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# I405V and -629C/A Polymorphisms of the Cholesteryl Ester Transfer Protein Gene in Patients with Coronary Artery Disease

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## ABSTRACT

**Background:** Cholesteryl ester transfer protein (CETP) plays a main role in high-density lipoprotein metabolism. CETP gene possesses several single nucleotide polymorphisms which have been associated with plasma high-density lipoprotein cholesterol (HDL-C) concentrations. The aim of this study was to determine the association of CETP -629C/A and I405V polymorphisms with coronary artery disease (CAD) in Iranian population. **Methods:** The presence of two CETP gene polymorphisms -629C/A and I405V were studied in 187 unrelated CAD cases and 136 controls. All the samples were clinically examined and lipid profile was estimated. Genotyping was performed using polymerase chain reaction/restriction fragment length polymorphism method. **Results:** The frequency of -629C/A and I405V allelic variants were found to be 0.732 and 0.366 in cases and 0.658 and 0.348 in controls, respectively. The frequency of A allele of -629C/A polymorphism in cases was significantly higher than that of controls. HDL-C in AA genotype was higher than CA and CC genotypes in controls. No significant effect of II, IV and VV genotypes was found in lipid profiles. **Conclusion:** No significant association was found between CETP I405V polymorphism and increased risk of CAD in Azeri population studied. AA genotype of -629C/A increased HDL but the risk of CAD in this genotype might be higher than CC genotype. *Iran. Biomed. J. 13 (2): 103-108, 2009*

*Keywords*: Cholesteryl ester transfer protein (CETP) gene, I405V, High-density lipoprotein (HDL) cholesterol,-629C/A

## INTRODUCTION

Coronary artery disease (CAD) has a multi-factorial etiology with many established risk factors [1]. Disturbances in lipoprotein metabolism play a major role in atherogenesis. A strong inverse relation exists between high-density lipoprotein cholesterol (HDL-C) plasma level and the risk of CAD [2]. Low HDL-C rather than elevated LDL-C is the most frequent lipid abnormality in men who present with coronary heart disease [3]. Cholesteryl ester transfer protein (CETP) plays a central role in HDL-C metabolism by shuttling cholesteryl esters from HDL particles to apolipoprotein B-containing particles in exchange for triglycerides [4]. The role of CETP in general population and how it may modulate the risk for CAD is unclear [5, 6]. CETP gene has been localized on chromosome16q21 and consisted of 16 exons [Accession id: ENSG00000087237]. The gene possesses several different single nucleotide polymorphisms (SNP) [7]. Some of these affect the CETP activity and HDL-C concentrations and have been studied as predictors of cardiovascular diseases [8].

The -629C/A (rs1800775) polymorphism is a functional SNP present in 629-bp upstream of the transcription start site in the promoter region of the CETP gene. This promoter polymorphism modulates CETP gene transcriptional activity *in vitro* [9].

*Corresponding Author; Mobile. (+98-913) 2800382; Fax: (+98-381) 333 0709; E-mail: kgsamani@yahoo.com. BMI, Body mass index; CETP, Cholesteryl ester transfer protein; CAD, Coronary artery disease; HDL, High-density lipoprotein; HDL-c, HDL cholesterol; LDL, Low-density lipoprotein; LDL-c, LDL cholesterol; TC, Total cholesterol; TG, Triglyceride.



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Importantly, it has been documented that this variant is involved in regulating plasma CETP levels [10]. The A-629 allele has been associated with lower CETP mass and higher HDL-C than the C allele [11].

The I405V (rs5882) polymorphism, a very common SNP, located in exon 14 of the CETP gene is caused by A to G transition in position 20206. It is characterized by alteration in the primary structure of the protein having either an isoleucine or a valine at codon 405 [12]. VV genotype of this polymorphism has been associated with lower plasma CETP concentration and higher HDL-C concentration [13].

The aim of the present study was to determine the prevalence of -629C/A and I405V polymorphisms in control and CAD patients and to examine if the subjects lipid profiles is influenced by the above mentioned CETP polymorphisms.

