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# Cholesteryl ester transfer protein (CETP) −629C/A polymorphism and it's effects on the serum lipid levels in metabolic syndrome patients

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**Abstract** Metabolic syndrome is a relatively common disorder with significant morbidity worldwide. Cholesteryl ester transfer protein (CETP) plays a central role in the metabolism of lipoproteins. In this study the effect of −629C/A polymorphism on the concentration of CETP and plasma lipids pattern was elicited in metabolic syndrome patients and control subjects. For this, a sample of 200 patients diagnosed with metabolic syndrome disorder was studied in comparison with 200 healthy controls. This study was performed by using polymerase chain reaction and restriction fragment length polymorphisms. Genotype distribution and allelic frequencies were determined and compared in metabolic syndrome and healthy controls. To determine the relationship between −629C/A polymorphism and lipid levels, lipids and CETP concentration were measured in metabolic syndrome and normal subjects. The results showed a significant difference between two groups in terms of FBS, cholesterol, TG, HDL-C, LDL-C levels as well as BMI, waist circumference, systolic and diastolic blood pressure. The genotype frequencies for this polymorphism differed significantly between metabolic syndrome patients and controls (in control group: CC% 20.5, CA% 76, AA% 3.5 and in patient group: CC% 28.5, CA% 53.5, AA% 18) ($p < 0.05$) while there was no significant difference in the frequency of the alleles. In the two groups, the levels of the cholesteryl ester transfer protein in AA genotype were lower than other genotypes. In the control group, individuals with AA genotype had the highest levels of LDL-C and TC plasma concentration. Considering the results of this study, it can be concluded that the −629 AA genotype was associated with high cholesterol; high LDL-C and low CETP level, so that it can be related to metabolic syndrome.

**Keywords** Metabolic syndrome · Cholesteryl ester transfer protein · −629C/A polymorphism

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## Introduction

Metabolic syndrome is a relatively common disorder, affecting about 47 million in the USA. The etiology of metabolic syndrome is very complicated and several environmental and genetic factors play role in the incidence and prevalence of this disorder [1]. Cholesteryl ester transfer protein (CETP) (Gene ID: 1071) is a single gene

consisting of a 25 kb genomic DNA and is located on the long arm of chromosome 16 adjacent to the lecithin cholesterol acyltransferase (LCAT) (16q12–16q21). It consists of 16 exons and 15 introns [2, 3]. CETP is a glycoprotein that contains 476 amino acids with molecular weight of 74 kDa. CETP is involved in the transfer of cholesteryl esters, triglycerides, retinal ester, and phospholipids. In fact, CETP is a plasma protein that facilitates the transport of cholesteryl esters and triglycerides between the lipoproteins. So that, it promotes the transfer of cholesteryl esters from HDL to apolipoprotein B (apoB)-containing lipoproteins, such as VLDL and LDL, in exchange for triacylglycerols [4, 5]. Several studies have shown that genetic changes in this gene can lead to change in the concentration and function of CETP and therefore the level of LDL-C and HDL-C [6–8]. These CETP gene polymorphisms include I405 V, −629C/A, Taq1B and D442G can cause disease due to the change in the serum lipids pattern [9–13].

Human and animal studies demonstrated evidence supporting both anti- and proatherogenic effects of CETP. Takata et al. [14] showed that CETP promoter −1337C>T polymorphism can be affected on plasma CETP concentration and lipid profile, in patients with familial hypercholesterolaemia. In the previous study, we have provided the association of the CETP TaqIB genotypes ($B_1B_2$ and $B_2B_2$ genotypes) with CETP activity and lipid levels in the Iranian population (primary hyperlipidemic and control) [6]. We showed that the presence of the $B_2$ allele is significantly associated with both low plasma CETP activity and high HDL-C levels. It has been reported that TaqIB polymorphism of CETP gene is not associated with HDL and LDL size, in non-insulin-dependent-diabetes mellitus [15]. In contrast, other study has been documented the presence of direct correlation between CETP and LDL size distribution [16]. Ohtani et al. [17] investigated novel mutations of cholesteryl ester transfer protein (CETP) gene in Japanese hyperalphalipoproteinemic subjects, and found that the GG genotype of D442G polymorphism causes a moderate decrease in CETP activity along with increase in HDL-C.

