The common PPARγ2 Pro12Ala polymorphism is associated with an increased risk of coronary artery disease (CAD) in Iranian patients with type 2 diabetes mellitus

Leila Saremi
Islamic Azad University
Shirin Lotfipanah
Farhangian University
Fatemeh Feizy
Hamedan University of Medical Science
Fatemeh Rostami Avval
Tarbiat Modares University
Zohreh Saltanatpour (zohreh_saltanatpour@yahoo.com)
Tehran University of Medical Sciences

Research

Keywords: coronary artery disease (CAD), Type 2 diabetes (T2DM), PPARγ gene, Pro12Ala

Posted Date: May 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-27376/v1

Abstract

Background. Type 2 diabetes (T2DM) is a risk factor for coronary artery disease (CAD) in patients with type 2 diabetes compared with subjects without diabetes. Many studies have been shown that CAD has resulted from the interaction of genetic markers implicated in dyslipidaemia and oxidative stress. The PPARγ gene is considered as a potential candidate gene for the link between diabetes mellitus and CAD in patients with diabetes mellitus. The purpose of the present study was to determine the association of Pro12Ala PPARγ2 polymorphism (rs1801282) with CAD in Iranian patients with T2DM.

Methods. We studied 290 unrelated Iranian subjects, including 145 healthy controls and 145 CAD patients with a history of T2DM. Genomic DNA was isolated from peripheral blood, and the PPARγ2 gene mutations were analyzed using the PCR–RFLP technique.

Results. Our results revealed a significant difference between the allele frequencies of PPARγ2 Pro12Ala polymorphism between the case and control subjects. However, no significant association was observed between Pro12Ala genotypes and physiologic variables.

Conclusion. In summary, it could be concluded that PPARγ2 Pro12Ala polymorphism may be an essential indicator of the increased risk of CAD in diabetic patients among the Iranian population.

Trial Registration. This article does not contain any studies with human participants by any of the authors.

Background

Coronary artery disease (CAD) is one of the cardiovascular complications of diabetes mellitus [1]. The risk of CAD for Type 2 diabetes mellitus (T2DM) patients is at least two to three times the risk in nondiabetic subjects [2]. Current data show that more than 75% of T2DM patients die as a consequence of cardiovascular diseases, including CAD in under-developed and developing countries[3]. Several studies have reported that CAD results from the interaction of environmental factors, such as lifestyle, obesity, smoking and sedentary life, and genetic factors. Several genetic variants implicated in dyslipidaemia and oxidative stress include proliferator-activator receptor gamma (PPARγ) and Cytochrome P450 (CYP) family[4-6].

Peroxisome proliferation-activated receptor (PPARs) belongs to the superfamily of nuclear receptors and has three isotypes, namely α, β and [7-9]. Of the three isoforms, PPARγ functions as the master regulator of glucose homeostasis, lipoprotein metabolism, and recent studies reported that it implicates various metabolic diseases such as diabetes mellitus, hyperlipidemia, and CAD [7, 10, 11]. Alternative use of PPARγ gene promoters and differential splicing of the PPARγ mRNA results in two isoforms γ1 and γ2 (major isoforms) and γ3 and γ4 (minor forms), which differ at their N terminus [12, 13]. The PPARγ2 is mostly expressed in adipose tissue; this characteristic is suggested that the role of PPARγ2 in CAD could

be mediated through its effects on adipogenesis regulation, lipid storage, insulin, and glucose metabolism [9, 13].

The most common single nucleotide polymorphism (SNPs) in the human PPARγ2 gene is the cytosine-guanine variation (rs1801282C > G) located in exon B which results in a change of proline into alanine at amino acid residue 12 (Pro12Ala)[[4, 10, 14]. This polymorphism was first identified by Yen et al. in 1997 and reduced the transcription of PPARγ2 [12, 15]. Up to now, many studies have been performed to explore the association between this mutation and complex traits, such as insulin sensitivity, obesity, T2DM, and CAD, but data are inconsistent [12, 16-19]. Association of the PPARγ2 Pro12Ala polymorphism (rs1801282) with CAD events has not been so consistently replicated, perhaps due to coronary artery disease complexity and heterogeneity among subjects.

In this study, we evaluated the correlation between the PPARγ2 Pro12Ala polymorphism (rs1801282) with coronary artery diseases (CAD) in Iranian patients with T2DM.

Methods

Study population

Our study included 290 unrelated Iranian subjects with an average age of 52, were consecutively recruited from Shahid Rajaei Cardiovascular Medical and Research Center in Tehran, Iran [1, 20]. The patients included 72 men and 73 women with coronary artery disease (CAD) and a history of diabetes. The diagnosis of CAD was confirmed by coronary angiography. Exclusion criteria for these patients were the presence of cardiomyopathy, diabetes mellitus, collagenases, infections or inflammatory diseases, chronic obstructive pulmonary disease, chronic liver disease, chronic alcohol abuse, thyroid disease, and drug abuse. The selection criteria also included no history of myocardial infarction (MI), coronary intervention, renal hemodialysis or organ transplantation, and stroke. The healthy control consisted of 71 men and 74 women with neither CAD nor the familial history of diabetes.

