Association of I405V polymorphism of colesteryl ester transfer protein gene with coronary artery disease in men with type 2 diabetes

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Original Article

Abstract

BACKGROUND: Colesteryl ester transfer protein (CETP) plays a key role in the metabolism of lipoproteins; therefore, polymorphisms of its gene can affect susceptibility to coronary artery disease (CAD) in diabetes mellitus. The aim of the present study was to investigate association between I405V polymorphism of CETP gene and risk of CAD in patients with type 2 diabetes mellitus.

METHODS: The current case-control study was conducted on 143 patients with type 2 diabetes and angiographically diagnosed CAD and 150 patients with type 2 diabetes and without CAD. Genotyping was performed through polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The presence of CAD was defined as higher than 50% reduction in coronary artery diameter.

RESULTS: The genotype frequencies of I405V polymorphism were II (27.3% vs. 23.2%), IV (61.5% vs. 67.5%), and VV (11.2% vs. 9.3%) in diabetic with CAD compared to diabetic without CAD ($\chi^2 = 1.164$) ($P = 0.55$). The I and V alleles were found at frequencies of 63.6% and 61.6% in the diabetic with CAD group and 36.4% and 38.4% in the diabetic without CAD group ($\chi^2 = 0.263$) ($P = 0.60$). No significant difference was observed between two groups in terms of genotype and allele frequency. Moreover, no significant association was observed between II, IV, and VV genotypes and lipid profiles in both groups. However, a significant difference was observed between genotype distributions of I405V polymorphism in men according to the severity of CAD.

CONCLUSION: It is speculated that I405V polymorphism may be associated with the severity of coronary artery stenosis only in men with type 2 diabetes mellitus.

Keywords: Cholesterol Ester Transfer Protein; Polymorphism; Type 2 Diabetes Mellitus; Coronary Artery Disease

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Introduction

Cardiovascular disease (CVD) and atherosclerosis are two common causes of mortality and morbidity and their related complications in patients with type 2 diabetes mellitus. Hyperlipoproteinemia is the main cause of atherosclerosis and its related conditions such as peripheral vascular disease and coronary heart disease (CHD).[1-3] Several studies have been determined an inverse relationship between plasma high-density lipoprotein cholesterol (HDL-C) and CVDs risk factors[4-6] and recommended that high plasma HDL has an anti-atherosclerotic role. Cholesteryl ester transfer protein (CETP), also known plasma lipid transfer protein, is a 74-KD plasma glycoprotein[7,8] consisting of 476 amino acids and its circulating form mainly bound to the HDL. It is a key enzyme in the metabolism of HDL and has a pivotal role in the redistribution of cholesterol ester and triglyceride (TG) between high dense lipoproteins

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such as HDL and low or very low-density lipoproteins including (LDL and VLDL). The role of CETP in the inverse cholesterol transport pathway is important for the elimination of accumulated cholesterol from vessel into the liver for its final catabolism.[9-11] It is still remains controversial whether circulating CETP acts in a pro- or anti-atherogenic manner in human.[12,13]

The CETP gene, consisting of a 25 Kb genomic DNA, located on chromosome 16 that is comprised of 16 exons and 15 introns (Gene ID 1071).[12] The gene has been reported extremely polymorphic and consisting of several single nucleotide polymorphisms (SNPs) in both its coding and non-coding regions which are responsible for changes in its transcription and sequence.[14] The CETP I405V polymorphism is a very common SNP (rs5882) located in exon 14 and is caused by A to G substitution at this locus. This mutation resulting in changes in the primary structure of CETP which identified by an isoleucine to valine substitution at codon 405 (I405V).[15] V allele is the less common allele (405V) and exists at a frequency of > 25% in the most populations.[16] A report indicated that VV genotype of this polymorphism has been associated with higher HDL-C levels and lower plasma CETP concentration.[17] In addition, V allele frequency is a very different in various ethnic groups.[10] In this study, we assessed the association between I405V variation in the CETP gene and risk of coronary artery disease (CAD) in Iranian subjects with type 2 diabetes mellitus.