Fat tissue is the main source of CETP and studies have shown that the overall mass of body fat is in direct relationship with the level of CETP, so that, with the diminution of total fat mass of the body, there was a significant decrease in the level of CETP [18]. Since the level of HDL-C, LDL-C, and body fat mass are important factors in metabolic syndrome, CETP gene polymorphism can be considered as an important pathogenic factor in metabolic syndrome.

Considering the important role of CETP protein in the metabolism of lipoproteins, it is expected that any change in the CETP gene could be involved in the metabolic syndrome. In addition to, there are yet no data available regarding the Iranian population with CETP −629C/A polymorphism. Thus, the main aim of this study was to determine the frequency of the −629C>A polymorphism in the promoter region of CETP gene of patients diagnosed with metabolic syndrome and its effect on CETP concentration and plasma lipid pattern in comparison with healthy controls.

## Materials and methods

This case–control study included 400 Iranian individuals (200 patients and 200 healthy individuals). A group of 200 patients with metabolic syndrome who were referred to an endocrinologist in Hamadan, west of Iran, from October 2009 to September 2010 were included in this study. The subjects with metabolic syndrome had at least three of the following five components: (1) a fasting plasma glucose level of ≥100 mg/dl; (2) a systolic blood pressure of ≥130 mmHg or diastolic blood pressure of ≥85 mmH; (3) a plasma HDL cholesterol level of <40 mg/dl for men or <50 mg/dl for women; (4) a plasma triglyceride level of ≥150 mg/dl; and (5) a BMI of ≥25 kg/m$^2$ [1]. Patients with renal disorders, high blood pressure, pregnant women, and patients taking anti hyperlipidemic agents were excluded from the study.

Patient demographic parameters such as sex, age, systolic and diastolic blood pressure, waist circumference, body weight, and BMI were recorded. Fasting blood samples (5 ml) were collected in tubes containing EDTA, and analysed for biochemical parameters. The plasma level of triglycerides, total cholesterol, HDL-C and fasting blood sugar was determined using spectrophotometry and commercially available kits (Pars Azmoun, Iran). The concentration of LDL-C was calculated using Friedwald formula and in the samples with higher level of TG (>400), direct measurement was used for quantification of LDL-C. The concentration of CETP was determined using ELISA kit from Cusabio company (China).

DNA was extracted using standard DNA extraction kits (Cinagen, Iran) and the quality and quantity of the extracted DNA was determined using spectrophotometry and electrophoresis techniques. PCR technique was used to replicate the 222 bp sequence of −629C/A in the promoter region of CETP gene. The PCR reaction was carried out in a total volume of 30 µl containing buffer 10× (3 µl), 0.3 µg genomic DNA, 10 mM Tris–HCl pH 8.4, 1.5 mM $MgCl_2$, 100 µM dNTPs, 40 pM of each primer and 0.5 U Taq DNA polymerase. The primers used for PCR were as follows [19]:

*F: 5′-ttc ttg gcc cca gct, gta gg-3′*
*R: 5′-gaa aca gtc ctc tat gta gac ttt cct tga tat gca taa aat acc act gg-3′*

The thermocycler conditions after optimizing the technique were: initial denaturation at 94 °C for 5 min followed by 30 cycles of amplification, each cycle consisting of 60 s at 94 °C, 60 s at 62 °C and 30 s at 72 °C, in a PTC-200 MJ-Research Peltier thermocycler. The reaction ended with an additional 10 min of extension at 72 °C.

The replication of the desired sequence was evaluated on agar gel 1 % and the replicated samples were prepared for adding restriction Enzymes. Into 10 µl of PCR product, 1 unit of restriction enzyme Van 91I and 3 µl buffer together with 16 µl nuclease free water (up to 30 µl) was added and then left for 2 h in 37 °C temperature. Then the mixture was exposed to 65 °C for 10 min in order to inactivate the enzyme.

### Statistical analysis

Data was analyzed using SPSS software, and presented as mean ± SD.

$p < 0.05$ was set as statistical significance level.

In order to compare clinical and biochemical findings of patients and controls, independent $t$ test was applied. Analysis of variance and multiple Tukey tests were used to analyze laboratory findings in three genotype groups among the patients and controls.

## Results

The demographic data, clinical status, and biochemical parameters of the studied population have been presented in Table 1.

