Original Paper

Impact of the C1431T Polymorphism of the Peroxisome Proliferator Activated Receptor-Gamma (PPAR-γ) Gene on Fasted Serum Lipid Levels in Patients with Coronary Artery Disease

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Abstract

Background/Aims: The C1431T polymorphism of peroxisome proliferator activated receptor-γ (PPAR-γ) gene is related to diabetes and metabolic-syndrome. However, studies have been inconclusive about its association with coronary artery disease (CAD) and there have been no studies analyzing the association of this polymorphism with fasted-serum-lipid levels in Iranian-individuals with CAD. We investigated the association of PPAR-γ C1431T-polymorphism with CAD and dyslipidaemia in 787 individuals. ***Methods:*** Anthropometric-parameters and biochemical-measurements were evaluated, followed by genotyping. The association of the genetic-polymorphisms with CAD and lipid-profile was determined by univariate/multivariate-analyses. ***Results:*** Patients with CT or CT+TT genotype were at an increased-risk of CAD relative to CC-carriers (adjusted odds ratio: 2.03; 95% confidence interval, 1.01–4.09; p = 0.046). However, in the larger population, CT genotype was present at a higher frequency in the group with a positive angiogram. Furthermore, CT+TT genotypes were associated with an altered fasted-lipid-profile in the initial population sample of patients with a positive angiogram, compared to the group

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with a negative-angiogram. The angiogram-positive patients carrying the T allele had a significantly higher triglyceride, serum C-reactive protein and fasting-blood-glucose. **Conclusion:** We have found the PPAR-γ C1431T polymorphism was significantly associated with fasted serum lipid profile in individuals with angiographically defined CAD. Since accumulating data support the role of PPAR-γ polymorphisms in CAD, further studies are required to investigate the association of this polymorphism with coronary artery disease.

Introduction

Peroxisome proliferator activated receptor (PPAR) is a family of ligand-activated transcription factors of the nuclear hormone receptor superfamily that comprise three subtypes: PPAR-α, PPAR-γ and PPAR-β [1, 2]. It has been shown that PPARγ plays a key role in controlling lipid and glucose metabolism, and is known to be associated with metabolic diseases such as hyperlipidemia, diabetes mellitus and coronary artery disease (CAD) [3–12].

A common variant of the PPAR-γ gene is the C161T polymorphism (also known as C1431T) that is characterized by C to T substitution at position 161 in exon6 [13]. The PPAR-γ C161T is associated with an unfavorable lipid profile with an increased risk of CAD in diabetes mellitus, obesity and metabolic syndrome [3, 13–20]. Wang et al. showed that the PPAR-γ C161T polymorphism was associated with a reduced risk of CAD [16], but several subsequent reports have been inconsistent [21, 22]. Furthermore, no studies have reported the association of the C1431T polymorphism with CAD risk in the Iranian population, as a country with high prevalence of CAD. The present study was designed to evaluate the potential implication of PPAR-γ C1431T polymorphism in 787 subjects with and without coronary artery disease.

Materials and Methods

Study Population

In the current cross-sectional study, 2 categories of patient population were recruited from 2 different hospitals of Mashhad University of Medical Science, Mashhad, Iran. CAD patients, who underwent coronary angiography, were divided into two groups: those with <50% stenosis and those with ≥50% stenosis. The presence of CAD was established by angiographic evidence of stenosis in epicardial coronary artery of >50% diameter. Patients with renal, heart or acute infectious diseases, pregnant patients and also history of past angiography were excluded. The study was approved by the local Hospital Ethic Committees.

Biochemical Analysis

Anthropometric parameters such as height, weight, body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP) and diastolic blood pressure (DBP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), fasting blood glucose (FBG) and serum C-reactive protein (CRP) were measured in all the subjects using standard procedures as described previously [23].

Genotyping

Genomic DNA was extracted from blood samples using the QIAamp® DNA Mini-Kit according to the manufacturer's protocol (Biogene, Mashhad, Iran). Genotype analysis of rs3856806 polymorphism was performed, using the following primers: forward primer: CTGTTTGCCAAGCTGCTCC, reverse primer: GAGCGGGTGAAGACTCATGTC, Probe #1 (Fam labelled): ATTGTCACGGAACACGT-GCAGCTACT, Probe #2 (Tet labelled): ATTGTCACGGAACATGT-GCAGCTACT. The Rotor-Gene 6000-Corbett or ABI-StepOne instruments (Applied Biosystems) equipped with the SDS version 2.0 software was employed to evaluate the allelic content of the samples.