## MATERIALS AND METHODS

***Subjects.*** Subjects were originated from Azeri ethnicity that attended for coronary angiography at the Emam Reza and Shahid Madani Hospitals in Tabriz (Iran). The subjects, who matched by age and sex, with abnormal (stenosis in coronary arteries) and normal coronary angiogram, were recruited as cases and controls, respectively. In total, 187 unrelated CAD cases and 136 controls were studied. The personal and clinical data were collected by a questionnaire. The study protocol was approved by the Tabriz University of Medical Sciences Ethics Committee and informed consent was obtained from all patients. Those with acute coronary bypass surgery, angioplasty, acute coronary syndromes, diabetes, hepatic or renal, uncontrolled hypothyroidism, neoplasia and receiving lipid-lowering drugs were excluded from the study.

***Blood sampling and biochemical determinations.*** Venous blood sample for, glucose, creatinine, lipids, lipoproteins and DNA analysis was collected from the subjects after an overnight fasting. Glucose, total cholesterol and triglyceride were assessed by standard enzymatic procedures. HDL-C and LDL-C were measured using direct method and apolipoprotein A1 and apolipoprotein B levels were determined by immunoturbidimeteric method. Creatinine was measured by Jaffe method to exclude renal patients. All biochemical tests were performed in serum using by BT 3000 automatic analyzer and commercial kits ( Pars Azmon Co., Iran). CETP concentration was measured in serum using the CETP test ELISA kits produced by ALPCO Diagnostic (USA).

***Molecular analyses.*** DNA was extracted using standard phenol-chloroform procedure. CETP I405V and -629C/A polymorphisms were determined by polymerase chain reaction/restriction fragment length polymorphism as described previously [14]. Shortly, the 308-bp PCR products of CETP I405V and 127-bp PCR products of CETP -629C/A were digested using *RsaI* and *AvaI*, respectively. The result and PCR fragments were visualized by silver staining method (Fig. 1).

***Statistical analysis.*** Continuous variables were reported as the mean ± SD. All statistical analyses were performed using statistical package SPSS 11.5 for windows and a $P<0.05$ was considered statistically significant. Allele frequencies were calculated from the genotype counts. The observed genotype counts were compared with those expected under Hardy-Wienberg equilibrium with a $\chi^2$ test. The genotypes were compared with lipid profile values using one-way ANOVA followed by Tukey's multiple comparison tests.

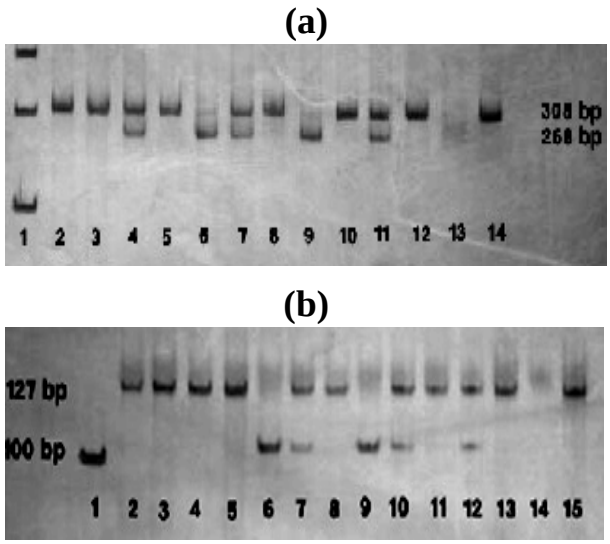


**Fig. 1.** Polyacrylamide gel electrophoresis for CETP polymorphisms. **(a)** I405V polymorphism. Lane 1 is DNA marker, lane 2, 3, 5, 8, 10 and 12 are related to the II genotype, lane 4, 7 and 11 are related to the IV genotype, lane 6 and 9 are related to the VV genotype. Lane 13 is negative control (blank), Lane 14 is DNA control (uncut). **(b)** -629C/A polymorphism. Lane 1 is DNA marker, lane2 -5 and 8 and 11and 13 are related to the AA genotype, lane7, 10 and 12 are related to the CA genotype, lane 6 and 9 are related to the CC genotype. Lane 14 is negative control (blank), Lane 15 is DNA control (uncut).