**Table 1** Characteristics of the study population

| | Control group | Patient group | $p$ value |
|---|---|---|---|
| Sex (men/women) | 105/95 | 91/109 | NS |
| Age (year) | 43.4 ± 11.3 | 45.1 ± 12.7 | NS |
| BMI (kg/m$^2$) | 25.9 ± 4.1 | 30.1 ± 4.9 | 0.001 |
| Waist (cm) | 88.8 ± 10 | 101 ± 9.5 | 0.001 |
| Systolic blood pressure (mmHg) | 115 ± 11.8 | 128 ± 17.8 | 0.001 |
| Diastolic blood pressure (mmHg) | 77 ± 7 | 83 ± 9.7 | 0.001 |
| FBS (mg/dl) | 88.6 ± 9.8 | 105.4 ± 35.5 | 0.001 |
| Cholesterol (mg/dl) | 175.2 ± 31.7 | 202.4 ± 36.5 | 0.001 |
| TG (mg/dl) | 128.3 ± 48 | 191.6 ± 70.4 | 0.001 |
| HDL-C (mg/dl) | 46.6 ± 8 | 41.3 ± 5.7 | 0.001 |
| LDL-C (mg/dl) | 103.3 ± 28 | 121.8 ± 32.7 | 0.001 |
| CETP (µg/ml) | 1.53 ± 0.34 | 1.64 ± 0.32 | 0.001 |

*NS* not significant

As it is shown in the table the BMI, waist circumference, blood pressure and fasting blood sugar, cholesterol, triglyceride, LDL-C, and CETP in patients were significantly higher than controls, whereas HDL-C was lower.

The primers have been used in this study were mismatch so that the presence of −629C/A polymorphism creates a restriction site for VAN 1I enzyme. Thus the existence of a restriction site for this enzyme in promoter region was referred to as A and it's absence as C.

Clinical findings, in both patients and controls in three genotypes CC, CA, and AA of −629C/A polymorphism in the promoter region of CETP gene have been shown in Tables 2 and 3.

In the control group, cholesterol and LDL-C levels were significantly higher in AA genotype, whereas systolic blood pressure was lower in these subjects.

In multiple comparison analysis using Tukey HSD, it was found that LDL-C and TC levels in AA genotype were significantly higher compared to CC and CA genotypes, whereas systolic blood pressure was lower in this genotype than in CC and CA genotypes. In the patient group there was not any significant difference between the genotypes.

Multiple comparison analysis using Tukey HSD revealed that the concentration of CETP in AA genotype was significantly lower than those of the CC and CA genotypes in the patients and controls ($p < 0.05$) (Tables 2, 3).

In the control group, 20.5 % were homozygous for the C and 3.5 % for the A allele, whereas in patient group the values were 28.5 and 18 %, respectively. The −629 A allele was found at frequencies of 41.5 and 45 % in the control and patient groups. The frequency of the three genotypes, AA, CA, CC was significantly different in patients compared to the controls ($p$ value $< 0.05$), so that CA genotype was the most common among the samples (76 and 53.5 % in control and patient groups, respectively) and AA genotype was higher in patient group. The frequency of the alleles, was not significantly different between the two groups ($p$ value $> 0.05$) (Table 4).

The odds ratio for metabolic syndrome was 1.54 for the −629 A allele, but it was not significant ($p = 0.064$).

## Discussion

The metabolic syndrome is characterized by disturbed lipid and carbohydrate metabolism and is clinically defined by abdominal obesity, hyperlipidemia, hyperglycemia and high blood pressure. Descriptions for the metabolic syndrome have been planned by the National Cholesterol Education Program (NCEP) and World Health Organization (WHO) [20, 21].

