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ORIGINAL ARTICLE

Taq1B Polymorphism of Cholesteryl Ester Transfer Protein (CETP) and Its Effects on the Serum Lipid Levels in Metabolic Syndrome Patients

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Abstract The metabolic syndrome (MetS) is one of the most important risk factors for type 2 diabetes and cardiovascular disease. This syndrome is characterized by abdominal obesity, hypertension, insulin resistance, and dyslipidemia. The plasma origin of Cholesteryl ester transfer protein (CETP) is responsible for transferring cholesterol esters from high-density lipoprotein particles to apolipoprotein B containing lipoproteins compartment. We conducted this study to investigate the association between CETP gene Taq1B (rs708272) polymorphism in the metabolic syndrome among Iranian subjects. A sample size of 200 patients diagnosed with

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MetS together with 200 healthy donors as control were enrolled in this study. The investigation of polymorphism was performed by the use of polymerase chain reaction and restriction fragment length polymorphism analysis. To determine the relationship between polymorphism and lipid profile, we measured lipids and CETP concentration in metabolic syndrome and control subjects. Genotype distribution and allelic frequencies of polymorphism were determined and compared in both groups. Our findings showed that all clinical and biochemical characteristics in patients differed from the control group. The results showed that genotype and allele frequency of the Taq1B polymorphism was not significantly different between two groups. Instinctively, CETP was significantly higher in metabolic syndrome (1.64 ± 0.32 μg/ml) than in control (1.53 ± 0.34 μg/ml). A low level of CETP was found in blood of B2B2 typified genotype. In spite of Taq1B polymorphism on ester transfer protein concentration, no direct correlation was found between this polymorphism and metabolic syndrome.

Keywords Cholesteryl ester transfer protein · Taq1B polymorphism · Metabolic syndrome

Introduction

Metabolic syndrome (MetS) is increasing and recognized as the main problem of public health (Isomaa et al. 2001). This syndrome correlates with the increased risk of type 2 diabetes and cardiovascular disease (CVD) (Lakka et al. 2002; Lorenzo et al. 2003). However, the etiology of metabolic syndrome is extremely complex and multi-environmental and genetic factors are involved in the occurrence and outbreaks of this disorder. This syndrome is clinically characterized by abdominal obesity, hypertension, insulin resistance, and dyslipidemia (Eckel et al. 2005). Cholesteryl ester transfer protein (CETP) gene (Gene ID: 1071) exists as a single copy with a 25 kb size and, located on the long arm of chromosome 16 (21q16), comprising 16 exons and 15 introns (Kadowaki et al. 2006). Humans CETP is a 74 kDa glycosylated protein with 476 amino acids produced by the liver, spleen, small intestine, adipose tissue, adrenal glands, kidneys, heart and skeletal muscle. This protein is highly hydrophobic and its non-polar amino acid content is approximately 44 % (Alan 1993). Based on the literature, this protein is responsible for transferring cholesterol esters from high-density lipoprotein (HDL) particles to apolipoprotein B (apoB) containing lipoprotein including very-low-density lipoprotein (VLDL), remnants of VLDL, intermediate-density lipoproteins, (IDL) and low-density lipoprotein (LDL-C). Studies indicated that genetic variations in the CETP gene were related to CETP concentration and its activity (Kuivenhoven et al. 1997).

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So far, several polymorphisms including −629 C/A, I405 V, D442G, −971 in the human CETP gene have been reported to cause disease by altering serum lipid profiles (Dachet et al. 2000; Ritsch and Patsch 2003). Because of the critical role of HDL-C, LDL-C, and CETP that facilitate transferring of Triglycerides (TG) from TG-rich lipoproteins to HDL and LDL cholesterol ester, CETP gene polymorphism may play an important role in the pathogenesis of the metabolic syndrome (Grundy et al. 2006). In the recent study, Li et al. showed that CETP TaqIB gene polymorphism was associated with high prevalence of CAD and concluded that the presence of the B1 allele in CETP TaqIB gene might be responsible for CAD in the Chinese Han population. In the previous study, we already investigated the relation between 629 C/A polymorphism of CETP and metabolic syndrome, our results showed that the −629 AA genotype was linked with high cholesterol; high LDL and low CETP level, therefore it can be related to MetS (Akbarzadeh et al. 2012). In this study we determined the frequency of the Taq1B polymorphism in the intron 1 region of CETP gene in patients diagnosed with MetS and studied its effect on CETP activity and serum lipid patterns in comparison with healthy controls.

