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Evaluation association between PON1 Q192R gene Polymorphisms with Arylesterase activity and plasma level Malondialdehyde in infertile man

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Objectives: **Infertility as a disorder reproductive system and incapacity to achieve a fulfill pregnancy with no contraceptive measures taken after reasonable time of sexual intercourse. PON gene family with paraoxonase, arylesterase, and lactonase activities consists of PON1, PON2 and PON3, are relationship with oxidative stress and lipid metabolism. According the important role of PON1 in oxidative stress and effect active oxygen species on infertility males, aim of this study was evaluation association between PON1 Q192R gene Polymorphisms with arylesterase activity and plasma level malondialdehyde in infertile man.** ***Materials and Methods:*** **In this study blood samples collected from 100 control subjects and 100 infertile men. Q192R variants of PON1 were determined polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) technique and to estimate the association between genotype and allele frequency in cases and controls, p-values were assessed by chi-square (χ2) analysis. In this study, was measurement malondialdehyde by Yagi method as oxidant and arylesterase enzyme as antioxidants in both groups.** ***Results:*** **The founds of this study indicate that the Q allele of PON1 Q192R gene polymorphism is significantly associated with infertility males and infertile individual either homozygote (p <0.029) and heterozygote (p <0.014), have shown a lower Q192R polymorphism, lower Paraoxonase activity and higher level of Malondialdehyde and Arylesterase activity.** ***Conclusion:*** **In the end, we found show the Q192 R polymorphism in the PON1 gene is strongly relationship with infertility males and the QQ genotype significant increase risk of idiopathic infertility males unlike RR genotype.**

INTRODUCTION

Infertility is basic problem reproductive system and defined as failure to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse (1). Infertility involves environmental and genetic factors that influence 20% of reproductive-age of couples. (2). Genetic factors such as aneuploidy and single-gene mutations (polymorphism) and systemic disorders such as cell aplasia, testicular cancer are important factors in infertility male (3,4). Idiopathic infertility occurs spontaneously or due to unknown reasons and more have genetic origins (5,6). Recently oxidative stress known as important factors in malfunctioning and reducing sperm motility (7). Increasing ROS accompany damage and sperm motility causes cell death that involved 60% of the cases of infertile males (8). Several studies reported that uncontrolled production of ROS by immature sperm and leukocytes in seminal fluid leads to disruption of normal spermatozoa (9). Therefore, oxidative stress influence sperm motility and fertilization ability by lipid peroxidation in sperm plasma membranes and induces sperm DNA fragmentation (10). Paraoxonase (PON) as an enzyme dependent to HDL consists of three PON1, PON2 and PON3 genes located on the long arm of chromosome 7. PON1 gene is a glycoprotein 43 KD with Paraoxonase, Arylesterase, and Lactonase activities. This enzyme with antioxidant activity and inhibits oxidation of LDL and HDL particles plays a key role in preventing lipid peroxidation (11). Precise role of PON1 gene are documented in various stages of spermatogenesis spermatogonia, spermatocytes, spermatids, Sertoli and Leydig cells in the male reproductive tract (12). In researches do by the verit et al, show over production of ROS in sub-fertile men may be a result of low PON1 activity in semen of subfertile men (13). Two type polymorphisms in the encoding area of PON1 gene are reported, one is in position 192 (replacement of glutamine with arginine) and position 55 (Leusin with methionine). Polymorphisms position 192 (Q192R) has been shown as a functional polymorphism (14). This role of this PON1 Q192R gene polymorphism in the male reproductive system and modifies Arylesterase and paraoxonase activity are associated with risk of infertility male. In various study, the PON1 Q192R gene polymorphism as basic factors in decreased sperm DNA damage and low risk of infertility male (15-16), can affect plasma lipoprotein levels (15,16). So,

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the Q192R polymorphisms of PON1 genotype can predict HDL cholesterol changes than polymorphism 55 (17). Regarding the role of PON1 in oxidative stress and effect of ROS upon infertility males, genetic variations of PON1 gene can be effective in infertility male. In order to approve this hypothesis, the PON1 mutations in area 192 investigated in infertile and healthy men. Also, for investigating the oxidative stress situation, measurementd the malondialdehyde levels and Arylesterase activity in infertile males and healthy. However, there is low information about the PON1Q192R polymorphism gene, and the question of whether the PON1 gene polymorphism distribution is different between fertile and infertile men or no?. In this study, we investigated PON1Q192 R gene polymorphism and its relationship with Arylesterase activity and the level of Malondialdehyde (MDA) in fertile and infertile men.

