat no K0721).**

Principle: Thermo Scientific Gene JET Genomic DNA Kits depend on the specific binding of DNA to the silica-based layer. The lysate is blended with ethanol that permits high DNA binding to Spin Column (Mini Kit). The DNA ties to the silica-based layer in the segment and pollution are expelled by careful washing with Wash Buffers. The genomic DNA is then eluted under low ionic quality conditions with the Elution Buffer., the yield of purified DNA was estimated by UV absorbance at 260 nm (Purity was determined by calculating the ratio of absorbance at 260 nm to absorbance at 280 nm. Pure DNA has an A260/A280 ratio of 1.7–1.9).

Amplification by Real-Time PCR: The isolated genomic DNA was amplified using sets of primers & TaqMan probes designed to detect the target polymorphism. (**Applied Biosystems. AB). (Cat. No:1511033).**

Each allele-specific TaqMan MGB probe has: A reporter dye at its 5′ end.

TAAACCCAAATACATCTCCCAGGAT [C/T]GTAAGTAGGGGTCAA GAA AATAGTG.

PCR was performed in thermal cycler according to the following thermal conditions: denaturation at 95′ for 15 s, annealing and extension at 60′ for 1 min for 35 cycles. The PCR amplification products were analyzed by Thermo Scientific PikoReal PCR software 2 for allelic discrimination [**Cat. No. 12076**]. The system software records the results on a scatter plot of Allele 1 (VIC® dye) versus Allele 2 (FAM™ dye).

6. Allelic discrimination (AD) analysis

In the allelic separation investigation, the Cq estimations of AD standard gatherings are looked at. PikoReal programming bunches the examples by figuring the separation between each example and the normal standard values.

7. Statistical analysis

The collected data were tabulated and analyzed using SPSS version 16 soft ware (Spss Inc, Chicago, USA). Quantitative data were expressed as mean ± SD and qualitative data were expressed as frequency and percentage. Independent samples *t*-test of significance was used when comparing two means. Categorical data were presented as number and percentages. Odds ratios (ORs) and 95% CI were calculated. Logistic regression analysis was used to detect the significant predictors of ischemic heart disease with dyslipidemia. The accepted level of significance in this work was stated at 0.05 ($P < 0.05$ was considered significant, $P < 0.001$ was considered highly significant).

8. Results

The present study comprised of 300 cases. Their age ranged from 39 years to 80 years old. They comprised of 168 (56%) males and 132 (44%) females.

They were randomly selected from Qaliubeya Governorate. They were unrelated, applying Hardy-Weinberg equation revealed that they were in equilibrium. Two hundred and forty cases (80%) suffered from hypertension, 108 (36%) from diabetes mellitus (DM), 186 (62%) had a family history of CVD, 162 (54%) were smokers, various drug administration was mentioned in (Table 1). Mean overall statin dose was 27.6 mg. TG, TC, LDL showed a significant decrease, while HDL showed significantly increased levels after treatment. No significant differences were found in baseline or after treatment laboratory parameters according to different genotypes in all studied cases. No significant differences were found in percent changes in laboratory parameters

Table 1
Clinical data and treatment of all studied cases.

Overall Statin dose (mg): mean ± SD	Patients N = 300	
	27.6 ± 9.8	
	N	**%**
Hypertension	240	80
DM	108	36
Family history of CVD	186	62
Smoking	162	54
B-blocker	150	50
calcium channel blocker	120	40
cardiac glycosides (Digitalis)	300	100
antithrombotic drugs (aspirin)	300	100
ACE inhibitors	12	4
Insulin	102	34
diuretics	228	76

according to different genotypes in all studied cases (Table 2).

Patients who have normal serum lipid profile after statin prescription were assessed according to criteria of the V Brazilian Guidelines on Dyslipidemia and Prevention of Atherosclerosis for primary prevention of CVD: TC < 5.18 mmol/L, LDL-C < 2.59 mmol/L, HDL-C > 1.55 mmol/L, and TG.