Materials and Methods

Sample Preparation

We designed a case-control study that included 400 Iranian individuals subdivided into main groups including 200 patients and 200 healthy people based on below formula. The patients group with MetS was selected among the patients who were referred to an endocrinologist in Hamadan, Iran, from October 2009 until September 2010. Our exclusion criteria were renal disorders, pregnancy, and taking anti hyperlipidemic agents. The Hamdan University of Medical Sciences Ethics Committee approved the study. Selection of patient with metabolic syndrome was done according to the standards of NCEP. All information about sex, age, systolic blood pressure, diastolic blood pressure, waist circumference and body mass index (BMI) was recorded. 5 ml of fasting blood in tubes containing EDTA for determining biochemical parameters was taken. The measurement of the plasma level of TG, total cholesterol, HDL and fasting blood sugar (FBS) was done using spectrophotometry and commercially available kits (Pars Azmoun, Iran). We used Fried Wald formula (Friedewald et al. 1972) for calculating the concentration of LDL-C and it was measured directly in the samples with higher level of TG (400 mg/dl). The concentration of CETP was revealed via using an ELISA kit (Cusabio, China).

Genetic Analysis

Genomic DNA was extracted using Cinagen DNA extraction kits (CN: DN 8115C). The quality and quantity of DNA were confirmed using electrophoresis and spectrophotometry respectively. Fragment of 535 bp in intron 1,Taq1B position in CETP gene was amplified using polymerase chain reaction (PCR) technique with primers as follows; Forward sequence: 5′-cac tag ccc aga gag agg agt gcc-3′ and

Reverse sequence: 5′-ggc agc cct gag ccc agc cgc aca cta ac-3′. Total volume of PCR reaction was 30 µl which contained 300 ng genomic DNA, 10 mM Tris–HCl) PH 8.4(2.4 mM $MgCl_2$ with 0.2 mM dNTPs, 10 pM each primer and 1 unit Taq DNA polymerase. The optimization was done and thermocycler conditions were the: initial denaturation at 96 °C for 5 min followed by 30 cycles of amplification, each cycle consisting of 60 s at 96 °C, 60 s at 58 °C and 45 s at 72 °C, in a PTC-200 MJ-Research Peltier thermocycler. The reaction completed with an additional 10 min of extension at 72 °C. The accuracy of the desired fragment was analyzed on 1 % agar gel. Then Restriction fragment length polymorphism(RFLP) technique was used for digesting PCR products. Next, the 10 µl of amplified samples were mixed with 1 unit of restriction enzyme Taq1 for 5 min at 65 °C and digestion were done.

Statistical Analysis

Data was analyzed by SPSS software. Quantitative variables stated as mean ± SD and $P < 0.05$ was considered significant. To compare the clinical and biochemical findings in two groups, t test was used. ANOVA and Tukey tests were applied to compare the results of laboratory tests in three genotypes of patients and control groups.

$$n = \frac{\left(Z1 - \alpha/2 + Z_{1-\beta}\right)^2 [P_1(1 - P_1) + P_2(1 - P_2)]}{(P1 - P2)^2}$$

Results

Demographic features of the study population are shown in Table 1. As shown in the Table 1, all clinical and biochemical characteristics in patients were significantly higher than the control group except HLD. The allele frequency and

Table 1 Demographic features of the study population

	Control group	Patient group	*P* value
Sex (men/women)	105/95	91/109	*NS*
Age	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	115 ± 11.8	128 ± 17.8	0.001
Diastolic blood pressure	77 ± 7	83 ± 9.7	0.001
FBS (mg/dl)	88.6 ± 9.8	105.4 ± 35.5	0.001
Chol (mg/dl)	175.2 ± 31.7	202.4 ± 36.5	0.001
Triglycerides (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

genotype distribution were 31 and 14 % respectively in healthy control group, which were homozygous for B1 and B2 alleles, while these values reached orderly to 33 % and 20.5 in non-healthy people enrolled to this study. No significant difference in frequency was obtained between the two groups.