MATERIALS AND METHODS

Blood sample collection and DNA extraction

In this case-control study, 100 patients diagnosed with idiopathic male infertility and 100 healthy men as control group between 22 and 45 years of age, referred to the Infertility center of Ahvaz Jihad University of Medical Sciences. Examples of semen infections, drug use, azoospermia, varicoceles, systemic diseases, testicular inflammation, antibodies against sperm and hypogonadism in this study are eliminated. The control group included healthy men who had at least one child between 1 and 5 years of age. After completing the questionnaire containing information and obtaining consent of patient, 500 microliter blood was collected for extraction of DNA in EDTA-containing tubes and stored at -20 ° C to be used for DNA extraction. Blood samples were centrifuged at 3000 g for 15 min and aliquots of plasma were immediately stored at -20°C until analyzed. In addition, blood leukocytes were used for DNA extraction. The genomic DNA was extracted by DNA prep 50 kits (Sinaghan Co., Iran), and concentration and quality of purified DNA was investigated by electrophoresis method on Agarose Gel. The evaluate the quality and concentration of DNA extracted, OD (DNA / protein ratio) was measured using a nanotrop spectrophotometer, Suitable OD between 1/8 - 2 is optimal and indicates the proper concentration of DNA extracted. After assessing the quality of the DNA extracted by 1% gel electrophoresis, DNA was stored at -20°C freezer (18,19).

Genotyping PON1 by technique PCR-RFLP and PCR conditions for proliferation of the polymorphic region included

Duplication of region 192 in the PON gene was performed using specific primers. Polymerase chain reactions were set up further genotyped using the RFLP technique (20). Primers designed for PCR amplification for PON1 Q192R polymorphism: 5′-TATTGTTGCTGTGGGACCTGAG -3′ (forward) and 5′-CACGCTAAACCCAAATACATCTC-3′ (reverse) and Five minutes of denaturation at 94^0 C, cycle conditions comprised 30 cycles of 30 seconds denaturation at 94 ^{0}C, 45 seconds at 61^0C for bonding primers (annealing), and 45 seconds at 72^0C to rearrange the DNA strand. The PCR amplification was performed by electrophoresis of the agarose gel to ensure the DNA reaction was performed. When using specific primers for the PON1 gene (Q192R polymorphism), a fragment of 279 bp is replicated. The timing for the PCR reaction was set up by Thermo cycler device. At the end, for identify genomic polymorphism in area 192 by RFLP and ALWI (Sinagan Co., Iran), For this purpose, 4 uL PCR product with 1 unit of enzyme mix and 4.5 ml of distilled water and 1 ml buffer was added to reach a volume of 10 ml. After incubation at 55^0C for area 192 was performed for 2 hours. Agarose Gel 2 % electrophoresis was used to determine the enzyme activity. After replication of parts to detect region polymorphism 192 by RFLP technique, this fragment is cut under the influence of the restriction enzyme ALW1. To evaluate the digestibility product (3 QQ, RR, QR), 2% Agarose Gel electrophoresis is used, with QQ of 96 bp, RR of 183 bp, 96 bp, and QR of 183 bp, 96 bp and 279 bp (22- 21).

Biochemical measurement oxidative stress markers

Systemic oxidative stress was evaluated by measuring paraoxonase activity and Arylesterase activity and the level of Malondialdehyde (MDA) as oxidant. The content of lipid peroxidation in plasma was measured by the reaction of thiobarbituric acid (TBA) with MDA according to the Yagi method [Yagi 1984]. The MDA level was measured spectrofluorometrically via excitation at 515 nm and emission at 553 nm and tetraethoxypropane was used as standard (23). Plasma arylesterase activity of PON1 was measured by spectrophotometric method as previously described. Phenylacetate was used as a substrate and phenol product of substrate hydrolysis was measured at 270 nm. Briefly 5 ml of the plasma sample was added to 3ml of the reaction mixture (1 mmol/L phenylacetate, 1 mmol/L CaCl2 and 20 mmol/L Tris-HCl buffer pH 8). The absorbance at 270 nm and 37_C was measured per min and PON1 activity was calculated using the molar absorption coefficient 1310 mol_1Lcm_1. Finally, results were expressed as U/mL (24- 28).