**Table 2** Clinical findings, in control group according to CETP/−629 genotype

| | CC $N = 41$ | CA $N = 152$ | AA $N = 7$ | $p$ value |
|---|---|---|---|---|
| BMI (kg/m$^2$) | 25.3 ± 4 | 26 ± 4.1 | 25.7 ± 4.7 | 0.58 |
| Waist (cm) | 86.8 ± 11.6 | 89.14 ± 9.4 | 93.14 ± 12.6 | 0.22 |
| Systolic blood pressure (mmHg) | 115 ± 13 | 115 ± 11.2 | 102 ± 9.5 | 0.02 |
| Diastolic blood pressure (mmHg) | 78 ± 0.7 | 77 ± 0.7 | 76 ± 0.9 | 0.4 |
| FBS (mg/dl) | 87.68 ± 8.2 | 88.8 ± 10.4 | 89.7 ± 4.4 | 0.78 |
| Cholesterol (mg/dl) | 172.68 ± 27 | 173.94 ± 32 | 217.14 ± 25 | 0.001 |
| TG (mg/dl) | 126.7 ± 37.5 | 128.5 ± 51 | 135.1 ± 32.7 | 0.90 |
| HDL-C (mg/dl) | 46.4 ± 6.7 | 46.34 ± 6.9 | 45 ± 6.4 | 0.88 |
| LDL-C (mg/dl) | 99.9 ± 26.5 | 102.36 ± 27.4 | 144 ± 23.1 | 0.001 |
| CETP (μg/ml) | 1.64 ± 0.3 | 1.50 ± 0.3 | 1.34 ± 0.2 | 0.017 |

* $p$ value calculated after adjustment for sex, age, family relation and alcohol use

**Table 3** Clinical findings in patients group according to CETP/−629 genotype

| | CC $N = 57$ | CA $N = 107$ | AA $N = 36$ | $p$ value |
|---|---|---|---|---|
| BMI (kg/m$^2$) | 30.9 ± 5.2 | 29.78 ± 5.2 | 29.9 ± 3.7 | 0.37 |
| Waist (cm) | 101.67 ± 9.9 | 100.88 ± 9.9 | 100.36 ± 7.7 | 0.79 |
| Systolic blood pressure (mmHg) | 128 ± 1.9 | 128 ± 1.8 | 127 ± 1.5 | 0.98 |
| Diastolic blood pressure (mmHg) | 84 ± 1 | 82 ± 1 | 83 ± 0.8 | 0.78 |
| FBS (mg/dl) | 101.53 ± 18.5 | 107.61 ± 40.9 | 105.22 ± 39.2 | 0.58 |
| Cholesterol (mg/dl) | 201.75 ± 41.4 | 201.01 ± 35.5 | 207.47 ± 30.9 | 0.65 |
| TG (mg/dl) | 186.75 ± 61.6 | 186.89 ± 70.4 | 213.11 ± 80.4 | 0.13 |
| HDL-C (mg/dl) | 41.16 ± 5.4 | 41.9 ± 6.2 | 39.53 ± 4.7 | 0.10 |
| LDL-C (mg/dl) | 121.07 ± 31.1 | 120.86 ± 34.2 | 125.83 ± 31.3 | 0.72 |
| CETP (μg/ml) | 1.74 ± 0.3 | 1.62 ± 0.3 | 1.52 ± 0.29 | 0.004 |

* $p$ value calculated after adjustment for sex, age, family relation and alcohol use

**Table 4** CETP/−629 genotype and allele frequencies in patient and control groups

| | Control (%) $n = 200$ | Patient (%) $n = 200$ |
|---|---|---|
| Genotype* | | |
| CC | 20.5 | 28.5 |
| CA | 76 | 53.5 |
| AA | 3.5 | 18 |
| Allele frequency** | | |
| C | 58.5 | 55 |
| A | 41.5 | 45 |

* $p$ value $< 0.05$; ** $p$ value$>0.05$

Several studies have shown that a number of chromosomal regions can be related to the syndrome such as APOA5, lipoprotein lipase (LPL), ApoA1, ApoE, Peroxisome Proliferator-activated receptor (PPAR) [22, 23].

The plasma cholesteryl ester transfer protein increases the transfer and substitution of cholesteryl ester and triglyceride between HDL-C and apo B-containing particles. Due to the main role of CETP protein in the metabolism of lipoproteins, it is assumed that genetic polymorphism in the CETP gene may be involved in the metabolic syndrome.

Our results revealed that the distribution pattern of CC, CA, and AA genotypes among patients and controls was significantly different while the frequency of the alleles was not significantly different. We found that the CETP −629 genotype/allele frequencies in the Iranian population are slightly different from those reported for other populations [9, 24].