Clinical characteristics were compared in patients and control groups of the three genotypes B1B1, B1B2, B2B2 of CETP Taq 1B polymorphism (Table 2, 3). In both groups, there was no significant difference between the measured parameters except CETP concentration with $P < 0.001$. Multiple comparison analysis using Tukey HSD showed that plasma CETP concentration in all genotypes in both groups was significantly different. Multiple logestic regression showed that the odds ratio for the B2 allele in metabolic syndrome was 1.09, but it was not significant ($P = 0.668$) (Table 4).

Discussion

Metabolic syndrome (MetS) is a relatively common disorder. The etiology of metabolic syndrome is very complicated and several environmental and genetic factors play role in the incidence and prevalence of this disorder. CETP is a plasma protein that simplifies the transport of cholesteryl esters and TG between the lipoproteins (Ford 2005; Kahn et al. 2005). It assembles TG from VLDL or LDL and exchanges them for cholesteryl esters HDL-C (Thompson et al. 2008). Because of the central role of CETP protein in the metabolism of lipoproteins, it is supposed that genetic polymorphism in CETP gene may be contributed to the metabolic syndrome (Sviridov and Nestel 2007). The allele and genotypic frequency of Taq1B polymorphisms in Iranian population was similar to other Asian population reported in previous studies (Cho et al. 2004; Ghasabeh et al. 2008; Schierer et al. 2012). Nearly all of previous studies have demonstrated that the frequency of alleles B1,

Table 2 Clinical findings, in control group according to *CETP*/Taq1B genotype

	B1B1 $N = 66$	B1B2 $N = 93$	B2B2 $N = 41$	P value
BMI (kg/m^2)	30.39 ± 5.1	29.98 ± 5.2	30.04 ± 4.3	0.87
Waist (cm)	100.08 ± 8.8	101.6 ± 9.9	101.05 ± 9.9	0.59
Systolic blood pressure	12.8 ± 1.9	12.7 ± 1.8	12.8 ± 1.4	0.96
Diastolic blood pressure	8.2 ± 0.9	8.3 ± 1	8.3 ± 0.7	0.68
FBS (mg/dl)	110.42 ± 34.5	100.94 ± 35.5	107.66 ± 36.6	0.23
Chol (mg/dl)	196.62 ± 36.6	202.08 ± 36.7	212.37 ± 34.2	0.09
Triglycerides (mg/dl)	184.15 ± 64.4	194.3 ± 70.4	197.32 ± 79.8	0.57
HDL-C (mg/dl)	41.39 ± 5.9	41.08 ± 5.7	41.46 ± 5.8	0.91
LDL-C (mg/dl)	116.5 ± 30.1	122.04 ± 33.2	129.9 ± 34.6	0.12
CETP (μg/ml)	1.95 ± 0.18	1.54 ± 0.15	1.35 ± 0.35	0.001

