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Original Article

Relationship Between the Paraoxonase 1 Gene Glutamine 192 to Arginine Polymorphism and Diabetes Mellitus in Ghanaian Subjects

Nii A. Aryee *[1], Steve A. Asante-Poku [1], Emmanuel A. Tagoe [2], Grace K. Ababio [1], Dorcas A. Muhyia Annan [3]

[1]Department of Medical Biochemistry, UGMS, University of Ghana, Accra, Ghana.
[2]Department of Medical Laboratory Science, SBHAS, University of Ghana, Accra, Ghana.
[3]Department of Vascular Biology and Molecular Pathology, Hokkaido University, Kita-Ku, Sapporo, Japan.

*Corresponding author: Nii A. Aryee; *naaryee@ug.edu.gh*

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Abstract

Introduction: The activity of human Paraoxonase 1 (PON1), an HDL-associated enzyme with anti-atherogenic properties, has been observed to be reduced in a number of diseases, including diabetes. This has partly been attributed to a PON1 Glutamine (Q)/Arginine (R) polymorphism at codon 192 of the PON1 gene. ***Aim:*** To determine the prevalence of PON1 Q192R polymorphism in Ghanaian patients with type 2 diabetes (T2DM), and it impact on lipid profiles of T2DM subjects. ***Methods:*** PON1 Q192R was genotyped in 112 individuals with type 2 diabetes mellitus (T2DM) and 97 nondiabetic control individuals, using polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) analysis. Other investigations determined using standard methods included fasting blood glucose (FPG), body mass index (BMI), lipid profile, atherogenic indices and hip-waist ratios. ***Results:*** The PON1 RR genotype found to be was the most common in both T2DM patients (74.6 %) and controls (57.1 %), whilst the QR genotype was the least frequent in both groups (7.3 % and 9.5% for T2DM and controls respectively). These genotype distributions were however not significantly different between the study groups. Allele frequencies in T2DM and the control groups were significantly different, with R allele being the most common in both T2DM patients and controls. The R allele was found to be increased in T2DM. The Q192R genotype does not consistently affect the lipid and lipoprotein concentrations of T2DM and healthy populations. ***Conclusion:*** The RR genotype was the most predominant in T2DM patients and healthy individuals within a Ghanaian population. The prevalence of the R allele in T2DM may have implications for the metabolism of oxidized lipoproteins as these oxidative modifications are central to the development of cardiovascular disease in T2DM.

Keywords: ***allele, Ghanaian, diabetes mellitus, paraoxonase 192 gene polymorphism, paraoxonase 1.***

Introduction

Paraoxonase 1 (PON1) is a calcium-dependent esterase enzyme, synthesized in the liver and secreted into plasma where it is tightly associated with high density lipoprotein (HDL) in blood [1], and plays a role in the metabolism of phospholipids, based on similarities in structure of organophosphates and phospholipids [2]. It is also known that PON1 hydrolyses many active metabolites of a number of organo-phosphorous insecticides, as well as the detoxification of neuro-toxic agents like sarin [3,4]. It has also been demonstrated that PON1 prevents oxidative modification of low- and high-density lipoproteins, which are atherogenic [5]. Human PON1 enzyme activity exhibits considerable inter-individual variation as a result of genetic and environmental factors [5,6]. Genetic factors that modulate the expression and catalytic activity of PON1 have mainly been consigned to polymorphisms in the coding and promoter regions of the PON1 gene [7-9]. A common single nucleotide polymorphism (SNP) in the coding region of the PON1 gene, which alters the PON1 phenotype is the Q192R Gln to Arg substitution [10]. This substitution leads to the formation of two isoforms that differ in Gln (Q) or Arg (R), at position 192 of the enzyme. It has been proposed that the PON1 R isoform hydrolyses paraoxon more efficiently than the Q isoform. Conversely, the PON1 Q isoform metabolizes either oxidized LDL (ox-LDL), or oxidized HDL (ox-HDL) more efficiently than the PON1 R isoform [11]. Investigations into the effect of the Q192R polymorphism on diabetes mellitus has often given inconclusive results. Nevertheless, there is evidence to show that serum PON1 activity is decreased in both insulin-dependent diabetes and non-insulin dependent diabetes [12]. The incidence of Type 2 diabetes mellitus (T2DM) is increasing worldwide, including in developing countries like Ghana due to sedentary lifestyles, urbanization, obesity, as well as an inclination for unhealthy diets [13,14]. Various factors, e.g. oxidative stress, genetics have been implicated in the development of diabetes and diabetic micro- and macro-vascular complications. Acting as an antioxidant, PON1 has been shown to reduce the susceptibility of T2DM patients to the