< 1.70 mmol/L [10]. When percentages of reaching lipid goals were analyzed for patients with Q192R (rs662) polymorphism, TG and HDL-C goals were less likely to be reached in RR homozygous patients than in Q allele carriers (Table 3). Logistic regression analysis was conducted for prediction of HDL < 1.55 mmol/L after treatment in all studied patients, using age, sex, hypertension, DM, smoking, family history of CVD, overall statin treatment, baseline laboratory data and rs662 as covariates. Higher baseline TC and LDL were associated with HDL < 1.55 after treatment. On the other hand, lower overall statin treatment, as well as Q allele carriers, were associated with protective effects on HDL in univariate analysis. Overall statin treatment and Q allele were considered as independent protective factors against low HDL (Table 4).

9. Discussion

The study was done to detect the relation between Q192R polymorphism of *PON1* gene and response to a statin in Egyptian patients with ischemic heart disease with dyslipidemia. Blood tests were done onall cases to evaluate lipid profile and afterwards all specimens were genotyped for the Q192R polymorphism of *PON1* gene utilizing TaqMan genotyping procedure.

Few previous studies addressed the effect of statins on PON1 activity. Simvastatin increased plasma PON1 in humans with hypercholesterolemia [11]. and stimulated PON1 gene expression in HepG2 cells [12]. Incontrast, Bianca et al. [13] reported that treatment of hypercholesterolemic subjects with simvastatin tended to reduce PON1 activity toward paraoxon and had no effect on activity toward phenyl acetate. Atorvastatin has been demonstrated to increase [14] or to have no effect on [15] plasma PON1. However, the results of human studies, especially performed in hyperlipidemic subjects, are affected by the fact that statins decrease LDL cholesterol in humans whereas hyperlipidemia *per se* decreases PON1 activity directly and by causing oxidative stress [16]. Thus, the beneficial effect of statins on plasma PON1 in hyperlipidemic patients could be secondary to the improvement of the plasma lipid profile [17].

In people, it has been demonstrated that diminished PON1 gene is related with expanded frequency of atherosclerosis and cardiovascular illnesses [16]. Low levels of HDL-C and abnormal amounts of TC, TG and LDL-C are significant predictors of atherosclerosis and CVD all through the populace [18]. Statins are generally utilized, compelling medications for the treatment and avoidance of dyslipidemia and cardiovascular sickness (CVD) [21]. There is bury singular fluctuation in the degree to which statins are clinically powerful at bringing down LDL-C levels and diminishing cardiovascular occasions [19] [20]. The paraoxonase1 chemical assumes a critical part in the direction of HDL cell and antioxidant anti-inflammatory activities [21]. PON1 represses the oxidation of LDL-C and keeps the gathering of oxidized lipids in vessels, along these lines restraining the movement of atherosclerosis and therefore decreasing the advancement of CVD [22] [23].

HDL-C is a critical, autonomous marker for atherosclerosis and for CVD. Our outcomes show that, for the Q192R polymorphism, RR homozygous patients less every now and again achieved their HDL-C lipid focus than did bearers of the Q allele. These discoveries are in obvious appear differently in relation to that saw by Malin et al. [23] and Fu et al. [24] yet our outcomes verify information with respect to CVD chance demonstrating a relationship between Q192R polymorphisms and CVD, revealing that the Q allele secured against CVD while the R allele had a malicious impact [25], [26].

Because HDL-C levels and statin responses are complex phenotypes, we performed regression analysis for prediction of HDL < 1.55 after treatment in all studied patients, using age, sex, hypertension, DM, smoking, family history of CVD, overall statin treatment, baseline laboratory data and rs662 as covariates. Higher baseline TC and LDL were associated with HDL < 1.55 after treatment. On the other hand, lower overall statin treatment, as well as Q allele carriers, were associated with protective effects on HDL in univariate analysis. overall statin treatment and Q allele were considered as independent protective factors against low HDL. All patients were advised to begin physical activity and diet control, but monitoring and evaluation of these activities were not part of this study. We believe that other genes may also be important factors to the variation in patient responses to statins.