Materials and Methods

The current case-control study consisting of 293 patients with type 2 diabetes mellitus (133 males, 161 females, mean age 51.92 ± 6.67), in which coronary angiographally were performed due to chest pain at the Department of Cardiology, Ahwaz Imam Khomeini Hospital, Iran. Information of data collection, including inclusion and exclusion criteria, the severity of CAD, processing, and relevant corresponding clinical characteristics, is published elsewhere.[18] Patients with infectious disease, renal disease, pregnancy, diagnosed myocardial infarction (MI) in recent 3 months, and current smoking were excluded from the study population. Diabetes was defined based on American Diabetes Association (ADA) criteria.[19] Furthermore, the CAD was determined as a reduction in luminal diameter of a major coronary artery branch by > 50%. According to the angiography results, diabetic patients were categorized into two groups as follow: 143 diabetic with CAD and 150 diabetic without CAD. Diabetic patients with CAD were classified based on the number of significantly stenosis in the coronary artery vessels into angiographically one-vessel (n = 39), two-vessel (n = 42), and three-vessel (n = 62) sub-groups. From all subjects was obtained written informed consent for participation in this study.

Venous blood was drawn from subjects who were, at least, 10-12 hours of fasting. A value of 2 ml of the sample was transferred into tubes containing ethylenediamine tetraacetic acid as an anticoagulant for DNA extraction and the remaining sample was collected in glass tubes. Full-fasted lipid profile containing of TGs, total cholesterol (TC), HDL-C, LDL-C, and plasma glucose concentration was measured using enzymatic method by Vital Scientific Spankeren autoanalyzer. Demographic parameters including systolic and diastolic blood pressure, height, weight and body mass index (BMI) were measured by standard methods and preliminary results previously presented elsewhere.[18]

Polymerase chain reaction (PCR) amplification and genotyping for SNP I405V

Genomic DNA was isolated from nucleated blood cells by salting out method and was frozen at -20 °C, as previously described elsewhere.[18] Genotyping of I405V polymorphism was characterized using PCR and restriction fragment length polymorphism (PCR-RFLP) method. Important advantages of the PCR-RFLP technique are that no expensive, no prior sequence information, and no requirement of advanced instruments, is required. Moreover, the primer design for PCR-RFLP analyses generally is easy and can be accomplished using public available programs. A 308 bp fragment in exon 14 was amplified using of the following oligonucleotide primer set: forward, 5′-GCA GAA CAG TAG TGG CCA AGC AGC G-3′, and reverse, 5′-GCG GTG ATC ATT GAC TGC AGG AAG CTC TGT A -3′. Amplification was done in a total volume of 25 µl comprising 12.5 µl available premix (AccuPower PCR Premix; Bioneer, Daejeon, South Korea) consisting of deoxynucleotide (dNTP), Taq DNA polymerase, $MgCl_2$, × 10 buffer, 2.0 µl (10 pmol/µl) of each primer, 2.0 µl (50 ng/µl) templates DNA, and 6.5 µl sterile nuclease-free water. The PCR state was as follows: primary denaturation at 95 °C for 5 minutes, and followed by 30 cycles of denaturation at 95 °C for 30 seconds, annealing at 66 °C for 30 seconds,

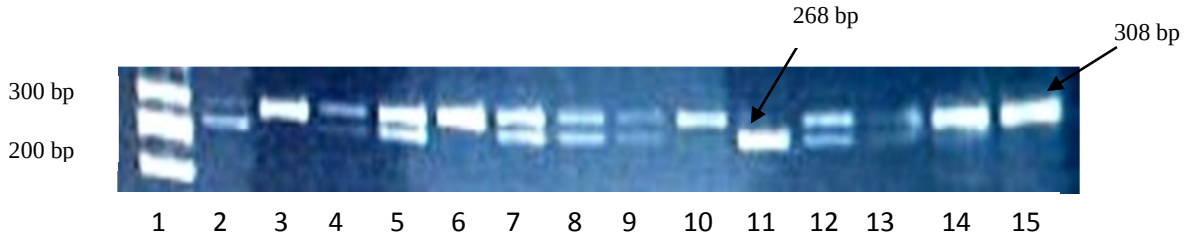

Figure 1. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) products of I405V polymorphism separated on 10% polyacrylamide gel
Lane 1 shows DNA size marker 50 bp; Lanes 2, 4,5,7,8,9,12 and 13 show IV genotype; Lanes 3, 6, 10, 14, and 15 show II genotype; Lane 11 shows VV genotype

extension at 72 °C for 30 seconds, and a final extension at 72 °C for 5 minutes. The PCR products were treated with RsaI restriction enzyme at 37 °C overnight and then fragments were electrophoresed on 10% native polyacrylamide gel that giving 40 and 268 bp length fragments in the existence of less common V allele (Figure 1).