development of diabetic complications by slowing down lipid peroxidation in lipoproteins, mainly LDL and HDL [11,15]. Lipid peroxidation is a significant contributor to the onset of diabetic complications [16,17]. The ability of PON1 to work in this manner has been shown to be modulated by PON1 gene polymorphism and its phenotypic expression in an individual [11]. Therefore, investigation of common PON1 gene polymorphisms which modulate its activity and phenotypic expression may give insight on how the PON1 Q192R polymorphism cold modulate the pathogenesis of T2DM in the Ghanaian population. The aim of this study was therefore to determine the PON1 Q192R genotype distribution in a Ghanaian population with T2DM and determine its impact on the lipid profile of T2DM subjects.

Materials and Methods

Patients for this study were recruited from the Out-Patients' clinic of the National Diabetes Management and Research Centre (NDMRC) of the Korle-Bu Teaching Hospital, Accra. Type 2 diabetes mellitus (T2DM) was diagnosed according to the guidelines of the World Health Organization Consultation Report [18]. 112 Ghanaian T2DM patients, and a control group of 97 non-diabetic, healthy individuals with normal fasting blood glucose, and a negative family history of diabetes among first degree relatives constituted the study groups. Informed consent was obtained from all subjects. Venous blood samples were drawn after an overnight fast and distributed into fluoride, EDTA and gel separation tubes respectively. Plasma obtained from fluoride tubes after centrifugation at 4000 rpm for 10 min was used for fasting plasma glucose (FPG) analysis. Total cholesterol (TC), triglycerides (TG) and HDL cholesterol (HDL-c) were measured by automated enzymatic methods. LDL cholesterol (LDL-c) was calculated according to Friedewald formula [19].

DNA extraction and analysis

EDTA tubes were centrifuged at 3000 rpm for 20 min, and the buffy coat harvested for DNA extraction. Genomic DNA was isolated from leucocytes by Quick-gDNATM Blood MiniPrep DNA extraction kits (Epigenetics Company, USA). This genomic DNA was used as template for PCR amplification. PON1 genotypes were determined according to a previously published protocol [20] with slight modifications. For the Q192R polymorphism, sense primer, 5' TATTGTTGCTGTGGGACCTGAG 3' and antisense primer, 5' CACGCTAAACCCAAATACATCTC 3' (Eurogentec North America Inc., USA), which encompass the 192 polymorphic regions were used. The PCR mixture contained 100ng of DNA template, 0.5 µM of each primer, 1.5mM $MgCl_2$, 200 µM dNTP mixture and 1 U Taq DNA polymerase (Thermo Fisher Scientific Inc., USA). After denaturing the DNA for 5 min at 95 °C, the reaction mixture was subjected to 45 cycles of denaturing for 1 minute at 94 °C, 30 sec annealing at 61 °C, and 1 min extension at 72 °C. The 99bp PCR product was digested with 8 U BspPI (AlwI) restriction enzyme (Thermo Fisher Scientific Inc., USA) for 2 hours at 37 °C and the digested products separated by electrophoresis on 3% agarose gel, and visualized using ethidium bromide. The Arg (Q) genotype contains a unique AlwI restriction site which results in a 65 and a 34 bp product, whereas the Gln (R) genotype will not be cleaved by this restriction enzyme.

Ethical Approval

Institutional ethics approval was given by the Ethical and Protocol Review Committee of the College of Health Sciences (CHS), University of Ghana, with approval number MS-Et/M.3 - P5.6/2011 -12.

Statistical Analysis

Baseline characteristics, clinical and biochemical measurements were expressed as mean ± S. D. (standard deviation) for continuous variables, and as percentages for categorical variables. Comparisons between T2DM and controls was done using students' t-test. Allele frequencies in different groups were compared by gene counting and chi-squared ($\chi 2$) analysis. Student s' t-test, ANOVA were used to compare mean values of continuous variables in cases and control, whereas chi-squared ($\chi 2$) analysis was used to compare categorical data. All analyses were performed with SPSS statistical software for windows, version 16.0 (SPSS Inc., Chicago Illinois, USA).

Results

Baseline characteristics of the two study groups are shown in Table 1.