**Table 1.** Baseline characteristics of study subjects.

| Characteristic | control | CAD patients | *P* value |
|---|---|---|---|
| Age (years) | 52.80 ± 11.1 | 54.60 ± 9.70 | 0.085 |
| BMI (kg/m2) | 26.90 ± 4.0 | 27.10 ± 4.14 | 0.640 |
| Cholesterol (mg/dl) | 172.60 ± 42.0 | 176.60 ± 46.70 | 0.226 |
| Triglyceride (mg/dl) | 184.90 ± 118.4 | 190.90 ± 101.80 | 0.990 |
| HDL (mg/dl) | 38.90 ± 11.4 | 36.70 ± 9.90 | 0.361 |
| LDL (mg/dl) | 96.70 ± 35.5 | 101.60 ± 41.20 | 0.219 |
| Apo AI (mg/dl) | 125.90 ± 21.4 | 120.50 ± 19.50 | 0.051 |
| Apo B (mg/dl) | 102.70 ± 26.3 | 104.30 ± 30.00 | 0.253 |
| CETP (µg/ml) | 2.31 ± 0.92 | 1.98 ± 0.75 | 0.011 |

Values are mean ± S.D., $P<0.05$ is significant.

## RESULTS

The characteristics and the lipid profile of the case (CAD) as well as control groups are summarized in Table 1. The mean age of cases and controls was 54.6 ± 9.7 and 52.8 ± 11.1, respectively. There was no significant difference between CAD and control groups regarding the mean concentrations of plasma lipids, body mass index and age. The genotype frequencies of the 2 polymorphisms of CETP gene in CAD patients and controls are shown in Table 2. The frequencies of A allele of -629C/A and V allele of I405V were 0.732 and 0.366 in cases and 0.658 and 0.348 in controls, respectively. The frequency of A allele of -629C/A polymorphism in cases was significantly higher than that of control group.

The allele frequencies of CETP gene polymorphisms in the present study are compared with some major populations (Table 3). This study represents a higher frequency of -629A allele compared to that of Asian, Caucasians, African Americans and Tamilians. No significant effect of different I405V alleles was found on lipid profiles.

When CETP level was analyzed among the three -629C/A polymorphisms, mean value was lower in the AA group compared to the CA and CC groups ($P<0.04$ and $P<0.01$, respectively). HDL-C in AA genotype was higher than CA and CC genotypes in controls (Table 4).

## DISCUSSION

CETP has both pro- and anti-atherogenic effects [15, 16].Various mutations in the CETP gene seem to cause changes in the HDL cholesterol level. VV genotype of I405V polymorphism is reported with low CETP, high cholesterol and elevation of the risk for CHD [17]. In this study, the relationship of I405V polymorphism in CETP gene with plasma CETP level, lipids, lipoproteins and coronary atherosclerosis was investigated. We failed to show a significant role of I405V variation of CETP either on lipoprotein metabolism or on atherogenesity in this study. The frequency of 405V allele was 0.35 in control group which is almost matches that of seen in Caucasians (0.318) and lower than that in Asians [14, 18]. It was shown in several studies that carriers of 405V allele have increased HDL-C concentration [11, 19], but in the present study, there was no

**Table 2.** Genotype frequencies of the two polymorphisms of CETP gene.

| CETP genotype | %Frequency (number) | | | | |
|---|---|---|---|---|---|
| | | CAD patients | | | |
| I405V | Control | 1 VD | 2 VD | 3 VD | Total |
| II | 43.000 (58) | 45.300 (29) | 39.300 (24) | 40.300 (25) | 41.700 (78) |
| IV | 44.400 (61) | 45.300 (29) | 45.900 (28) | 38.700 (24) | 43.300 (81) |
| VV | 12.600 (17) | 9.400 (6) | 14.800 (9) | 21.000 (13) | 15.000 (28) |
| Total | 100.000 (136) | 100.000 (64) | 100.000 (61) | 100.000 (62) | 100.000 (187) |
| V allele | 0.348 | 0.320 | 0.377 | 0.403 | 0.366 |
| -629C→A | | | | | |
| AA | 44.900 (61) | 56.300 (36) | 60.700 (37) | 59.700 (37) | 58.800 (110) |
| CA | 41.900 (57) | 32.800 (21) | 27.900 (17) | 25.800 (16) | 28.900 (54) |
| CC | 13.200 (18) | 10.900 (7) | 11.400 (7) | 14.500 (9) | 12.300 (23) |
| Total | 100.000 (136) | 100.000 (64) | 100.000 (61) | 100.000 (62) | 100.000(187) |
| A allele | 0.658 | 0.771 | 0.746 | 0.726 | 0.732 |