Ethical principles

This article has been adapted from a research project approved by the code of HLRC-9510 and ethics code ajums. IR.AJUMS.REC.1395.739 in the Student Research Committee University of Ahvaz Jundishapur University of Medical Sciences.

Statistical analysis

Data were analyzed using the SPSS software for Windows version 18.0 (SPSS, Chicago, IL, USA and the results were expressed as mean±SD. According to One-Sample Kolmogorov-Smirnov test results the variables were normally distributed for continuous variables in each group. Differences between plasma MDA concentration and enzyme activities of control and infertile men were tested using Independent sample t-test. The continuous variables of the case and control groups were compared using the Student's t-test and the Mann–Whitney U test. Genotypes and allele frequencies in the groups were analyzed using the $\chi 2$ test. A two sided P-value less than 0.05 was considered statistically significant. Chi-square test was used to test the difference between genotypes in two groups and the level of significance was less than 0.05. Comparison of allele, genotype, and phenotype frequencies and semen parameters between groups were determined by Chi-Square test. One-way ANOVA test was used to compare the means of quantitative parameters in different genotypes and statistical significance was assumed at the $p<0.05$ level.

RESULTS

Genotype distributions of the Q192R Polymorphisms and determination plasma levels of MDA and PON1 activities in healthy and infertility individuals

In this study, in order to investigate the relationship between PON1-Q192R polymorphism with plasma level MDA and Arylesterase activity in infertile men, using of Chai square analysis showed a significant difference between genotype distribution and frequency of alleles in

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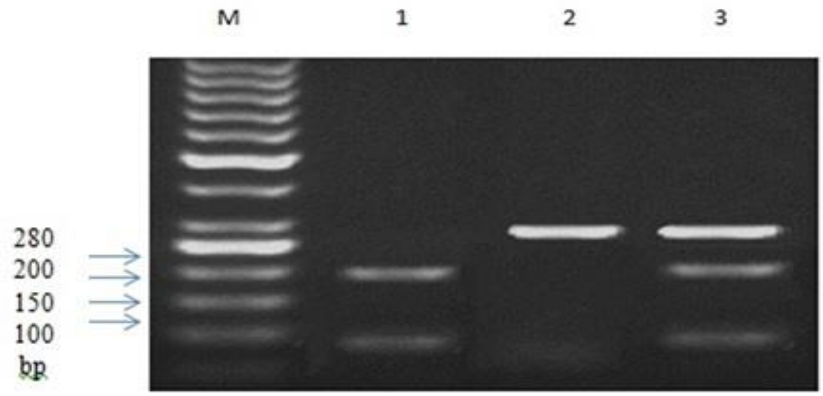

Figure 1 Genotype analysis PON1 Q192R polymorphism with using of PCR-RFLP methods. PCR products were digested by AlwI restriction enzyme, run on a 2% polyacrylamide gel, and visualized using the silver-staining method. The products obtained of RFLP, column1 homozygous RR, column 2 homozygous QQ and column 3 is heterozygous QR. Column M: Molecular Mackrosole, the ladder was 50-bp.

Table 1 Frequency of PON1 (Q192R) genotypes alleles and odds ratios in healthy subjects and infertile males