All statistical analysis was performed using the statistical software package SPSS (version 20, SPSS Inc., Chicago, IL, USA). Normal distribution of the data was tested by the Kolmogorov-Smirnov test, a P value more than 0.050 considered as the calculated variable distribution is not statistically significant difference from the expected normal distribution. The quantitative data are reported as mean ± standard deviation (SD) and qualitative data are introduced as number and percentage. Genotypes and alleles frequency were compared between groups using the Chi-square (χ^2) analysis. Hardy-Weinberg equilibrium was calculated for the expected genotype distribution. Comparison of mean serum lipid profiles among different genotypes was performed by one-way ANOVA test. The association of various genotypes with the risk of CAD were estimated by logistic regression using odds ratio (OR) and 95% confidence intervals (95% CI). The comparison of V allele frequency between Iranian population and other four major populations was tested using weighted χ^2 test. In all statistical analyses, value of $P < 0.050$ was considered to be significant.

Results

Demographic and biochemical characteristics of the studied subjects

Demographic indices consisting of BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as a full-fasted lipid profile containing TG, TC, HDL-C, LDL-C were measured and results presented elsewhere.[18] briefly, diabetic patients with CAD were significantly older than those without CAD ($P < 0.001$). Furthermore, the mean value of BMI and blood glucose in patients with CAD was significantly higher than those in patients without CAD ($P = 0.010$). According to the lipid profile, the mean TC and TG in patients with CAD were significantly higher than those in patients without CAD ($P = 0.030$). While the mean HDL-C in patients without CAD was higher than that in patients with CAD ($P < 0.001$).

Association of SNP I405V of CETP gene with the risk of CAD

The CETP I405V genotype and allele frequencies in diabetic with CAD and without CAD groups are shown in table 1. The genotype frequencies were not consistent with Hardy-Weinberg equilibrium for I405V polymorphism. Between group with and without CAD, the frequency of genotype and allele of SNP I405V were not significantly different ($P = 0.550$ and $P = 0.600$, respectively) (Table 1). Moreover, no significant difference was observed in the distribution of genotypes between two groups based on gender (results not shown here). The frequency V allele of CETP gene in the current studied population was compared with the other four major populations (Table 2). Our result indicated that there was a significant difference according to the V allele frequency between Iranian studied population and Tamilians ($P = 0.023$), Asians ($P < 0.001$), and African Americans ($P = 0.001$). However, similar difference was not found between Iranians and Caucasians (Table 2).

Finally, we analyzed the association of this polymorphism with the risk of CAD, which was not found a significant association between various genotypes and increased risk of CAD in the studied population. The OR related to the IV and VV genotypes for the risk of CAD were (OR = 1.292; 95% CI = 0.754-2.21, P = 0.350 and OR = 0.975; 95% CI = 0.417-2.28, P = 0.950), respectively.

Table 1. Distribution of I405V genotype and allele frequency and association of genotype with the risk of coronary artery disease (CAD) in studied population

Variables	Diabetic with CAD [n (%)]	Diabetic without CAD [n (%)]	χ^2	P	OR (95% CI)	P
Genotypes						
II	39 (27.3)	35 (23.2)	1.077	0.580	1.00	
IV	88 (61.5)	101 (67.4)			1.292 (0.75-2.21)	0.350
VV	16 (11.2)	14 (9.3)			0.975 (0.41-2.28)	0.950
Alleles						
I	181 (63.6)	186 (61.6)			1.00	
V	104 (36.4)	116 (38.4)	0.263	0.600	1.022 (0.78-1.52)	0.830

The χ^2 test was used to determine the significant differences were observed between two groups. Logistic regression analysis was used to estimate the OR for CAD in studied population.
CAD: Coronary artery disease; OR: Odds ratio; CI: Confidence interval

Regarding to the frequency of SNP I405V genotype based on the number of coronary artery stenosis, a significant difference was observed in diabetic with CAD (P < 0.010) (Table 3). Similarly, concerning to the frequency of SNP I405V genotype based on the number of coronary artery stenosis, a significant difference was observed only in men subjects with CAD (P = 0.020) (Table 3).

Association of I405V genotypes with measured characteristics

Association of I405V genotype with baseline characteristics in diabetic with CAD and without CAD is summarized in table 4.

No significant relationship was observed between II, IV and VV genotypes of I405V polymorphism and anthropometric indices, clinical status, and biochemical parameters in the patients with and without CAD.

Discussion

In the several population-based study, results demonstrated that CETP has both pro- and anti-atherogenic effects.[20,21] Variations in the CETP gene seem to cause changes in the HDL-C level. Results from the Rotterdam study indicated that VV genotype of I405V polymorphism was correlated with low CETP level, increased HDL levels and decreased risk of CAD.[22] In the current study, the relationship between I405V polymorphism of CETP gene and demographic indices, lipid profiles, and CAD in subjects with type 2 diabetes was investigated. We failed to show a statistically significant relationship between I405V polymorphism of CETP, lipid profiles and CAD. The frequency of 405V allele of CETP gene in our population was 0.37 which is higher than that reported from Caucasians (0.318) and lower than that reported from Asians, Tamilians, and African Americans.[10,23] Several studies reported that subjects whom carrying of 405V allele had increased plasma levels of HDL-C,[24,25] but our study, there were no variations in the plasma levels of HDL-C according to the different I405V genotypes.