Table 1: Baseline characteristics of the study population

Variable	Controls (n = 97)	T2DM (n = 112)	*p*-value (*t*-test)
Age (years)	50.04 ± 10.46	55.27 ± 11.89	0.8830
BMI (kg/m^2)	27.05 ± 7.60	28.72 ± 7.18	0.1042
SBP (mmHg)	120.94 ± 24.22	127.07 ± 19.51	0.0441
DBP (mmHg)	69.86 ± 15.42	75.00 ± 10.27	0.0045
Waist-Hip Ratio	0.90 ± 0.10	0.90 ± 0.20	1.0000

Values are presented as means ± standard deviation; $p < 0.05$ was considered statistically significant. BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure

TD2M patients were not significantly different from the control group with respect to age, BMI and waist-hip ratio. TD2M patients however had significantly higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) than controls.

Biochemical variables of the two groups are presented in Table 2.

Table 2. Clinical and Biochemical variables of the study population

Variable	Controls (n = 97)	T2DM (n = 112)	*p*-value (*t*-test)
FPG (mmol/L)	5.27 ± 1.19	9.96 ± 4.75	0.0001
TC (mmol/L)	4.35 ± 1.25	5.38 ± 1.88	0.0001
HDL-c (mmol/L)	1.28 ± 0.41	1.27 ± 0.38	0.8551
LDL-c (mmol/L)	2.74 ± 1.43	3.48 ± 1.84	0.0015
TG (mmol/L)	0.90 ± 0.49	1.40 ± 0.44	0.0001
Atherogenic index	2.89 ± 2.09	3.68 ± 2.46	0.0139

Values are presented as means ± standard deviation; p < 0.05 was considered statistically significant. FPG= Fasting plasma glucose; TC = Total cholesterol; HDL-c = High density lipoprotein cholesterol; LDL-c = Low density lipoprotein cholesterol; TG = Triglycerides; Atherogenic index = [(TC-HDL-c)/HDL-c].

There was no significant difference in HDL-c levels between TD2M patients and the control group. However, FPG, TC, TG, LDL-c and atherogenic indices for TD2M patients were significantly higher than that of the control group.

Table 3 shows results of the genotype distribution and allele frequencies in the studied groups.

Table 3: Genotype and allele frequencies of the study population

Genotype	Controls (N = 42) n (%)	T2DM (N = 55) n (%)	χ^2	*p*-value
RR	24 (57.14)	41 (74.55)	3.26	0.084
QQ	14 (33.33)	10 (18.18)	2.94	0.101
QR	4 (9.52)	4 (7.27)	NA	NA
Allelic Frequency				
Allele	**Controls n (%)**	**T2DM n (%)**		
R	52 (62.00)	86 (78.20)	6.15	0.016
Q	32 (38.00)	24 (21.80)	6.15	0.016

n= frequency of alleles/genotype. NA= sample too small for χ2 analysis. p < 0.05 was considered statistically significant.

Frequencies of PON1 192 genotypes RR (Arg/Arg), QQ (Gln/Gln) and QR(Gln/Arg) were 0.75, 0.18 and 0.07 among T2DM patients, and 0.57, 0.33 and 0.10 among controls. The RR genotype was the most common in both T2DM patients and controls, whilst the QR genotype was the least frequent in both groups. These genotype distributions were however not significantly different between the study groups ($\chi2$ = 3.432, P = 0.1798). The R allele was the most common in both T2DM patients and controls, but was more prevalent in T2DM than in controls (75 % in T2DM patients compared to 57 % in controls). Allele frequencies in T2DM and the control groups were significantly different.

Table 4 shows a comparison of lipid variables among the genotypes of T2DM patients and controls.

Table 4: Comparison between PON1 Q192R genotypes and lipid variables within the type 2 diabetic and control populations

Variable	T2DM			*p*-value (ANOVA)	Controls			*p*-value (ANOVA)
	QQ (n = 10)	RR (n = 41)	QR (n = 4)		QQ (n = 14)	RR (n = 24)	QR (n = 4)	
TC (mmol/L)	4.90 ± 1.45	5.68 ± 2.14	5.32 ± 0.82	0.530	4.32 ± 0.82	4.82 ± 1.45	3.50 ± 0.97	0.120
HDL-c (mmol/L)	1.19 ± 0.21	1.31± 0.41	1.11 ± 0.25	0.445	1.17 ± 0.44	1.24 ± 0.39	1.02 ± 0.29	0.576
LDL-c (mmol/L)	3.04 ± 1.25	3.75 ± 2.05	3.46 ± 0.72	0.560	2.73 ± 0.99	3.19 ± 1.62	2.07 ± 1.25	0.287
TG (mmol/L)	1.46 ± 0.25	1.39 ± 0.45	1.63 ± 0.30	0.517	0.93 ± 0.60	1.00 ± 0.62	0.91 ± 0.28	0.921

Values are presented as means ± standard deviation; p < 0.05 was considered statistically significant. TC = Total cholesterol; HDL-c = High density lipoprotein cholesterol; LDL-c = Low density lipoprotein; TG = Triglycerides.