The coronary angiography exhibited stenosis greater than %50 of one vessel was graded as 1VD, 2 vessels stenosis greater than %50 was graded as 2VD and 3 vessels stenosis greater than %50 was graded as 3VD.





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**Table 3.** Comparison of allele frequencies of subjects with other major populations.

| | Other populations | | | | Present study | |
|---|---|---|---|---|---|---|
| Alleles | Tamilians [18] (n = 171) | Caucasians [17] (n = 2188) | African Americans [17] (n = 30) | Asians [17] (n = 148) | Non-CAD (n = 136) | CAD (n = 187) |
| V * | 0.530 | 0.318 | 0.611 | 0.617 | 0.348 | 0.366 |
| A ** | 0.640 | 0.482 | 0.573 | 0.500 | 0.658 | 0.732 |

$P<0.05$ is significant. V*, V allele of I405V ($P = 0.35$ for non CAD and CAD); A**, A allele of -629C/A ($P = 0.02$).

change in HDL-C among the I405V genotypes. V allele frequency was 0.320, 0.377 and 0.403 in 1VD, 2VD and 3VD, respectively but they were not statistically significant.

Another genetic variant in CETP gene is -629C/A promoter polymorphism [20]. It is likely that the -629C/A CETP gene variant directly affects regulation of plasma CETP mass levels [21]. The frequency of A allele of CETP-629C/A polymorphism in this study was 0.66 in control group and it corroborates with the fact that Asian have a higher frequency of the -629A allele compared to that of found in the European populations [22]. In this study, there was an increase in HDL-C in carriers of AA genotype compared to CC in control but there was no significance difference in CAD patients. A allele has higher prevalence in CAD patients but it is not protective for CAD. Remarkably, CETP gene variations that result HDL-C increase may not affect cardiovascular protection [23]. In fact, in the largest prospective population based study to date, recently was documented that the -629A allele, which determine a lower plasma CETP mass and a higher HDL-C are associated with increased cardiovascular risk, particularly when the effect of these CETP gene variants on HDL cholesterol is taken into account [24].

It is therefore of relevance to explore potential mechanisms responsible for this paradoxical relationship. Among other possibilities, an influence on CETP-mediated processes affecting the ability of plasma to stimulate cellular cholesterol removal could be involved in the apparent cardio protective role of CETP gene variation that relates to higher expression of this lipid transfer protein [25]. The -629C/A CETP promoter variant does not alter the molecular structure of this lipid transfer protein but affects its circulating mass and, hence, the amount of active CETP in serum [26].

One of the limitations in the study is the use of coronary stenosis for the magnitude of coronary atherosclerosis. The region that appears normal in coronary angiography would often be considered atheromatous when examined by intravascular ultrasound. Thus the extent of the stenosis does not always indicate the clinical severity of CAD [27].