In the present study, traditional risk factors were characterized according to the standards and recommendations advocated by the European Society of Cardiology [21]. Height (cm), weight (kg), body mass index (BMI) ( ). Hypertension was considered present if the systolic pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg or if patients were treated with antihypertensive drugs. All participants had plasma glucose level ≥ 6.95 mmol/L in the fasting state. Hypercholesterolemia was established if total cholesterol serum levels were ≥5 mmol/L or if the patients were undergoing treatment with the cholesterol-lowering drug. The clinical features of the study participants are given in Table 1. Each participant gave informed consent, and the institutional ethics committee approved the study. After inclusion, Clinical and laboratory findings were collected for each CAD patients from the clinical charts. In the present study, fallowing variables including Fasting Blood Sugar (FBS), total serum cholesterol (TC), Creatine (Cr), Triglyceride (TG), high-density lipoproteins (HDL), low-density lipoproteins (LDL), microalbumin, and hemoglobin A1c (HbA1c) were considered and analyzed.

DNA extraction and genotyping

DNA was purified from venous blood samples by using Bioneer's DNA Extraction-USA kit. PCR amplification and PCR–restriction fragment length polymorphism (RFLP) analysis were performed to evaluate the prevalence of mutations in the PPARγ2 gene in the patient and control groups. The primers used for amplification of the Pro12Ala (CCG-GCG) SNP were 5'-TGTCTTGACTCATGGGTGTATTC-3' as the forward primer and 5'-ATCAGTGAAGGAACCGCTTT-3' as the reverse primer. A mixture of 100ng of genomic DNA, 0.5 of dNTP, 2.5 10X PCR buffer, 0.8 of , 2 units of Taq polymerase, and 0.5 of each primer (10 pmol) was used at a total volume of 25 . The PCR reaction was carried out as follow: 95 for 5 minutes, then 30 cycles of 95 for 30 seconds, 57.4 for 30 seconds, and 72 for 30 seconds. Then it was followed by incubation at 72 for 5 min. The PCR amplification was digested by restriction endonuclease Bs1I (Fermentas) and the restriction site was confirmed in a 2% agarose gel. The Pro12 allele (homozygote) produced two fragments with sizes 23 and 162-bp, the Ala12 allele (heterozygote) produced only a single 185-bp fragment (Figure 1).

Statistical analysis

SPSS version 12.0 software (SPSS, Chicago, IL, USA) was used to analyze the clinical data. The was used to genotypic and allelic distributions in both groups and continuous variables by Students' t-test. The association between CAD and gene polymorphism were calculated using odds ratios (OR) with confidence interval (95% CI). Data were expressed as means ± standard deviation (SD) for continuous variables and p values of less than 0.05 were assumed to be significant for all tests.

Results

Analysis of allele and genotypes distribution of Pro12Ala PPARγ2 gene SNPs in CAD patient and control subjects are shown in Table 2.

Analysis of the associations between the Pro12Ala polymorphisms and physiologic variables are shown in Table 3. After genotyping, the effects of the Pro12Ala (rs1801282) polymorphisms on quantitative and categorical variables were analyzed. As can be shown in Table 2, in the CAD patients, 30% of the subjects were of the CC genotype (Pro), and 70% were of the GC genotype (Pro/Ala). In the control groups, 53.3% of the subjects were of the CC genotype, and 46.7% of subjects had the GC genotype. When compared with CC genotype, the heterozygote GC genotype was associated with a significantly increased risk of CAD ($p<0.01$) (adjusted odds ratio (OR)= 2.66, 95% confidence interval (CI) = 1.5-29.5).

We further analyzed the associations between Pro12Ala polymorphism and physiologic variables, which are shown in Table 3. The results showed that there was no significant difference between CC and GC genotypes in CAD patients and controls were detected in FBS, lipid profile (TG, TC, LDL-C, HDL-C), micro albuminuria, BMI, Cr, and HbA1c levels were noticed. It could be concluded that there is no association between the Pro12Ala mutation and these physiologic variables in both groups.

Discussion

CAD is the most common cause of death among diabetic patients. Adult diabetic patients have an increased risk of mortality due to heart disease and stroke from 2-4 times more than those without diabetes [22]. Dyslipidemia, obesity, and hypertension are the leading cause of elevating the risk for CVD observed in T2DM patients [1, 23]. The identification of genetic markers implicated in dyslipidaemia and oxidative stress, such as the PPARγ gene, is one possible approach to determine an individual risk profile.

