Original Article

The Relationship Between Genetic Variations of the Cholesteryl Ester Transfer Protein Gene and Coronary Artery Disease in Turkish Subjects

Türkler'de Koroner Arter Hastalığı ve Kolesterol Ester Transfer Proteinin Genetik Varyasyonu Arasındaki Ilişki

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Abstract

Objective. Although the relationship between cholesteryl ester transfer protein (CETP) and cholesterol metabolism has been characterized in recent years, the effect of CETP genetic variants associated with coronary artery disease (CAD) is still unclear. Therefore, we investigated the association between CETP gene polymorphism and levels of lipid in patients with CAD.

Materials and Methods. We conducted a case-control study that included 194 unrelated subjects who underwent coronary angiography for suspected ischemic heart disease. This group was divided into 96 patients with angiographically documented CAD and 98 subjects (individuals matched for age and gender) without angiographically documented CAD (CAD-free subjects), all of whom were studied to examine the genotypic distribution of the CETP gene polymorphism in CAD. Genotyping was performed via polymerase chain reaction.

Results. Of the 96 patients with CAD, 38 (40%) were B1B1, 42 (44%) B1B2 and 16 (16%) B2B2, compared with the control subjects, of which 35 (36%) were B1B1, 44 (45%) B1B2 and 19 (19%) B2B2. There were no significant differences between patients with CAD and control subjects in the distribution of the CETP gene polymorphism. Patients with the B1B1 genotype had lower high-density lipoprotein-cholesterol (HDL-C) and higher triglyceride (TG) levels than patients with the B2B2 genotype ($p<0.05$). In addition, among control subjects HDL-C levels were significantly higher in subjects with the B2B2 genotype than in subjects with the B1B1 genotype ($p<0.01$).

Conclusion. Our results suggest that genetic variations of the CTEP gene may be responsible for low HDL-C levels but may not be considered as a risk factor for CAD in the Turkish population.

Keywords: Coronary artery disease, Coronary angiography, Cholesteryl ester transfer protein, Genetic

Özet

Amaç. *Son yıllarda kolesterol metabolizması ile kolesterol ester transfer proteini (KETP) arasındaki ilişki bilinmesine rağmen, KETP'nin genetik varyantlarının koroner arter hastalığı (KAH) ile ilişkisi hala açık değildir. Bu nedenle çalışmamızda, KAH'lı hastalarda lipid düzeyleri ile KETP gen polimorfizmi arasındaki ilişki araştırmayı amaçladık.*

Gereç ve Yöntem. *İskemik kalp hastalığı şüphesiyle koroner anjiyografi ile incelenen 194 hasta üzerinde olgu-kontrol çalışması yapıldı. Anjiyografi ile 96 kişinin KAH ve 98 kişininde (cinsiyet ve yaş eşleşmiş) KAH olmadığı belgelenerek, KAH'da KETP gen polimorfizminin genotipik dağılımı çalışıldı. Genotip, polimeraz zincir reaksiyonuyla belirlendi.*

Bulgular. *Koroner arter hastalığı olan 96 hastanın 38'i (40%) B1B1, 42'si (44%) B1B2 ve 16'sı (16%) B2B2 olup kontrol bireyleri ile kıyaslandığında 35'i (36%) B1B1, 44'ü (45%) B1B2 ve 19'u (19%) B2B2 idi. KETP gen polimorfizminin genotipik dağılımı için kontrol bireyleri ile KAH'lı hastalar arasında önemli farklar yoktu. B1B1 genotipine sahip hastalar B2B2 genotipine sahip hastalara oranla daha yüksek trigliserid ve daha düşük yüksek-dansiteli lipoprotein kolesterol (HDL-K) düzeyine sahipti ($p<0.05$). Ayrıca, kontrol bireyleri arasında HDL-K düzeyleri B2B2 genotipine sahip bireylerde B1B1 genotipine sahip bireylere göre önemli oranda yüksek bulundu ($p<0.01$).*

Sonuç. *Bulgularımız gösterdiki, Türk toplumunda düşük HDL-K düzeyleri için KETP'nin genetik varyantları sorumlu olabilir. Ancak KAH için bir risk faktörü olma ihtimali göz ardı edilebilir.*

Anahtar Kelimeler: *Koroner arter hastalığı, Koroner anjiyografi, Kolesterol ester transfer protein, Genetik*

Introduction

Plasma lipoprotein profile is one of the major factors used to assess the risk of atherosclerotic cardiovascular disease. The inverse association between high density lipoprotein–cholesterol (HDL-C) levels and coronary artery disease (CAD) risk has been known for over 25 years [1,2]. Plasma HDL-C levels are regulated by genes and environmental factors. The cholesteryl ester transfer protein (CETP) functions in the process of reverse cholesterol transport by transferring esterified cholesterol from HDL-C to low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) in exchange for triglycerides (TG) [3].