**Table 4.** distribution of anthropometric and metabolic parameter in different CETP genotype groups.

| CETP I405V | Non-CAD | | | CAD patients | | |
|---|---|---|---|---|---|---|
| | II | IV | VV | II | IV | VV |
| Age (year) | 52.50 ± 12.10 | 53.30 ± 11.10 | 53.00 ± 9.90 | 55.80 ± 9.90 | 56.20 ± 9.60 | 54.90 ± 9.80 |
| BMI | 26.70 ± 4.30 | 26.80 ± 3.50 | 28.30 ± 4.40 | 26.90 ± 4.00 | 27.50 ± 4.50 | 26.50 ± 3.40 |
| TC (mg/dl) | 170.00 ± 41.40 | 175.00 ± 39.50 | 172.00 ± 49.30 | 174.00 ± 50.50 | 177.00 ± 44.70 | 184.00 ± 41.10 |
| TG (mg/dl) | 176.00 ± 107.10 | 179.00 ± 77.60 | 186.00 ± 66.20 | 194.00 ± 88.90 | 187.00 ± 100.90 | 193.00 ± 137.20 |
| HDL-c (mg/dl) | 38.20 ± 10.80 | 39.00 ± 12.90 | 40.60 ± 8.30 | 36.30 ± 8.90 | 37.10 ± 9.70 | 37.40 ± 12.60 |
| LDL-c (mg/dl) | 93.80 ± 32.90 | 100.30 ± 33.10 | 95.00 ± 44.80 | 99.20 ± 46.40 | 102.30 ± 35.80 | 107.80 ± 41.30 |
| apo AI (mg/dl) | 126.70 ± 19.70 | 123.90 ± 23.80 | 129.70 ± 20.00 | 121.70 ± 17.80 | 118.90 ± 20.40 | 122.80 ± 21.60 |
| apo B (mg/dl) | 103.10 ± 25.70 | 103.10 ± 27.40 | 102.40 ± 25.70 | 103.40 ± 35.00 | 106.10 ± 27.60 | 102.90 ± 21.30 |
| CETP (μg/ml) | 2.40 ± 0.89 | 2.16 ± 0.98 | 2.29 ± 1.04 | 2.14 ± 0.77 | 1.93 ± 0.74 | 1.70 ± 0.57 |
| **CETP -629C/A** | **AA** | **CA** | **CC** | **AA** | **CA** | **CC** |
| Age (year) | 52.40 ± 12.60 | 52.20 ± 10.30 | 53.70 ± 10.70 | 55.80 ± 9.90 | 55.80 ± 9.50 | 56.00 ± 9.60 |
| BMI | 26.40 ± 4.10 | 27.20 ± 3.70 | 27.80 ± 4.40 | 27.10 ± 4.50 | 27.00 ± 3.70 | 26.80 ± 3.50 |
| TC (mg/dl) | 170.00 ± 35.70 | 170.00 ± 50.10 | 176.00 ± 29.30 | 178.00 ± 49.00 | 173.00 ± 42.30 | 180.00 ± 46.50 |
| TG (mg/dl) | 164.00 ± 68.40 | 182.00 ± 90.40 | 223.00 ± 133.70 | 188.00±111.30 | 194.00 ± 96.50 | 195.00 ± 61.10 |
| HDL-c (mg/dl) | 41.90 ± 12.40* | 36.60 ± 10.40* | 35.10 ± 8.70* | 38.10 ± 9.90 | 34.80 ± 8.60 | 34.90 ± 11.00 |
| LDL-c (mg/dl) | 95.70 ± 30.60 | 97.20 ± 40.10 | 96.50 ± 27.00 | 101.80 ± 43.90 | 99.50 ± 36.30 | 105.80 ± 39.90 |
| apo AI (mg/dl) | 129.90 ± 24.80 | 121.10 ± 18.20 | 126.40 ± 16.70 | 122.70 ± 19.30 | 114.80 ± 17.40 | 123.80 ± 23.50 |
| apo B (mg/dl) | 99.80 ± 24.10 | 103.90 ± 29.20 | 110.50 ± 22.40 | 103.40 ± 28.20 | 106.60 ± 34.80 | 103.70 ± 26.90 |
| CETP (μg/ml) | 2.19 ± 0.99 | 2.33 ± 0.90 | 2.51 ± 0.99 | 1.82 ± 0.66 | 1.99 ± 0.69 | 2.74 ± 0.82 |

Values are mean ± S.D., *The mean difference is significant by Tukey's test at the 0.05 level.




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In conclusion, in the present study CETP mass level decreased and HDL-C increased by -629 C→A polymorphism but this high HDL-C didn't reduced risk of CAD. We failed to show a significant role of I405V genotypes either on lipoprotein metabolism or on atherogenesity.

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