PPARγ is express in all significant cells of the vasculature: vascular smooth muscle cells, human endothelial cells, and macrophages [24, 25]. Furthermore, PPARγ has a significant role in lipoprotein metabolism, vascular homeostasis, and glucose homeostasis [14, 26]. Therefore PPARγ is a potential candidate gene for the link between diabetes mellitus and CAD in patients with diabetes mellitus, and its variation has been reported associated with several metabolic syndromes such as T2DM, cardiovascular diseases (CVD) and hyperlipidemia [12]. Although some studies have been conducted to investigate the association between the PPARγ2 Pro12Ala polymorphism and CAD risk, the results obtained from these studies have remained conflicting [10, 14, 27-30]. Therefore, we carried out this work to further explore the association between the PPARγ2 Pro12Ala polymorphism and the risks of CAD.

The idea of this study was based on determining a genetic marker for early detection or prediction of CAD in diabetic patients and in the current study based on Iranian population, we found that the common variant of PPARγ2, rs1801282 (c.34C>G, Pro12Ala), is significantly associated with higher CAD risk. Our findings are in agreement with various studies that carried out in different populations and ethnic groups. Hasan et al. (2017) reported that PPARγ Pro12Ala polymorphism was associated significantly with the development of CAD in T2DM Egyptian subjects [12]. They are also suggested that the SNP at the Pro12Ala was associated with BMI, weight, DBP, SBP, and LDL in patients suffering from CAD with or without T2DM. However, our report demonstrates that there is no significant difference between this polymorphism and physiologic variables in both patient and control groups. Wu, Z et al. (2012) performed a meta-analysis and indicated that the Pro12Ala polymorphism might be a risk-conferring locus for the progression of CAD in the Caucasians population, but not among Asians and other population [10]. In an American study, Pischon et al. (2005) demonstrated that the Ala12 allele had a significantly increased risk for CAD and that these results were more significant in overweight (but not normal weight) subjects, suggesting that the involvement of PPARγ Pro12Ala polymorphism in the vasculature might occur in association with obesity [19]. These results suggest a high possibility of involvement of Pro12Ala polymorphism in the occurrence and risk for CAD in patients with T2DM.

On the other hand, Rhee et al. (2007) suggested that this polymorphism had no significant association with CAD in Korean subjects, the similar results were also found in Galgani et al. (2010), Bluher et al. (2002) and Youssef SM et al. (2013) studies in Italian, Germany, Tunisia populations, respectively [24, 27, 29, 31].

The reason for the difference between these studies can be explained by a relatively small size of samples in some enrolled studies, ethnic factors, the limited statistical power of single studies, different

distributions of potential effect modifiers in the study populations, and genetic heterogeneity in disease identification strategy.

In summary, our study indicates that Pro12Ala polymorphism in exon B of PPARγ showed a significant association with higher CAD risk in Iranian patients with T2DM. As a result, it could be concluded that this polymorphism could be an essential indicator for an increased risk of CAD in diabetic patients. More prospective registered studies with a larger sample size will help to confirm or refute this association.

Abbreviations

CAD: Coronary Artery Disease

T2DM: Type 2 Diabetes Mellitus

PPARγ: Proliferator-Activator Receptor Gamma

CYP: Cytochrome P450

PPARs: Peroxisome Proliferation-Activated Receptor

SNPs: Single Nucleotide Polymorphism

MI: Myocardial Infarction

BMI: Body Mass Index

SBP: Systolic Pressure

DBP: Diastolic Blood Pressure

FBS: Fasting Blood Sugar

TC: Total Serum Cholesterol

Cr: Creatine

TG: Triglyceride

HDL: High-Density Lipoproteins

LDL: Low-Density Lipoproteins

HbA1c: Hemoglobin A1c

RFLP: Restriction Fragment Length Polymorphism

OR: Odds Ratios

SD: Standard Deviation

CI: Confidence Interval

CVD: Cardiovascular Diseases

Declarations

Acknowledgment

We thank all participants for contributing to the present study. Furthermore, we thank the staff of the referral centers of Shahid Rajaei Cardiovascular Medical and Research Center in Tehran, Iran.

Author contributions

Leila Saremi and Zohre Saltanatpour designed study and performed study; Fatemeh Feyzi Prepared the samples. Shirin Lotfipanah wrote the paper. Fatemeh Rostami Avval participated in writing, editing and submitting the paper; All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1: Characteristics of the study population.