Plasma CETP is a highly hydrophobic glycoprotein consisting of 476 amino acids and 4 N-linked glycosylation sites [4]. The human CETP gene contains 16 exons, encompassing 25 kbp genomic DNA, and is located on the long arm of chromosome 16 near the lecithin cholesterol acyltransferase (LCAT) gene [5]. Several polymorphisms at the CETP locus have been identified [6], of which TaqIB is the most studied. This polymorphism is characterized by a silent base mutation affecting the 277th nucleotide in intron 1. The allele carrying the cutting site for the TaqI enzyme is called B1, whereas the one in which the cutting site is missing is known as B2.

The B2 allele has been shown to be associated with lower levels of CETP activity and with higher levels of HDL-C in most [7-11], but not all [12,13] studies. The discrepancies in these reports could be attributed to ethnic differences [12-14], environmental factors [10,15,16] or gender [15]. The frequency of the less common B2 allele has been consistently reported to be about 44% in Caucasians [7,8,11,15], somewhat lower in Koreans (38%) [17] and higher in South East Asians (51%) [18].

The east Anatolia region of Turkey presents an unusually high rate of cardiovascular mortality that, at the present time, is the highest in the country [19]. Therefore, the aim of this study was to estimate allele frequencies of the TaqIB polymorphism, and to investigate the relationship between this polymorphism and plasma lipid levels, taking into account other biological and environmental factors in Turkish patients with CAD from the east Anatolia region of Turkey. The results of this study should contribute to our understanding of the genetic and environmental factors associated with cardiovascular risk.

Materials and Methods

Selection of cases and controls

The study group was compiled between October 2004 and April 2006, and was comprised of individuals who had been referred for coronary angiography because of chest pain or for noninvasive tests that were compatible with myocardial ischemia at the University Research Hospital. Patients above the age of 75 years, those receiving lipid-lowering drugs and those with a history of coronary bypass surgery and/or angioplasty were excluded from the study. This study was conducted on 96 unrelated patients with an age ranging from 48 to 72 years with angiographically proven CAD. Diagnosis of CAD was based on the presence of >50% stenosis in one of the coronary arteries. The control group consisted of 98 unrelated subjects who were referred to the cardiology department of the university hospital for coronary angiography because of suspected ischemic heart disease. All patients in the control group were between the ages of 47-69 and were evaluated during the same period; their clinical histories, physical examination and angiographies excluded the presence of ischemic heart disease. Subdivision of CAD patients into stable angina pectoris and acute coronary syndrome was performed on the basis of combining the medical history, ECG and cardiac Troponin changes.

Patients and control subjects came from the same geographical area (northeast Turkey). Participating patients and controls were interviewed regarding their history in terms of diabetes, hypertension, hyperlipidemia, smoking and body mass index. The grading of the stenosis was based on the consensus opinion of the two cardiologists who were blinded for the history and lipid profile of the patients. The diagnosis was also made by two cardiologists blinded with respect to the lipid and CETP data. Ethical clearance was obtained from the institute.

Sample collection

Twelve hour fasting blood samples were taken after informed consent had been given by patients and controls, and these were analyzed for serum lipids including cholesterol, TG, LDL, HDL-C, C-reactive protein (CRP) and ethylenediaminetetraacetate (EDTA) tubes for analysis of the fibrinogen levels.

DNA preparation

We obtained a 10-mL venous blood sample from the antecubital vein in EDTA-treated vacutainers and DNA was extracted from these samples using QIAGEN DNA elution columns.