Statistical Analysis

Data were analyzed using SPSS 20 software (SPSS Inc., Ill., USA). The normality of distribution was determined using the Kolmogorov-Smirnov test. Descriptive statistics including mean, frequency, and standard deviation (SD) were determined for all variables and was expressed as mean ± SD for normally distributed variables (or as the median and IQR for not normally distributed variables). For normally distributed variables, the t-student test was used to compare the clinical characteristics and baseline demographics between the groups. A Bonferonni correction was applied for multiple comparisons. The Mann-Whitney U test was used for continuous variables if they were not normally distributed. Chi-square or Fisher exact tests were used for categorical variables. Odds ratios (ORs) with 95% confidence interval (CI), adjusted for age, gender and genotype, were calculated by comparing each phenotype to wild type through binomial logistic regression analysis. All the analyses were two-sided and statistical significance was set at $p < 0.05$.

Results

Characteristics of the Populations

These analyses illustrated that patients with angiographic evidence of stenosis in epicardial coronary artery of >50% diameter (Angio+) had a significantly higher BMI, WC, weight, FBG, hsCRP, TG, SBP and DBP ($p < 0.05$). The differences between angiogram negative and positive groups in both groups were detected for gender,

age, serum hsCRP, HDL, TC and FBG (table 1). Similar results for FBG, hsCRP, TG, SBP and DBP were identified in the larger population (comprising the initial and expanded sample) between control and angiogram positive groups (table 1).

PPAR-γ C1431T Polymorphism and CAD

To investigate whether there was any relationship between CAD and PPAR-γ polymorphism, we performed genotyping using genomic DNA extracted from peripheral blood samples. The distribution of genotypes was in accordance with the Hardy-Weinberg equilibrium, as calculated with the SNP analyzer software. The wild-type PPAR-γ C1431T genotype (CC) had a frequency of 74%, whereas the CT and TT genotypes were found in 21.4 and 4.6% of the patients (Angio-positive), respectively. Moreover, the frequencies of the CC, CT, and TT genotypes in the angiogram negative group were 86.7, 11.7 and 1.6%, respectively. Moreover, individuals with PPAR-γ CT genotype or CT+TT genotypes were overrepresented in the angiogram positive group, with an OR of 2.13 (95% CI: 1.1–4.2; p = 0.03) or 2.28 (95% CI: 1.2–4.3; p = 0.012), respectively (table 2). Additionally, further adjustment for age, gender and smoking habit did not change the magnitude of the association. Similar results were observed when all the CAD patients with angiographic evidence of more and less than 50% stenosis in epicardial coronary artery were combined. Subjects with CT genotype or CT+TT genotypes had an OR of 1.91 (1.09–3.63) or 1.90 (1.03–3.47), respectively (p < 0.05; see online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000381358).

We have also investigated the association of this polymorphism in a larger population. This analysis showed the genotype frequencies of 29.9, 67.6 and 2.5% for CC, CT, and TT genotypes for patients samples, respectively, while these frequencies in control group were 31.3, 66.1 and 2.6% for CC, CT, and TT genotypes, respectively. However, analysis of the association of the polymorphisms with CAD using logistic regression model in the larger population suggested the lack of its relationship with CAD (data not shown).

We then explored the association of the genotypes of the first population with lipid profile. This data showed that CG+GG genotypes were significantly associated with increased levels of TG, FBG and hsCRP in subjects with Angio+, compared to the control group (fig. 1a–c). However, this analysis did not remain statistically significant in larger population.

Table 1. Baseline characteristics of the individuals with and without coronary artery disease