10. Conclusions

The results of this study show that the Q192R polymorphism of *PON1* gene may assume a part in interindividual variety in accomplishment of HDL-C objectives because of statins.

Ethical approval

This study was approved by an Ethical Committee according to

Table 2
Comparison between percent changes in laboratory parameters according to different genotypes in all studied cases.

	QQ N=102		*QR N=150*		*RR N=48*		*P1*	*P2*	*P3*	*P4*	*P5*	*P6*	*P7*
	Mean	SD	Mean	SD	Mean	SD							
TG (mmol/L)	−12.2	2.3	−11.5	3.3	−13.1	2.6	.449	.265	.322	.769	.215	.479	.525
Total cholesterol (mmol/L)	−25.4	4.2	−26.1	9.5	−28.6	5.5	.851	.582	.727	.883	.573	.727	.801
HDL (mmol/L)	4.4	1.6	2.5	.65	2.3	.28	.739	.505	.861	.556	.553	.438	.771
LDL (mmol/L)	−42.7	9.3	−41.8	7.7	−45.6	9.5	.694	.908	.727	.294	.975	.567	.412

P1, the comparison between 3 genotypes, p2, between QQ and QR, p3, between QQ and RR, p4, between QR and RR; p5, the comparison between QQ versus others; p6, the comparison between QR versus others; p7, the comparison between RR versus others.

Table 3
Comparison between lipid profiles (mmol/L)after treatment according to genotype in all studied cases.

	QQ N = 102		*QR N = 150*		*RR N = 48*		*P1*	*P2*	*P3*	*P4*	*P5*	*P6*	*P7*
	N	%	N	%	N	%							
TG < 1.70	60	58.8	108	72	6	12.5	.484	.374	.038	.005	.584	.239	.007
TG > 1.70	42	41.2	42	28	42	87.5							
TC < 5.18	42	41.2	66	44	24	50	.172	.555	.504	.541	.506	1	.502
TC > 5.18	60	58.8	84	56	24	50							
HDL < 1.55	48	47.1	60	40	42	87.5	.062	.445	.047	.039	.999	.164	.048
HDL > 1.55	54	52.9	90	60	6	12.5							
LDL < 2.59	48	47.1	108	72	42	87.5	.106	.102	.088	.643	0.062	0.370	.237
LDL > 2.59	54	52.9	42	28	6	12.5							

P1, the comparison between 3 genotypes; p2, between QQ and QR; p3, between QQ and RR; p4, between QR and RR; p5, the comparison between QQ versus others; p6, the comparison between QR versus others; p7, the comparison between RR versus others.

Table 4
Regression analysis for prediction of HDL < 1.55 mmol/L in all studied patients.

	Univariate				Multivariate			
	p	OR	95% CI		p	OR	95% CI	
Age (years)								
Sex	.364	1.1298	.343	3.948				
Hypertension	.375	2.762	.677	3.287				
DM	.654	.687	.123	6.309				
Family history of CVD	.236	.876	.123	4.987				
Smoking	.543	1.498	.876	8.498				
Overall statin dose	.038	.765	.598	.983	.047	.907	.824	.999
Baseline Creatinine	.768	1.741	.044	9.151				
Baseline TG	.429	.841	.548	1.291				
Baseline Total cholesterol	.008	2.289	1.242	4.217	.454	.692	.187	5.827
Baseline HDL	.427	.173	.002	13.174				
Baseline LDL	.003	3.081	1.464	6.483	.132	2.876	.4428	12.987
rs662 (QQ + QR versus RR)	.002	.254	.087	.965	.023	.192	.043	2.872

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Author contribution

Eman R. AbdElgwad, Fathy M. Swailemand Eman G. Behiry.

- Substantial contributions to the conception and design of the work and acquisition of data.
  -Drafting the work.
  -Final approval of the version published.
  -Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Seham G. Ameen, Dalia M Abdelhasib*, Rabab O. Abd Elhamid, Eman G. Behiry.
Statistical analysis, and interpretation of data.

-Drafting the work and revising it critically for important intellectual content.
-Final approval of the version published.
-Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated

Conflicts of interest

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