Analysis of CETP gene mutations

After DNA extraction, amplification of a fragment containing 535 bp in intron 1 was obtained via polymerase chain reaction (PCR) according to the method of Fumeron et al. [16]. Briefly, 0.5 Ag of DNA, 50 pmol of each primer, 5 µL of PCR buffer and 0.25 U of Taq DNA polymerase (Q Biogene, France) were mixed in a final volume of 50 µL. The amplification program was 5 min at 95°C, with the following cycle repeated 35 times: 30 s at 62°C, 1 min at 72°C and 30 s at

95°C, and a final step of 3 min at 72°C. The PCR product was hydrolyzed with 10 U of Taq I (Appligene, 10 U/µL) at 65°C for 2 h. After separation by electrophoresis on a 2% agarose gel, the digestion products were revealed by ethidium bromide staining.

Statistical analysis

Data analyses were conducted using SPSS 11.0 software. The results are summarized as means ± SD. Univariate testing of independent factors was performed using the 2 statistic for dichotomous variables and Student's t test for continuous variables. This statistical test was also performed to examine whether the genotype frequencies were in Hardy-Weinberg equilibrium. In the analysis of CETP subtypes, variance analysis or Kruskal-Wallis tests were used depending on the distribution of data (for normally and abnormally distributed data, respectively). Risk factors for CAD development were also analyzed via multivariate logistic regression. Statistical significance for all analyses was accepted at a level of $p<0.05$.

Table 1. Baseline characteristics of the studied population

	Patients (n=96)	Controls (n=98)
Age (years)	58.8±9.4	58.6±9.7
Gender (M/F), n	72/24	73/25
Family history of CAD, (n), %	(49) ,51	(24), 25***
Smoking, (n), %	(48), 50	(42), 43
Alcohol consumers, (n), %	(24) 25	(19) 20
Diabetes, (n), %	(14), 15	(6), 6*
Hypertension, (n), %	(37), 39	(26), 27*
Body mass index, kg/m^2	27±4	26±4
Waist circumference, cm	96.4±9.4	91.3±8.3**
Total cholesterol, mg/dL	190±50	180±36
HDL cholesterol, mg/dL	35±8.7	35±8.3
LDL cholesterol, mg/dL	123±46	118±33
Triglycerides, mg/dL	173±93	142±72**
CRP, mg/dL	20±29	14±24*
Fibrinogen, mg/dL	258±94	238±78*
B1B1, (n), %	(38), 40	(35), 36
B1B2, (n), %	(42), 44	(44), 45
B2B2, (n), %	(16), 16	(19), 19

The results are shown as mean ± SD. n: number of individuals.
Significantly different from healthy subjects.
*p<0.05; **p<0.01; ***p<0.001.

Results

Ninety-six angiographically proven CAD cases (72 males, 24 females) and 98 normal, angiographically proven CAD-free controls (73 males, 25 females) were evaluated. The mean age of the patients was 58.8±9.4 years, while that of the controls was 58.6±9.7 years. As expected, CAD patients had more conventional risk factors than did control subjects. Table 1 displays baseline characteristics of the patients and controls.

The prevalence of diabetes mellitus, hypertension and a positive family history of CAD was significantly higher in patients than in controls. Mean plasma fibrinogen, waist circumference, TG and CRP levels were significantly higher in the patient group as compared with the control group. In addition, median values of LDL, total cholesterol and body mass index (BMI) were higher in the patient group when compared with the control group; however, the differences were not significant.

The frequencies of the CETP genotypes in the 98 population controls were 35 (36%) for B1B1, 44 (45%) for B1B2 and 19 (19%) for B2B2. The B1B1, B1B2 and B2B2 genotypes were found in patients with CAD at frequencies of 38 (40%), 42 (44%) and 16 (16%), respectively. There were no significant differences in the allele distribution at this polymorphic locus between the control sample and patients with CAD.

There was a clear association of the B1 allele with HDL-C levels. Patients with the B1B1 genotype had lower HDL-C levels compared to those with the B1B2 and B2B2 genotypes ($p<0.05$). However, in the patient group, the TG levels were significantly higher in association with the B1B1 genotype than with the B1B2 and B2B2 genotypes ($p<0.05$). Table 2 shows plasma lipid levels by CETP TaqIB and clinical characteristics in the patients. In the control group, B1B1 carriers showed significantly lower HDL-C levels compared with B1B2 and B2B2 carriers ($p<0.01$). The B1B1 genotype smokers had lower HDL-C compared with the B1B1 genotype nonsmokers, but the difference was not significant. These data are not shown.