Table 3 Clinical findings, in patient group according to *CETP*/Taq1B genotype

	B1B1 $N = 62$	B1B2 $N = 110$	B2B2 $N = 28$	P value
BMI (kg/m^2)	26.27 ± 4.2	25.68 ± 4.2	25.74 ± 3.8	0.66
Waist (cm)	89.55 ± 9.7	88.16 ± 10.3	89.7 ± 9.9	0.60
Systolic blood pressure	115 ± 1.2	11.4 ± 1.3	11.5 ± 0.8	0.87
Diastolic blood pressure	76 ± 0.9	7.7 ± 0.6	7.8 ± 5.2	0.47
FBS (mg/dl)	89.8 ± 7.4	88.2 ± 11.6	8.7 ± 5.9	0.45
Chol (mg/dl)	181.84 ± 34.7	170.52 ± 29.9	178.86 ± 29.5	0.063
Triglycerides (mg/dl)	136.34 ± 34.7	127.08 ± 48.4	115.43 ± 29.7	0.15
HDL-C (mg/dl)	46.4 ± 7.2	45.68 ± 6.7	48.54 ± 6.4	0.14
LDL-C (mg/dl)	106.44 ± 30.4	99.85 ± 27.1	110.41 ± 24.8	0.12
CETP (μg/ml)	1.88 ± 0.24	1.45 ± 0.16	1.07 ± 0.17	0.001

Table 4 Multiple logistic-regression analysis of the genotype

Groups	P-value	95 % CI	Odds ratio
B2B2 + B1B2	0.668	0.72–1.67	1.09
B1B1	Reference	Reference	Reference

B2 in both control and patients groups did not show a significant difference and in the present study we also observed it (Ahmed et al. 2011).The effect of Taq1B polymorphisms on the contributing factors of metabolic syndrome such as age, waist circumference, systolic and diastolic blood pressure, FBS, TG, cholesterol, LDL, HDL was investigated in this study, and no significant difference was observed. The study performed by Sandhofer on the effects of Taq1B polymorphisms and risk of metabolic syndrome demonstrated that these polymorphisms significantly influenced the levels of HDL and LDL size and genotype B2B2 reduced the risk of metabolic syndrome by 32 % (Sandhofer et al. 2008). The effect of Taq1B polymorphism on the dyslipidemia and metabolic syndrome of Turkish population was studied, demonstrating that the B2B2 genotype was related to increased levels of HDL (Ozsait et al. 2008). Despite many studies which confirmed higher prevalence of HDL level in people with genotype B2B2, there are some studies which did not approve this issue (Boekholdt et al. 2005). Shu Meguro et al. studied patients with type 2 diabetes mellitus (Japanese population) and demonstrated that the concentration of HDL was not significantly different between various genotypes (Meguro et al. 2001). We also found similar results in our study. Most previous studies have shown that individuals with B1B1 genotype have lowest HDL and individuals with genotype B2B2 have highest HDL-C but we did not observe it in the present study (Ridker et al. 2009). In the present study, association of CETP concentration and Taq1B polymorphism were similar to previous studies. We found that B2B2 genotypes had lowest level of CETP concentration and B1B1 genotypes had highest level of it in both groups (Brousseau et al. 2002; Kauma et al. 1996).Wu et al. demonstrated that individuals with B2B2 allele had lowest level of

CETP and highest level of HDL (Wu et al. 2001). In another study, klerkx et al. showed that the concentration of CETP in B1B1, B1B2, B2B2 genotypes were 1.62, 1.87, and 1.95 μg/ml respectively. Therefor, B1B1 genotype had lower concentration of CETP and B2B2 genotypes had higher level (Klerkx et al. 2003). Because of the location of Taq1B polymorphism in intron-1 position of CETP gene, it is likely that this polymorphism is not functional and cannot directly regulate gene transcription, RNA splicing and ultimately has no effect on the activity and concentration of CETP (Hassanzadeh et al. 2009). Recently, it has been identified that this polymorphism is strongly correlated with other CETP polymorphisms. Most studies have shown that −629C/A polymorphism could be a good candidate to explain the observed effects of Taq1B polymorphism (Ahmad et al. 2011; Tenkanen et al. 1991). According to previous studies, it becomes clear that the relationship between CETP polymorphisms and its concentration is complex and ambiguous and changes in the concentration and activity of CETP cannot be easily attributed to specific polymorphisms. Thus, the effect of unfunctional polymorphisms such as Taq1B on the CETP concentration can be correlated with other functional polymorphisms. The causes of differences and similarities observed in many studies on the Taq1B polymorphism is not clear but could be due to various reasons such as differences in sample size, environmental factors, ethnic factors, selection criteria of patients and control groups, life style and diet.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflict of interest.

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