The current study shows there is no significant difference in genotype distribution and allele frequency of I405V polymorphism between two studied groups. Moreover, according to the gender-based analysis, similar results were obtained. BMI, SBP and DBP in diabetic with CAD were significantly higher than those in diabetic without CAD. CETP plays a key role in reverse cholesterol transport and modulating of HDL-C concentrations and may therefore alter the susceptibility to CAD.

Kolovou et al.[26] reported TaqIB polymorphism is important in screening individuals who are at higher risk for CAD, also there was no any association between I405V polymorphism and CAD. In a study conducted by Dogru-Abbasoglu

Table 2. The comparison of V allele frequency of I405V polymorphism in Iranian population with other major populations

Allele	Current study (n = 293)	Tamilians[26] (n = 171)	Caucasians[25] (n = 2188)	Asians[27] (n = 148)	African Americans[27] (n = 30)
V	0.374	0.530	0.318	0.617	0.611
P*	-	0.023	0.457	< 0.001	0.001

*P < 0.050 is significant when Iranian population compared to the other population.
V: V allele of I405V polymorphism

Table 3. Genotypes distribution of I405V polymorphism in diabetic with CAD according to the severity of vessel stenosis

Genotypes	Number of vessels involved				P
	1 VD [n (%)]	2 VD [n (%)]	3 VD [n (%)]	Total [n (%)]	
Male					
II	5 (26.3)	6 (27.3)	7 (21.2)	18 (24.3)	0.020
IV	14 (73.7)	16 (72.7)	18 (54.6)	48 (64.9)	
VV	0 (0.0)	0 (0.0)	8 (24.2)	8 (10.8)	
Total	19	22	33	74	
Female					
II	7 (35.0)	7 (35.0)	7 (24.1)	21 (30.4)	0.250
IV	13 (65.0)	11 (55.0)	16 (55.2)	40 (58.0)	
VV	0 (0)	2 (10.0)	6 (20.7)	8 (11.6)	
Total	20	20	29	69	
Total					
II	12 (30.8)	13 (30.9)	14 (22.6)	39 (27.3)	0.010
IV	27 (69.2)	27 (64.3)	34 (54.8)	88 (61.5)	
VV	0 (0)	2 (4.8)	14 (22.6)	16 (11.2)	

The χ^2 test was used to determine the significant difference were observed in each gender.
VD: Vessel stenosis more than 50% reported by angiography; 1VD: One vessel stenosis more than 50%; 2VD: Two vessel stenosis more than 50%; 3VD: Three vessel stenosis more than 50%, CAD: Coronary artery disease

et al.[27] in a Turkish population, the allele frequencies of TaqIB and I405V polymorphisms were 0.38 and 0.46, respectively, which is similar to some European populations. The mean HDL-C levels were higher in VV genotype compared to the II genotype. TG levels and gender have an influence on the relationship between HDL-C and I405V polymorphism; therefore, this polymorphism may affect HDL-C levels in this population. Moreover, there was no significant association between TaqIB polymorphism and HDL-C concentrations. In some populations such as Iranian[28] Chinese[29] and Framingham populations,[21] a significant association of the B2 allele with increased HDL-C was also determined, and suggested the protective effects of B2 allele in these studies were due to decreased CETP activity and increased HDL-C levels.

Furthermore, our results indicated there was no significant difference in allele frequency of this polymorphism based on gender in two studied groups. Since I405V mutation of CETP was not sex-related, the absence of any relationship between it and gender was predictable.

Padmaja et al.[10] studied the common variants in the gene of CETP and their relationship with lipid profile in a population healthy subject from south India. They reported no statistically significant difference for studied variables between men and women participated in the study. Furthermore, they found no a statistically significant difference between genotypes of the TaqIB and I405V polymorphisms in men, women and total population of Tamilian. Moreover, the I405V genotypes were not associated with HDL-C level. Moreover, there was an increase in HDL-C and decrease in TG in carriers of B2B2 genotype in men; this result was in contrast to the results was observed in women.[8]

In a study conducted by Okumura et al.[17] in Japanese subjects, the effect of TaqIB and I405V polymorphisms of CETP gene on LDL particle size was investigated. Plasma CETP concentration was lower in patients with VV genotype and LDL particle size was also significantly smaller in this patients. Similar effects were observed for B2B2 genotype with the exception that the B2B2 genotype had no effect on the LDL particle size. The results of their study showed that loss of CETP activity resulting fromI405V polymorphism but not by TaqIB polymorphism is associated with increased CAD, despite the fact that both are increasing HDL-C concentration.