Within both groups (T2DM and control), the RR genotype had insignificantly higher TC, HDL-c and LDL-c, but lower TG levels compared to QQ and QR genotypes. TG level was highest for the QQ genotype within the T2DM group. However, in the T2DM group, the QR genotype had the lowest HDL-c and LDL-c, but the highest TG level, whereas the QQ genotype had the lowest TC. For the control group, the RR genotype had insignificantly higher TG than the QR and QQ genotypes. The QR genotype had the lowest TC, HDL-c and LDL-c. These differences were statistically insignificant.

Discussion

Although PON1 Q192R genotype distribution has been determined in some other populations [21], there is no report we know of that has documented this in a Ghanaian T2DM population. From this study we expect give insight into the influence of PON1 Q192R polymorphism on selected lipid variables in T2DM patients. As results from our study show, T2DM patients were found to have higher BMI, SBP, DBP, than controls. T2DM subjects also had higher FPG, TC, LDL and atherogenic indices than the control group. A common polymorphism in the coding region of the PON1 gene, Q192R has been proposed as a genetic susceptibility factor to the development of diseases such as T2DM [22]. In this study, the RR genotype was found to be the most common in both T2DM patients and controls, whereas the QR genotype was the least frequent in both T2DM patients and healthy controls. We found no significant differences in the distribution of these PON1 Q192R genotypes between T2DM patients and healthy controls. Our results are consistent with those from a study in Egypt, which found the RR genotype to be the most frequent, and the QR genotype the least common in T2DM patients, and healthy individuals from the same population [23]. In the above-mentioned cited study and ours, T2DM patients with complications were not included in the study. Our results are however inconsistent with those of El Fasakhany (2007) who from an earlier study of another Egyptian population, found the QQ genotype to be the most frequent in both T2DM patients and healthy individuals, and the RR genotype to be least common in both groups [24]. This inconsistency could result from differences in sample size, as the sample sizes of the studies pertaining to the Egyptian populations and ours are different. A number of reports on PON1 192 gene polymorphism have described the QQ genotype to be most common in T2DM [11,25]. These studies, it appears have mainly looked at Caucasian populations. Significant differences in the allele frequencies between T2DM patients and the control population have been reported by Agachan et al. [25]. The R allele it has been suggested, is more active in hydrolysing paraoxon than the Q isoform, but shows reduced efficiency when it comes to

metabolizing either ox-LDL, or ox-HDL [11]. The prevalence of the R allele may have implications for the metabolism of oxidized lipoproteins, as these oxidative modifications could be central to the development of cardiovascular disease in T2DM.

Conclusion

The RR genotype was predominant in T2DM patients and healthy individuals within the studied population. The study also demonstrated that the Q192R genotype may not consistently modulate lipid and lipoprotein concentrations of T2DM and healthy populations. Additional studies in more localities may be required to establish the frequency of the Q192R polymorphism, and other common PON1 gene polymorphisms in the Ghanaian population.

Disclosures

Human subjects

Consent was obtained or waived by all participants in this study. Ethical and Protocol Review Committee of the College of Health Sciences (CHS), University of Ghana issued approval MS-Et/M.3 - P5.6/2011 - 12. Institutional ethics approval was given by the Ethical and Protocol Review Committee of the College of Health Sciences (CHS), University of Ghana, with approval number MS-Et/M.3 - P5.6/2011 - 12.

Animal subjects

All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest

In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services information

All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships

All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships

All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Availability of data and materials

Not applicable.

Authors' contributions

Nii Ayite Aryee conceived, designed and supervised the study. Grace Korkor Ababio Emmanuel Ayitey Tagoe and Steve Asante-Poku provided additional supervision. Material preparation, data collection and experiments were performed by Dorcas Muhyia-Annan. The final manuscript was written by Ni Ayite Aryee. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

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