Characteristics	First population						Total population					
	control (n = 128)	Angio– (n = 110)	Angio+ (n = 131)	p¹	p²	p³	control (n = 285)	Angio– (n = 221)	Angio+ (n = 281)	p¹	p²	p³
Age, years	49.7±9.2	52.1±10.7	57.7±11.4	0.195	<0.001	<0.001	54.1±9.6	054.3±11.9	59.1±10.3	0.987	<0.001	0.001
Gender, male, n (%)	59 (46.1)	35 (31.5)	78 (59.5)	0.024	0.035	<0.001	82 (52.2)	37 (33.3)	82 (54.7)	0.02	0.665	0.001
BMI, kg/m²	25.4±3.6	26.3±4.8	27.4±4.67	0.249	0.001	0.108	25.9±3.7	27.1±4.6	26.7±4.6	0.075	0.214	0.803
Weight, kg	65.2±10.4	67.7±14.2	70.83±13.3	0.284	0.001	0.141	67.6±12.0	69.3±13.1	69.0±13.1	0.533	0.593	0.984
HC, cm	97.8±8.2	98.9±7.9	99.7±9.3	0.595	0.192	0.760	98.5±5.9	100.4±8.4	100.3±8.5	0.110	0.087	0.998
WC, cm	86.2±10.9	91.9±11.5	94±12.1	<0.001	<0.001	0.336	91.4±11.1	94.3±13.0	94.0±12.3	0.131	0.142	0.981
TC, mg/dl	192.4±35.2	176.8±48.2	163.8±43.3	<0.001	<0.001	0.027	191.6±40.6	167.5±45.2	173.1±42.9	<0.001	<0.001	0.296
TG, mg/dl	94 (70–121)	132 (103–144)	143 (104–164)	<0.001	<0.001	0.051	120 (81–171)	131 (99–140)	143 (109–169)	0.434	0.001	0.001
HDL, mg/dl	43.9±9.1	43.0±11.4	40.4±14.4	0.505	<0.001	0.003	42.2±10.1	41.8±9.1	42.1±18.1	0.794	0.948	0.843
LDL, mg/dl	119.4±33.5	105.2±38.7	95.2±33.6	<0.001	<0.001	0.072	123.5±34.9	97.9±37.1	102.0±34.9	<0.001	<0.001	0.360
FBG, mg/dl	83.4±22.3	117.2±59.1	133.8±66.4	<0.001	<0.001	0.005	84.4±22.9	120.2±53.1	136.7±63.3	<0.001	<0.001	0.007
SBP, mm Hg	117.6±14.9	135.8±24.4	141.1±27.0	<0.001	<0.001	0.135	124.9±18.4	131.1±22.9	134.0±25.8	0.027	<0.001	0.299
DBP, mm Hg	73.7±9.3	82.4±11.3	84.4±12.6	<0.001	<0.001	0.141	73.3±10.7	80.3±11.6	81.9±11.8	<0.001	<0.001	0.248
hsCRP, mg/dl	1.5 (0.9–3.4)	4.3 (1.6–4.95)	5.5 (2.1–6.5)	<0.001	<0.001	0.003	1.3 (0.9–1.8)	4.6 (2.4–5.2)	5.9 (2.3–6.6)	<0.001	<0.001	0.004

Values are expressed as mean ± SD, median and interquartile range for normally and non-normally distributed variables, respectively. BMI = Body mass index; WC = waist circumference; TC = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; FBG = fasting blood glucose; HC = hip circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure. ¹ Comparison between the control and Angio– group. ² Comparison between the groups of control and Angio+. ³ Comparison between the groups of Angio– and Angio+. Total population (787 subjects) includes first cohort (369 subjects) plus second cohort (418 subjects) from different hospitals of Mashhad city.
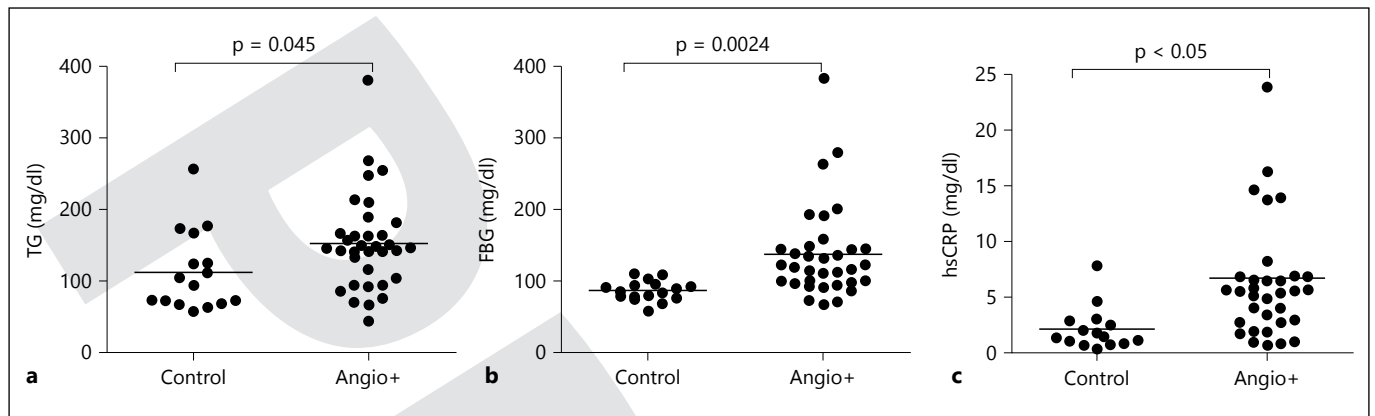
Fig. 1. Association of PPAR-γ C1431T polymorphism with serum TG, FBG and hsCRP in subjects with angiographically defined CAD. Association of (**a**) TG, (**b**) FBG and (**c**) hsCRP levels with CAD patients (angiographic evidence of stenosis in epicardial coronary artery of >50% diameter (Angio+)) with C1431T-CG+GG genotypes versus control group.