Although, results from a study performed on 504 patients with verified CHD and 338 controls in Indian population[30] revealed that the B1B1 genotype of the CETP TaqIB mutation was related to increased CHD risk. However, no statistically significant relationship between the I405V mutation and CHD was reported. In a population-based study, it was reported that the B2 and V alleles of the TaqIB and I405V polymorphisms despite an increased HDL-C, were not associated with a reduced risk of CAD. In addition, they reported that the less common allele 405V of I405V mutation was feebly related to CHD risk after matching of HDL-C.[13]

Table 4. Clinical findings in diabetic with and without CAD according to I405V genotypes

Variables	Diabetic with CAD			P	Diabetic without CAD			P
	Genotypes				Genotypes			
	II	IV	VV		II	IV	VV	
Age (year) (mean ± SD)	53.89 ± 5.62	54.13 ± 6.08	56.69 ± 6.52	0.250	51.06 ± 6.95	49.34 ± 6.18	47.13 ± 6.65	0.230
BMI (kg/m^2) (mean ± SD)	26.70 ± 3.45	27.58 ± 5.30	27.35 ± 3.61	0.630	25.95 ± 2.57	26.02 ± 5.66	25.24 ± 3.72	0.850
FPG (mg/dl) (mean ± SD)	149.58 ± 42.21	154.38 ± 48.44	169.91 ± 42.54	0.430	143.71 ± 40.21	138.48 ± 37.96	136.41 ± 45.09	0.800
SBP (mm Hg) (mean ± SD)	135.57 ± 19.31	129.14 ± 29.76	128.33 ± 25.16	0.470	123.67 ± 18.45	126.16 ± 16.22	130.91 ± 17.29	0.460
DBP (mm Hg) (mean ± SD)	82.00 ± 10.99	85.10 ± 17.71	82.08 ± 16.44	0.600	75.91 ± 10.26	78.13 ± 10.08	84.55 ± 14.74	0.060
TC (mg/dl) (mean ± SD)	185.93 ± 56.98	179.92 ± 44.46	209.33 ± 45.17	0.250	168.96 ± 20.22	174.43 ± 24.85	173.82 ± 23.9	0.620
HDL-C (mg/dl) (mean ± SD)	41.83 ± 12.24	38.27 ± 9.99	39.63 ± 8.28	0.360	44.09 ± 9.33	46.38 ± 10.36	46.69 ± 14.32	0.520
LDL-C (mg/dl) (mean ± SD)	112.77 ± 52.59	111.81 ± 38.09	131.50 ± 36.62	0.490	101.06 ± 32.26	109.22 ± 35.03	100.23 ± 27.10	0.380
TG (mg/dl) (mean ± SD)	181.84 ± 85.15	158.30 ± 64.76	183.64 ± 55.12	0.260	145.42 ± 50.81	151.34 ± 56.65	163.43 ± 36.54	0.750

Comparisons were made using one-way ANOVA followed by Tukey's post-hoc test. $P < 0.050$ was considered to be significant.
BMI: Body mass index; FPG: Fasting plasma glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; HDL-C: High density lipoprotein-cholesterol; LDL: Low density lipoprotein-cholesterol; TG: Triglyceride; CETP: Colesteryl ester transfer protein; CAD: Coronary artery disease

Isaacs et al. reported a positive association between the 405V allele and reduced risk of myocardial infraction.[22] The significant deference was observed between genotype of I405V polymorphism in men according to the severity of CAD, in part possibly consequence of sex hormones difference that might regulate lipoprotein metabolism or CETP activity between men and women in different fashion. Our result is inconsistent with the finding reported by Ghatreh Samani et al.[31] from a study performed in other Iranian CAD patents, including, they found no statistically significant difference in genotype distribution of I405V polymorphism based on severity of CAD.

Conclusion

Although, results of the current study indicated there was no significant association between CETP I405V polymorphism and CAD risk in Iranians subjects with type 2 diabetes. However, a statistically significant difference was observed between genotypes of I405V polymorphism according to the severity of CAD only in men. It is speculated that I405V polymorphism may be involved in the severity of CAD only in men subjects with type 2 diabetes.

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Conflict of Interests

Authors have no conflict of interests.

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