The frequencies of the B2 allele of the TaqIB polymorphism of the CETP gene were determined in patient and control subjects to be 0.39 and 0.42, respectively. The differences in CETP TaqIB polymorphism allele frequencies between patients and controls were not significant. In patients, carriers of the B2 allele had a considerably smaller waist circumference than carriers of the B1 allele ($p<0.05$), though there was no relationship between LDL and total cholesterol concentrations and CETP TaqIB polymorphism allele frequencies. There were no significant differences in terms of LDL, TG and total cholesterol concentrations between carriers and non-carriers of the B2 allele in the control group.

A family history of CAD was found to be significantly more prevalent (51%) in the patient group compared with the control group (25%, $p< 0.001$, OR=3.2, 95% CI=1.9-5.3). Waist circumference was significantly higher in the patient group than in the control group (96.4±9.4 cm vs. 91.3±8.3 cm, $p< 0.01$, OR=2.1, 95% CI=1.1-4.1). We also found increased TG levels in the patient group over the control group (173±93 mg/dL vs. 142±72 mg/dL, $p< 0.01$, OR=1.7, 95% CI=1.1-2.9). When we compared the CETP TaqIB polymorphism in the patients with acute coronary syndrome and stable angina pectoris, no differences were found.

Discussion

The allele frequency of the CETP TaqIB polymorphism varies across populations. The current study reports the association of the CETP TaqIB polymorphism with lipid parameters and CAD in Turks from the East Anatolia region of Turkey, and was designed using a population of homogeneous ethnic origin and place of residence. A previous study [7] investigating the association of the TaqIB polymorphism with plasma lipoproteins in 14 university student populations from 11 European countries, concluded that the overall frequency of the B2 allele in these countries was 0.44 (95% CI: 0.406–0.466), with no significant variation across Europe. Allele frequencies of the CETP TaqIB polymorphism found the East Anatolia region were similar to those reported in Caucasians [7,8,11,15], but differed from those reported for Koreans [17], South East Asians [18], and Chinese [20]. In our study population, the allelic frequency for the B2 allele was found to be 0.40. The prevalent rate observed in our results is similar to rates reported in one other study conducted in Turkey [21], as well as in studies with Koreans [17], and Chinese [20]. However, the B2 allele frequency was slightly lower in our study than has been reported in Caucasians [7,8,11,15]. The reason for this lack of consistency among studies is unclear but the prevalence of the TaqIB polymorphism significantly varies in different populations. There may be other causes for these discrepancies, such as differences in the prevalence of other genetic and environmental risk factors in different populations and in different selection criteria.

The significance of the CETP polymorphism in the development of atherosclerosis is still controversial [22]. Ordovas et al. [8] reported an association of the B2 allele with lower CAD risk only in males, but this association was no longer present after adjustment for various risk factors. The B2 allele of the TaqIB polymorphism of the CTEP gene was associated with high plasma HDL-C levels and could be related

to a lower risk of myocardial infarction in alcohol consumers [16]. In another study, the B2 allele was shown to have a protective effect against the progression of atherosclerosis in subjects with previous signs of CAD, but no implications could be drawn from these data regarding the risk of developing CAD [11]. Corbex et al. [23] did not observe any significant association between the TaqIB polymorphism and the risk of myocardial infarction. In another study, no relationship was found between the CETP TaqIB polymorphism and the overall risk of CAD [13]. The results of these studies support our results, since we did not find any relationship between the CETP TaqIB polymorphism and the risk of CAD. A possible explanation for the variability across populations could be the composition of the groups of subjects included in each study in terms of ethnic origin, dietary habits, customs, and other genetic predisposition factors. To minimize the influence of such factors on our results, age and gender were matched in the studied population. Goto et al. [24] reported that the B2B2 genotype in the CETP TaqIB polymorphism, may act as a protective factor against atherosclerosis only when it decreases the CETP level. It should also be noted that the CETP mass in general correlates to total and LDL cholesterol, making it an indirect atherogenic parameter. On the other hand, Kuivenhoven et al. [25] investigated heterogeneity at the CETP gene locus, which influences plasma CETP concentration and HDL cholesterol levels. These authors reported that the presence of a TaqIB site in intron 1 (B1 allele), the presence of an Msp 1 site in intron 8 (M1 allele) and the presence of an Rsa 1 site in exon 14 (R2 allele) were strongly associated with decreased plasma HDL cholesterol. In another study by Horne et al. [26], TaqIB is a less precise marker of CAD risk than a combination of other less common CETP SNPs (single nucleotide polymorphism), and should therefore be replaced by these markers in future studies. Since CETP mass and CETP SNPs were not analyzed in our study, the relationship between the CETP TaqIB polymorphism and the risk of CAD was not examined using

