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Original Research Article

Association of Cholesteryl Ester Transfer Protein Gene Taq1B Polymorphism and the Associated Lipoprotein Levels with Coronary Artery Disease

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Conflict of interest: Nil

Abstract:

Background & Objectives: Cholesteryl ester transfer protein (CETP) is a hydrophobic glycoprotein with a crucial role in high-density lipoprotein cholesterol (HDL-C) metabolism. Its primary function is to transfer cholesteryl esters from HDL to apolipoprotein-B-containing particles in exchange for triglycerides. This process leads to a decrease in HDL-C concentration and an increase in non-HDL-C, contributing to the predisposition to atherosclerosis. The TaqIB polymorphism, located in intron 1 of the CETP gene, has been linked to plasma HDL-C concentrations. The study aimed to investigate the association between CETP gene TaqIB polymorphism, lipoprotein levels, and coronary atherosclerosis.

Materials and Methods: Genotype analysis was done on 146 patients with angiographically proven coronary atherosclerosis and 145 control subjects by polymerase chain reaction followed by restriction digestion. Serum lipoprotein levels were analyzed by enzymatic endpoint methods using an autoanalyzer.

Results: Patients had a significantly higher frequency of B1B1 genotype than control subjects (0.38 versus 0.21; p=0.000) with the age and sex-adjusted odds ratio of 2.4 (95% CI 1.6 to 3.2; p = 0.001), for developing coronary atherosclerosis. Significantly lower HDL-C (38.5 $\pm$9.7 mg/dL versus 48.2$\pm$9.9, p=0.000) was observed in coronary atherosclerosis patients as compared to control subjects.

Conclusion: The B1B1 genotype and the associated low HDL-C were significantly associated with coronary atherosclerosis.

Keywords: Cholesteryl ester transfer protein gene, Taq1B polymorphism, Lipoprotein, High-density lipoprotein cholesterol, Coronary atherosclerosis, Coronary Artery disease.

Introduction

In humans, lipoproteins play a crucial role in the development of coronary artery disease (CAD). The studies have demonstrated that high-density lipoprotein cholesterol (HDL-C) and atherosclerosis are inversely related.[1] Serum HDL-C levels are influenced by various genetic, hormonal, and environmental factors within distinct populations.

In addition to its anti-inflammatory and antioxidative effects, HDL-C also plays an important role in reverse cholesterol transport (RCT). Through RCT cholesterol is transported from the peripheral tissues to the liver with the help of HDL.[2] The cholesteryl ester transfer protein (CETP) plays an important role in RCT and the metabolism of HDL. [3,4] The hydrophobic glycoprotein CETP has 476 amino acids. Being a member of the lipid transfer lipopolysaccharide-binding protein family, it facilitates the transfer of cholesteryl esters from HDL-C to non-HDL-C in exchange for triglycerides.[5] Consequently, it alters the concentration of HDL-C and promotes atherogenesis. [6] Low levels of HDL-C [6,7] and elevated Low-density lipoprotein cholesterol (LDL-C) are linked to elevated plasma CETP levels.[8] Worldwide studies have shown that high CETP levels to be atherogenic. [9,10]

The CETP mRNA encodes a polypeptide of Relative molecular mass (*M*r) 53000 in humans. Then it is *n*-glycosylated at 4 sites and gives a mature form of CETP of *M*r 74000.[11] Evidence shows that CETP is primarily expressed in the liver, spleen, and adipose tissue whereas lower levels are found in the

small intestine, adrenal gland, heart, kidney, and skeletal muscle. [11,12] The CETP gene in humans is made up of 16 exons and spans 25 kilobase pairs. There it is, adjacent to the lecithin-cholesterol acyl transferase gene on chromosome 16q21. The CETP gene locus has several well-documented restriction fragment length polymorphisms (RFLPs). [13,14]

The most studied variation is the TaqIB polymorphism, which impacts the 277th nucleotide of the first intron of the CETP gene and is produced by a silent base alteration [13]. Two new alleles, B1 and B2, are the result of this polymorphism. The CETP TaqIB polymorphism influences the risk of CAD by altering the plasma CETP and HDL-C concentrations. [15,17] People who have the B1 allele tend to have higher levels of CETP activity, CETP mass, and lower levels of HDL-C, compared to those who carry the B2 allele. [16] The B1 gene has been linked to CAD in most of the studies, including those in Asians. [18,19]

In view of this, we have analysed the distribution of Cholesteryl ester transfer protein gene Taq1B polymorphism and the associated lipoproteins levels in CAD patients."