Characteristics	Patients	Controls	p value
N (m/f)	72/73	71/74	0.831
Mean Age (years)	53.9 ±9	51.3 ± 10	0.423
Mean Weight (kg)	89.2 ± 3.8	86.3 ± 4.4	0.577
BMI[1] ( )	29.4 ± 4.5	24.6 ± 2.6	0.756
Systolic BP[2] (mmHg)	139.5 ± 24.8	131.2 ± 19.8	0.001
Diastolic BP (mmHg)	80.2 ±11.8	83.6 ±9.4	0.002
FBS[3] (mg/dL)	182.1 ± 20.3	189.6 ± 43.1	0.572
2h plasma glucose (mmol/L)	9.1 ± 3.1	5.4 ± 7.4	0.012
Total cholesterol (mg/dL)	204.1 ±28.4	198.8 ± 34.1	0.001

Note. All data expressed as a mean (±SD)

Table 2: Genotypic association of the Pro12Ala polymorphism with CAD.

Variable	Genotype (%) N=145		OR (95% CI)	P-value
	CC N(%)	GC N=(%)		
CAD[4] patients	30%	70%		
Control subjects	53.3%	46.7%	2.66 (1.5 – 29.5)	0.007

Table 3: Analysis of physiologic variables in the patients and control groups.

Variable	CAD[5] patients			Control subjects		
	CC	GC	P-value	CC	GC	P-value
N	54	91	-	87	58	-
BMI[6] (kg/)	29.3±4.9	29.2±4.3	0.96	24.7±3.7	24.3±3.1	0.58
FBS[7] (mg/dL)	88.7±2.1	81.6±2.3	0.07	89.2±9.2	87.8±9	0.37
Cr.[8] (mg/dL)	1±0.3	0.9±0.3	0.28	1±0.3	1±0.4	0.94
TG[9] (mg/dL)	119.3±2.1	97.5±1.9	0.39	77.3±1.4	70.1±1.5	0.84
Total cholesterol (mg/dL)	47.5±1.9	45±1.7	0.11	49.1±1.7	43±1.6	0.43
HDL-C[10] (mg/dL)	51.3±12	50.3±11.9	0.63	39.4±11	40.1±11	0.69
LDL-C[11] (mg/dL)	92.4±37	87.3±32.3	0.38	49.8±11.9	53.7±13.7	0.07
HbA1c (mg/dL)	8.5±1.8	8.4±2.1	0.9	7.7±1.4	7.9±1.7	0.41
Microalbumin (mg/dL)	21±7.8	20.4±6.2	0.62	6.4±2.1	6.7±1.8	0.36

Data are shown as means ± SD

Figures

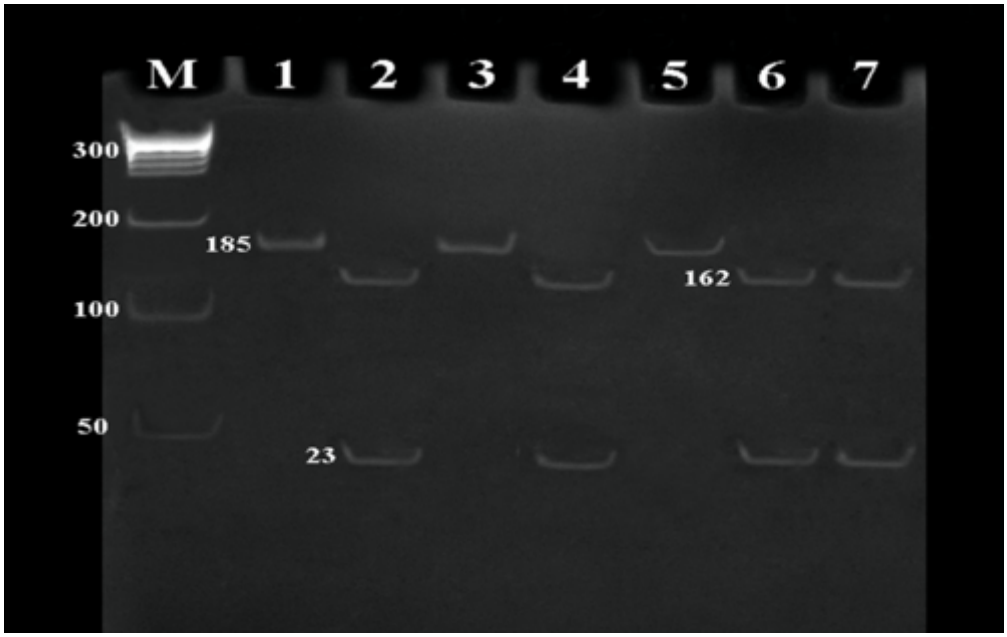

Figure 1

RFLP detection of the Pro12Ala polymorphism of PPARγ2 gene using gelelectrophoresis. M: Ladder 50bp, lane 1, 3 and 5: GC genotype (Pro12Ala) (185bp), lane 2, 4, 6, and 7: CC genotype (Pro12Pro) (162, 23bp).