Table 2. Clinical and biochemical characteristics according to CETP Taq IB genotypes in the patient group

	B1B1 (n=38)	B1B2 (n=42)	B2B2 (n=16)
Age, (years)	61±10	60±13	55±11
Gender (M/F), n	28/10	30/12	10/6
Family history of CAD, (n) %	(20), 53	(21), 49	(8), 50
Smoking, (n), %	(22), 59	(18), 44	(8), 50
Alcohol consumers, (n), %	(9) 24	(11) 26	(4) 25
Diabetes, (n), %	(5), 13	(7), 16	(2), 12
Hypertension, (n), %	(14), 37	(17), 40	(6), 38
Body mass index, kg/m^2	27±4	26±3	25±4
Waist circumference, cm	95.2±8.2	92.4±9.4	93.4±8.3
Total cholesterol, mg/dL	189±44	192±55	189±47
HDL cholesterol, mg/dL	33±6	36±5	40±7*
LDL cholesterol, mg/dL	127±38	123±53	116±40
Triglycerides, mg/dL	229±89	184±83	162±10*
CRP, mg/dL	19±32	17±26	26±34
Fibrinogen, mg/dL	280±102	247±95	248±56

n: number of individuals. *p<0.05 Kruskal-Wallis.

these parameters in the present study.

Several studies have examined the CETP TaqIB polymorphism and have reported its association with plasma lipid levels. The results of these studies have been inconsistent and there have been discrepancies among the different studied populations. Some studies reported that TaqB2 allele is not associated with increased HDL-C levels among Italian migrants to Australia [12] and among healthy African Americans [27]. On the other hand, the association between the B2B2 genotype and high HDL-C levels has been reported previously in several studies [7,16,21,28]. In addition, in a study by Arca et al. [29], the association between TaqB2 and HDL-C level was not found in a group of 415 subjects with angiographically documented CAD. In contrast, B2B2 carriers were significantly associated with increased HDL-C level among the population control in this study. We also found a similar effect of the TaqIB B1B1 genotype on HDL-C levels in patients with CAD and control subjects. Furthermore, we found HDL-C levels to be lower in our study population than has been reported for Caucasian populations [8,30,31], which confirms the low HDL-C level previously reported in Turkish populations [21,32,33]. This difference cannot be completely explained by the CETP TaqIB polymorphism. In another study related to this issue, it was reported that there was a higher hepatic lipase activity in Turkish men and women than in non-Turkish controls [34]. Thus, with respect to factors affecting HDL-C levels, elevated hepatic lipase activity stands out as a distinguishing characteristic between Turkish and non-Turkish groups.

An interesting result of the present study was that TG levels were significantly higher in B1B1 genotypes than in B1B2 and B2B2 genotypes among the patient group. This finding has been supported by published data showing that plasma HDL-C levels correlate with CETP only in hypertriglyceridemic humans and monkeys [35], strongly suggesting that its regulation occurs mainly via hetero-exchange of cholesteryl ester in HDL-C with TG in other lipoprotein fractions. Another reasonable explanation for this finding is the interaction of CETP with hypertriglyceridemia, which may contribute to low-HDL-C levels [35].

Study limitations

The most important limitation of the present study was the small size of the patient and control groups. In addition, we did not have the opportunity to perform intravascular ultrasonography, and the definition of CAD-free subjects was made by coronary angiography.

In conclusion, our results suggest that the TaqIB polymorphism may be responsible for low HDL-C levels in Turkish populations. The present study does not support the hypothesis that the TaqIB polymorphism is associated with a reduced risk of CAD in the Turkish population. These results show that the effect of CETP polymorphism on HDL-C concentration and CAD depends on a person's ethnic origin.

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Conflict interest statement The authors declare that they have no conflict of interest to the publication of this article.

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