Materials and Methods"

In this case-control study, 145 people without a history of heart disease served as controls, whereas 146 people with CAD were considered cases. Participants had to have a significant coronary artery stenosis of more than 50% to be included in the study. A myocardial infarction that occurred within the last three months and a reduced degree of blockage were both used as exclusion criteria. Ethical approval was obtained and informed consent was provided by all participants. Outpatient department controls were chosen at random and matched on age, sex, and potential confounding variables such as alcoholism, smoking, hypertension, and diabetes. The research only included diabetes controls whose treadmill tests came back negative.

The study involved recording height, weight, recumbent blood pressure, and a 12-lead ECG for all participants. Blood samples were obtained following an overnight fast, with two test tubes utilized for collection. One sample was treated with EDTA as an anticoagulant, while the other was collected in a plain non-additive tube. Serum obtained from the latter was used for estimating lipid profiles. The anticoagulated sample underwent centrifugation at 2000 rpm for 20 minutes to obtain the buffy coat for DNA extraction.

The assessment of serum lipoprotein levels involved enzymatic methods with a fully automated clinical chemistry analyser (XL 300). The Esterase Oxidase method was employed for determining total cholesterol, while triglycerides were measured using a colorimetric enzymatic method. "HDL-C and LDL-C were analysed using the Immunoinhibition method, which relies on a modified precipitation technique utilizing polyvinyl sulfonic acid (PVS) and polyethylene-glycol methyl ether (PEGME). The accuracy of the method was enhanced by optimizing the quantities of PVS/PEGME and selected detergents meticulously."

CETP gene Polymorphism Screening

The extraction of DNA from the buffy coat utilized a modified high salt method [20]. Subsequently, a 535bp target region in the CETP gene was amplified through PCR using the forward primer 5'-CACTAGCCCAGAGAGAGGAGTGCC–3' and the reverse primer 5'-CTGAGCCCAGCCGCACACTAAC–3'. The amplification reaction, conducted with 1µg of genomic DNA, included 0.3µmol/L of each primer, a red dye master mix (Bangalore Genei) comprising 100µmol/L of each dNTP, 2.5µL of 10x reaction buffer, and 0.6 units of Taq DNA polymerase in a 25µl reaction volume. The PCR process involved DNA denaturation at 95ºC for 5 minutes, followed by 30 cycles of denaturation at 95ºC for 1 minute, annealing at 65ºC for 1 minute, and extension at 72ºC for 1 minute. A final extension was carried out at 72ºC for 10 minutes. Visualization of the PCR product representing the CETP gene (535bp fragment) was achieved through 2% agarose gel electrophoresis. Subsequently, the Taq1B polymorphism in the CETP gene was identified by digesting the PCR product with the Taq1 restriction enzyme (4 units for 2 hours at 65ºC) and analysing the fragments via 2% agarose gel electrophoresis. The B2 allele, lacking the restriction site, produced a 535bp fragment, while the B1 allele, possessing the restriction site, yielded cleaved fragments of 361bp and 174bp. Analysis was performed using a 100bp DNA ladder from Bangalore Genei.

For statistical analysis, genotype frequencies were determined by counting genotypes. Age, BMI, and serum lipid levels were compared between control subjects and patients using Student's t-test, with significance set at $p < 0.05$. The distribution of genotype frequencies between cases and controls was compared through chi-squared analysis. Additionally, the genotype frequencies in patients with single, double, and triple vessel disease, as well as controls were analysed using the chi-squared test.

To compare serum lipid levels between CETP Taq1B genotypes among cases and controls, a one-way ANOVA test was employed. Logistic regression analysis was performed to evaluate the interaction between human CETP Taq1B genotypes and other variables concerning the prevalence of coronary artery disease. Independent variables included in the analysis were age (quantitative) sex (male/female), smoking (yes/no), alcoholism

(yes/no), hypertension (yes/no), diabetes (yes/no), serum levels of cholesterol, triglycerides (quantitative). The analysis was executed by the SAS Statistical program Version 6.10 for Macintosh.

Results

Table 1 displays information on age, sex, distribution of conventional risk factors, BMI, and levels of total cholesterol, triglycerides, HDL-C, and LDL-C among patients and control subjects. It is noted that all confounding factors were matched, resulting in no significant differences between the two groups. However, significant differences were observed in total cholesterol, triglycerides, HDL-C, and LDL-C levels among the groups.