Polymorphism	Controls	Patients	OR (95% CI)	*p*-value
GG(RR)	15 (15%)	6 (6%)	0.275 (0.099-0.76)	0.013
AG(QR)	39 (39%)	27 (27%)	0.475 (0.256-0.882)	0.018
AA(QQ)	46 (46%)	67 (67%)	1.0-ref	
Dominant				
GG(RR)	15 (15%)	6 (6%)	0.319 (0.118-0.863)	0.024
AG + AA(QR+ QQ)	75 (75%)	94 (94%)	1.0-ref	
Recessive				
GG+ AG(RR+ QR)	54 (54%)	33 (33%)	0.42(0.237-0.744)	0.003
AA(QQ)	46 (46%)	67 (67%)	1.0-ref	
Alleles				
G(R)	69 (34.5%)	39 (19.5%)	0.46 (0.292-0.725)	0.001
A(Q)	131 (65.5%)	161 (80.5%)	1.0-ref	

both healthy and infertile groups (P < 0.05). Determination genotype PON1 Q192R polymorphism with use of (PCR-RFLP) technique and DNA fragments were visualized by silver staining, the results are shown in (Figure 1). Moreover, genotype distributions and allele frequencies of Q192R Polymorphisms and odds ratio of the healthy subjects and the infertile patients are described in detail in (Table 1). Distribution PON1 genotype at healthy and infertile subject consistent with predicted genotype by the Hardy-Weinberg equilibrium. This results show that distribution of PON1 genotypes and alleles significantly different between fertile and infertile, and presence of PON1 Q192R genotypes (including QQ, QR, and RR) and alleles are not risk factor for male infertility. Our founds show that individuals with QR and RR variant have low risk for idiopathic infertility male. In other words, R allele in the infertile group was significantly lower than the control group and frequency of R allele than Q allele in the infertile group was significantly lower than the control group. So the likelihood of occurrence of this polymorphism in the infertile individual is low (RR: OR= 0.275, 95% CI=0.099-0.76, P= 0.013. QR: OR= 0.288, 95% CI= 0.132-0.394, P=0.0001). All of the above points indicated the prevalence and frequency of R allele in infertile individual is less than healthy and this polymorphism protects individuals against infertility or in other words, R allele has a protective role against infertility. So, distribution genotypes QQ, QR and RR were significantly different between healthy subjects and infertile. Determination association of PON1 Q192R genotype with the infertility showed that there was an increase QQ genotype compared to the RR genotype in infertile male. This information in Table 2, showed plasma levels of MDA and arylesterase activities in healthy and infertile individual. This results indicated that plasma MDA levels and arylesterase activities were significantly higher in the infertile patients than in the healthy subjects (p <0.001). The higher PON1 arylesterase activity and plasma levels of MDA in the infertile males were dependent to the PON1 192 genetic polymorphism. Indeed, plasma levels of MDA and arylesterase activity was significantly higher in the infertile patients for all three allele PON1 192 genotypes compared to the healthy subjects (Table 3). The plasma levels of MDA as well as arylesterase activities of PON1were measured in fertile and infertile men (Table 3). MDA and arylesterase activity levels were significantly higher in infertile men compared with fertile males (p<0.001). In contrast, paraoxonase activity levels were statistically higher in fertile subjects than in infertile men (p50.05).

Relationship between plasma levels of Malondialdehyde and Arylesterase activity with different genotypes of PON1 Q192R gene polymorphism

These results show that arylesterase activity in individuals with Q192R polymorphism, in the either heterozygote (QR) or homozygote (RR) was

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Table 2 Plasma levels Malondialdehyde and Arylesterase enzyme in healthy and infertile males

	CONTROL	PATIENT	P VALUE
ARYLESTERASE	**48.81±10.89**	**54.15±9.12**	**<0.001**
MALONDIALDEHYDE	**1.03±0.19**	**1.25±0.19**	**<0.001**

Table 3 Relationship between different genotypes of PON1 Q192R gene polymorphism with plasma levels of Malondialdehyde and Arylesterase activity

		ARYLESTERASE	*P*-VALUE	MALONDIALDEHYDE	*P*-VALUE
CONTROL SUBJECTS	QQ	51.21±9.89	REF	1.09±0.19	REF
	QR	48.8±10.4	0.15	1.02±0.14	0.05
	RR	47.5±8.35	0.087	0.92±0.22	0.024
PATIENTS	QQ	57.3±11.5	REF	1.29±0.17	REF
	QR	55.8±9.55	0.05	1.18±0.23	0.038
	RR	52.2±10.2	0.031	1.11±0.13	0.024