The genotype's frequency of −629C>A polymorphism in Iranian population is similar to that seen in the Icelandic population [25]. They reported a significant difference between control group and patients with myocardial infarction, so that CA genotype was the most common among the all individuals (50.6 % in controls group and 54.2 % in MI subjects) [25]. These findings are consistent with our study. We indicated that the CA genotype is the most common among the samples (76 and 53.5 % in control and patient groups, respectively.) These results have confirmed by several studies [9, 24].

The frequency of A allele of CETP −629C/A polymorphism in this study is 45 and 41.5 %, in the patient and control groups, respectively. We obtained that frequency of

A allele in patient group is higher than control group. This finding is different from previous report that performed by Eiriksdottir et al. [25]. In their study, the frequency of the A and C alleles were 52 and 48 % in controls, while it was 48 and 52 % in patients group. Other studies showed that the frequency of A allele was 0.469 in Belfast population [9] and 0.64 in Tamilian population [24]. The frequency of A allele has been reported to be 48 and 52 % in healthy withe and East Asian individuals [26]. These findings are in agreement with the fact that Asian Indians have a high frequency of A allele [9, 24].

The effects of gene polymorphisms on the factors involved in the metabolic syndrome and the level of CETP was investigated by several studies [24–30] racial.

Dachet et al. [9] reported −629C/A polymorphism in 563 healthy individuals, so that they were men aged 25 to 64 years who were randomly sampled from the population of Lille (northern France), Toulouse (southwestern France), Belfast (northern Ireland), and Strasbourg (eastern France) . In this study A allele of this polymorphism was associated with higher level of HDL-C. Healthy individuals with CC genotype had lower concentration of HDL-C, while in CA genotype their concentrations were in the middle of two AA and CC genotypes.

Eiriksdottir et al. [25] in a study on 388 patients with myocardial infarction in comparison with 794 controls (Icelandic men) demonstrated that in the case of −629C/A polymorphism, the risk of disease is 1.16 fold more than when there is not this polymorphism. They demonstrated that individuals with AA genotype had higher concentration of HDL-C compared to the CC genotype.

In a study on the effect of −629C/A polymorphism on the lipid pattern of healthy volunteers, Padmeja et al. [24] demonstrated that the concentration of HDL-C, LDL-C, cholesterol, and TG was not different among different genotypes. This study reported that the concentration of HDL-C was high in AA genotype and was low in CC genotype group. We did not find similar results in our study. Our results showed that in AA genotype, the concentration of LDL-C and TC was higher in the control group; however there was no significant difference in the patients group. This paradox can be due to sampling and related limitations of the study. Therefore we assume that with increasing the sample size we can get more accurate results.

Our results on the effect of −629C/A polymorphism on the CETP concentration was in accordance with previous findings by others [9, 19]. We found that the highest level of CETP was in CC genotype (1.64 ± 0.30 μg/ml in the control group and 1.74 ± 0.30 μg/ml in the patient group) and the lowest concentration was related to the AA genotype (1.34 ± 0.20 μg/ml in the control group and 1.52 ± 0.29 μg/ml in the patient group) while CA genotype had intermediate level of CETP concentration (1.50 ± 0.3 μg/ml in the control group and 1.64 ± 0.3 μg/ml in the patient group).

Dachet et al. [9] showed that in the presence of A allele of −629C/A polymorphism the CETP concentration was lower compared to the others.

Klerkx et al. [19] also studied the concentration of CETP protein in three genotypes AA, CC, and CA. They found that the lower concentration of CETP was in AA group (1.63 μg/ml), while CC genotype had the highest concentration (1.99 μg/ml) and CA genotype revealed the intermediate level of CETP concentration (1.88 μg/ml).

This region of CETP gene includes several regulatory elements. The human CETP concentration and its' expression controlled by several factors, such as corticosteroids, fatty acids, cellular cholesterol content and transcription factors. Goff et al. [31] reported that the SP1 and SP3 transcription factors can bind to −629 site in CETP promoter, thus CETP concentration can be regulated by −629 site.

Therefore the effect of the CETP promoter −629C/A polymorphism on the concentration and control of CETP can be explained. It can be concluded that the −629 AA genotype was associated with high cholesterol; high LDL-C and low CETP level, so that it can be related to metabolic syndrome. However, we need the larger samples for increase precision of our study and further information of metabolic and environmental factors that modulate the expression of the CETP gene is essential.

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