Table 1: Characteristics of CAD patients and controls

"Variables"	"Case"	"Control"	"p-value"
"Age"	50.82 ± 9.3	"50.81 ± 8.8"	"0.99 –NS"
"Sex male"	131 (89.7%)	"128 (88.3%)"	"0.69 –NS"
Female	15 (10.3%)	"17 (11.7%)"	
Diabetes mellitus	48 (51.1%)	"46 (48.9%)"	"0.83 –NS"
Hypertension	61 (48.8%)	"64 (51.2%)"	"0.69 –NS"
Smoking	87 (54%)	"74 (46%)"	"0.14 –NS"
Alcoholism	"66 (52.8%)"	59 (47.2%)	"0.44 –NS"
Body mass index	"25.36 ±3.25"	24.99 ± 3.14	"0.27 –NS"
Total cholesterol	"180.9 ±26.7""	"159.9 ±23.2"	"0.000 –S"
Triglycerides	"161.6 ±42.8"	"128 ±27.6"	"0.000 –S"
"High-Density lipoprotein"	"38.5 ±9.7"	"48.2±9.9"	"0.000 –S"
"Low-Density lipoprotein"	"106 ±25.3"	"82.1±25.1"	"0.000-S"

S-Significant, NS-Non-significant

Table 2 illustrates the genotype frequencies of the CETP gene in patients with CAD and control subjects. The observed genotype frequencies were B1B1 = 87, B1B2 = 138 and B2B2 = 66. The distribution of genotypes revealed that the B1B1 genotype was more prevalent among cases (38.4%) compared to controls (21.4%). Conversely, the B2B2 genotype was more common among controls (32.4%) than cases (13%).

The B1B2 genotype showed a higher frequency among cases (48.6%) compared to controls (46.2%). The p-value was 0.000, indicating statistical significance.

Table 2: CETP genotype frequencies among cases and controls

Genotype	Control	Case	p-value
"B1B1"	"31 (21.4%)"	"56 (38.4%)"	p= 0.000 – S
"B1B2"	"67 (46.2%)"	"71 (48.6%)"	
"B2B2"	47 (32.4%)	19 (13%)	

S-Significant.

For controls, single vessel, double vessel, and triple vessel disease groups the frequency of the CETP gene genotype is displayed in Table 3. The genotype frequencies of B1B1, B1B2, and B2B2 were respectively: 21.4%, 46.2%, and 32.4% in the control group; 16.4%, 63.6%, and 20% in the single vessel disease group; 26.8%, 63.4%, and 9.8% in the double vessel disease group and 72%, 20%, and 8% in the triple vessel disease group. The p-value was 0.000, indicating statistical significance."

Table 3: Genotype frequencies in control, single, double, and triple vessel disease groups

Genotypes & Alleles	Control n=145	Single vessel n=55	Double vessel n=41	Triple vessel n=50	p-value
B1B1	31 (21.4%)	9 (16.4%)	11 (26.8%)	36 (72%)	0.000-S
B1B2	67 (46.2%)	35 (63.6%)	26 (63.4%)	10 (20%)	
B2B2	47 (32.4%)	11 (20%)	4 (9.8%)	4 (8%)	

S-Significant.

Table 4 shows the difference in biochemical parameters between CETP Taq1B genotypes in controls. Significantly low HDL-C could be observed among the B1B1 genotype (41.87±8.73 mg/dL) when compared to B1B2 and B2B2 genotype individuals (p=0.00). There were significantly high triglycerides (137.65±26.53 mg/dL) and high LDL-C (92.62±24.79 mg/dL) among the B1B1 genotype when compared to other genotypes, the p-value was 0.01. Total cholesterol levels did not differ significantly among groups.

Table 4: Biochemical parameters among Taq1B genotypes in controls

Variables	B1B1	B1B2	B2B2	p-value
Total cholesterol (mg/dL)	166.01±21.03	159.78±22.96	155.69±24.64	0.17
Triglycerides (mg/dL)	137.65±26.53	129.98±27.1	117.91±26.59	0.01
High-density lipoprotein (mg/dL)	41.87±8.73	47.74±9.42	53.45±8.76	0.00
Low-density lipoprotein (mg/dL)	92.62±24.79	82.05±23.55	74.66±25.61	0.01

Table 5 shows the difference in biochemical parameters between CETP Taq1B genotypes in CAD patients. The HDL-C level was decreased in the B1B1 genotype (34.04±8.96 mg/dL) and it significantly differed among groups. There was a significantly high LDL-C (112.51±22.57 mg/dL) among the B1B1 genotype when compared to other genotypes, p value was 0.04. In patients with CAD total cholesterol and triglycerides were not differed significantly among genotypes.