Table 2. Association of C1431T and coronary artery disease in first cohort

	Angio–	Angio+	Odds ratio (95% CI)	p value	Odds ratio (95% CI)*	p value*
rs3856806	128	131				
CC	111 (86.7)	97 (74)	Ref cat			
CT	15 (11.7)	28 (21.4)	2.13 (1.07–4.23)	0.030	2.09 (0.99–4.41)	0.052
TT	2 (1.6)	6 (4.6)	3.43 (0.67–17.40)	0.136	1.74 (0.32–9.31)	0.514
CT+TT	17 (13.3)	34 (26)	2.28 (1.20–4.35)	0.012	2.03 (1.01–4.09)	0.046
HWE	0.249	0.138				
C	237 (93)	222 (85)	Ref cat			
T	19 (7)	40 (15)	2.24 (1.26–3.99)	0.006		

Ref cat = Reference category; CI = confidence interval; HWE = Hardy-Weinberg equilibrium. Logistic regression analysis was used to calculate association of polymorphisms and CAD. * After correction for age, sex, HDL, FBG and TC.

Discussion

Coronary artery disease (CAD) is one of the major health problems [25, 26], which is characterized by the presence of atherosclerotic plaques in epicardial coronary arteries, that progressively narrow the coronary artery lumen and impair blood flow. Defects in insulin signaling could lead to insulin resistance that is associated with obesity, type 2 diabetes mellitus and CAD. It has been shown that peroxisome proliferator activated receptor-gamma (PPAR-γ) promotes insulin-stimulated tyrosine phosphorylation of tyrosyl phosphorylation of insulin receptor substrate 1/2 and PI3K activity associated with insulin receptor substrate proteins [27].

There is a growing body of evidence showing an association between the PPAR-γ polymorphism with CAD [15, 28, 29]. Our recent study found associations between this polymorphism and their haplotypes with susceptibility to metabolic syndrome as an increased risk factor of CAD [17, 30]. Similarly, Liu and colleagues recently showed that C161T polymorphisms were associated with some important risk factors for cardiovascular disease in hemodialysis patients in the Han Chinese population [31]. In contrast with these observations, a recent meta-analysis showed that PPAR-γ C161–>T substitution was associated with a reduced CAD risk in Chinese population but not among Caucasians [32]. Zhou et al. showed that this polymorphism was associated with decreased risk of CAD in Chinese Han population [15]. On the other hand, several other studies have reported inconsistent data [5, 14, 28, 29]. In particular, Vats and colleagues showed the lack of association between the allelic

and genotypic frequencies of cases and controls [14]. This lack of a relationship might be explained at least in part by variations in the life style, diet, small sample size, ethical background and/or medication. Therefore, in the present study we investigated the relationship between C1431T polymorphism of PPAR-γ gene and CAD in an Iranian population.

To the best of our knowledge, this is the first study evaluating the role of PPAR-γ polymorphism and its relationship with lipid profile in Iranian patients with CAD, a group that has a high prevalence of CAD. We observed that patients with CT+TT genotypes were at an increased susceptibility to CAD with OR of 2.28 (95% CI: 1.2–4.3; p = 0.012) in our initial population sample. However, we found that this relationship did not remain significant for the larger population sample. This is consistent with, a recent meta-analysis demonstrated the lack of association of PPAR-γ C1431T polymorphism with CHD susceptibility [33]. Of note, a recent report by Grugni and colleagues showed that the Iranian population is highly diverse, as measured through Y chromosome haplogroup analysis [34]. This diversity might also to be present in autosomal chromosomes which would impact the disease association studies in the Iranian population.

We observed that CAD patients of the original cohort with CT+TT genotypes had a significantly higher level of TG, FBG and hsCRP, compared to the control group. In agreement with these observations, several recent studies have shown the effects of the C161T polymorphism on lipid profile and apolipoprotein ratios [19, 20, 29, 35]. Additionally, several other studies showed the associations of other polymorphisms of PPAR-γ with lipid parameters, such as TG, TC, LDL and HDL [36–40]. In particular, Zhou and colleagues showed that this polymorphism was associated with a higher HDL-C level and a lower blood glucose level in CAD patients [15, 39].

A major strength of the present study is that it was performed in a large number of individuals and provides a new insight regarding the relationship between PPAR-γ C1431T polymorphism and its association with lipid profile. Conversely, the main limitation of this study is cross-sectional study design. In addition, subjects with Angio– had a significantly different mean age with respect to the Angio+ group; however, this variable was adjusted in logistic regression model and multivariate analysis for exploring the role of this polymorphisms and CAD.

In conclusion, we illustrate the important role of PPAR-γ C1431T polymorphism with lipid profile in CAD. Since accumulating data is supporting the role of PPAR-γ polymorphisms in CAD, further studies are required to investigate the association of this polymorphism with coronary artery disease.

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Disclosure Statement

The authors have no conflict of interest to disclose.

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