lower than reference QQ genotype. Statistically only in infertile patients either heterozygous (p <0.05) homozygote (p <0.027) is significant. According to (Table 3) the R mutant allele is relationship with the level Arylesterase enzyme. Therefore, in Table 3 show the association of plasma level Malondialdehyde and Arylesterase activity with different genotypes of this polymorphism in infertile and control individuals suggests that the level of Malondialdehyde and Arylesterase activity in infertile individuals is high and shows scale lower polymorphism and the level of R allele either heterozygote (QR) or homozygote (RR) is lower. According to the results of this study, infertile individual either homozygote (p <0.029) and heterozygote (p <0.014), show a lower Q192R polymorphism and higher level of Malondialdehyde and Arylesterase activity.

DISCUSSION

In this study, investigated the possible role paraoxonase 1 gene and its Q192R polymorphism in infertility males as an antioxidative and atheroprotective candidate gene (29). In of population studies, PON1 gene reported as basic gene at infertility, also approved simultaneous associations between PON1 gene polymorphisms with plasma levels of Malondialdehyde, Arylesterase activity in infertility (30). The aim of the study was investigation PON1 genotype and determines whether the Q192R polymorphisms in the PON1 coding region can predict infertility complications in this population or no? In present study, our founds showed that Q192 R polymorphisms and oxidative stress status might influence the Arylesterase activity and plasma levels MDA in infertile individual. The results show that there is a significant difference between the PON1 genotype and allele distribution in fertile and infertile male (31). Previous studies do by Volk et al show conflicting results on the distribution of the PON1 Q192R polymorphism between fertile and infertile males (32). While, Kim et al, showed that there are positive relationship between PON1 Q192R allele and sperm motility (33). Our results shown various genotypes of PON1 are probably risk factor for infertility man. Also this result indicated significant relationship between Q 192 R polymorphism of PON1 gene with male idiopathic infertility. We results indicated individual with QR and RR genotype less likely to have idiopathic infertility and R allele has a protective effect against infertility male. Previous studies, report conflicting results on the distribution of this polymorphism (34). So, can say the Q allele of PON1 Q192R polymorphism in infertile patients may be a risk factor for infertility, and QQ allele of the PON1 polymorphism created the lowest protection against LDL and HDL oxidation compared to other (QR, RR) allele PON1 polymorphisms. In the other hand, researches showed QR and RR genotypes of PON1 polymorphism had higher sperm progressive motility and normal morphology compared with the QQ genotype and men with R allele have higher sperm motility than carriers the Q allele (35). According to important role of PON1 and its polymorphisms in the pathogenesis of diseases such as Autism, Alzheimer's, Parkinson's, Schizophrenia, Depression and Endometriosis, we in this study investigation potential role of this 192QR polymorphic region of PON1 gene as one of the factors affecting upon infertility. For this aim, we evaluated PON1 genotype and allele distribution at fertile and infertility individual. Our founds indicated patients with QQ allele have higher plasma levels MDA and Arylesterase activity than the RR and QR alleles (p<0.05), Our founds indicated patients QQ allele had higher plasma levels MDA and Arylesterase than the RR, QR alleles (p<0.05), which in turn, approved the hypothesis low effect HDL antioxidant in patients with QQ allele, also explain why the Q allele may risk factor for infertility and individual with QR and RR genotype are less likely to have idiopathic infertility. The Q allele carriers of PON1 Q192R genotype have higher lipid peroxidation (higher plasma MDA levels) and Arylesterase activity than R allele carriers, which may describe the effect of various PON1 genotypes on sperm parameters (36-38). Therefore, the RR genotype of PON1 Q192R polymorphism by high antioxidant activity cause to improves motility and morphology of sperm and reducing lipid peroxidation. Nevertheless, other genes involved in the oxidative stress process, environmental factors and even other known polymorphisms of this gene can be considered and further investigated in the development of idiopathic infertility. So for obtaining definite results we are requires studies with grater statistical community. This result may change by alteration population size.

CONCLUSION

Results of this study indicated that QQ allele of PON1 Q192R polymorphism have positive relationship with development of idiopathic infertility among a population of Ahvaz men. Also, frequency QR and RR allele in infertile group was significantly lower than control group.

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Conflict of interest
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