Table 5: Biochemical parameters among Taq1B genotypes in CAD patients

Variables	B1B1	B1B2	B2B2	p-value
Total cholesterol (mg/dL)	184.53±22.03	179±27.83	177±34.5	0.41
Triglycerides (mg/dL)	169.95±40.84	158.81±42.16	147.48±48.15	0.11
High-density lipoprotein (mg/dL)	34.04±8.96	40.41±9.01	44.82±8.47	0.00
Low-density lipoprotein (mg/dL)	112.51±22.57	102.84±24.91	98.67±30.62	0.04

The risk of atherosclerosis among persons with the B1B1 genotype was evaluated using univariate analysis, as shown in Table 6, which illustrates the odds ratio calculation. The 95% confidence interval is 1.8 to 5.4, and the odds ratio is 3.1; the p-value is 0.000.

Table 6: Univariate analysis

Study Group	N	B2B2	B1B2	B1B1	p-value
Case	146	19	71	56	0.000 -S
OR (95% CI)		1	2.34 (1.3—3.8)	3.1 (1.8-5.4)	
Controls	145	47	67	31	

S-Significant.

The age and sex-adjusted odds ratio for developing coronary atherosclerosis, with the B1B1 genotype was 2.4 (95% CI 1.6 - 3.2; p = 0.001).

The CETP B1B1 genotype showed a statistically significant positive correlation coefficient in the multivariate analysis, even after adjusting for all potential confounding variables. These results point to an increased risk of atherosclerosis being linked to the CETP B1B1 genotype. On the flip side, HDL-C levels were negatively correlated with atherosclerosis risk, showing that higher HDL-C levels are associated with lower risk.

Discussion:

In humans, environmental and genetic factors together lead to coronary artery disease (CAD). [21] These factors could differ among different groups of people. [22,23] Research on the association between CETP genetic polymorphisms and coronary artery disease risk has been conducted on a global scale. [24,25] In this context, we performed this study to determine the association of CETP gene TaqIB polymorphism and its associated lipoprotein levels with coronary atherosclerosis.

Participants were 145 healthy individuals and 146 individuals with angiography-confirmed coronary heart disease (CAD). With a p-value of 0.000, suggesting statistical significance, genotyping analysis showed that the B1B1 genotype was much more prevalent among cases (38.4% than controls (21.4%). Cases were more likely to have the B1B2 genotype (48.6%) than controls (46.2%). This confirms the results of other large-scale investigations that have linked a specific CETP Taq1B variant to an increased risk of coronary atherosclerosis. [15,17]

The available evidence indicates that the B1B1 genotype was more frequent in patients with triple vessel disease (72%) compared to those with double vessel disease (26.8%) and single vessel disease (16.4%), as well as controls (21.4%). Control subjects were more likely to have the B2B2 genotype (32.4%) than patients with triple vessel disease (8%), double vessel disease (9.8%), or single vessel disease (20%). A statistically significant correlation between the B1B1 genotype and coronary atherosclerosis severity was shown by the p-value of 0.000.

In CAD patients, the HDL-C levels were varied by genotype, with B1B1 genotype persons having considerably lower levels (34.04±8.96 mg/dL) compared to B2B2 genotype individuals (44.82±8.47 mg/dL). A low HDL-C level increases the risk of atherosclerosis, and the B1B1 genotype is

related to a low HDL-C level (p = 0.000). Therefore, the B1B1 genotype and the low HDL-C that follow can be seen as separate variables that increase the occurrence of atherosclerosis. Consistent with previous research on populations in Scotland [26], the Netherlands [27], and the Framingham Study, we found that the B1B1 genotype was associated with reduced HDL-C. [17]

Additionally, compared to the B2B2 genotype (44.82+8.47 mg/dL), the B1B2 genotype was linked with substantially lower HDL-C levels (40.41+9.01 mg/dL) in CAD patients (p = 0.00). Because it is located within an intron, this polymorphism probably isn't part of a functional regulatory site, but it might be a marker for another one. Several base alterations in the 5′ promoter region lead to polymorphism like −1337C/T, −629C>A, and −971G/A. The link to these base changes might explain its effect on plasma CETP concentration, CETP activity, and HDL-C levels. [28,29] Those who possess the B1B1 genotype are 3.1 times more likely to be at a greater risk compared to those who do not, as indicated by the odds ratio of 3.1in the univariate analysis (95% CI 1.8 to 5.4). A 2.4 (95% CI 1.6 to 3.2; p = 0.001) odds ratio for developing coronary atherosclerosis was associated with the B1B1 genotype after controlling for age and sex.

According to multivariate analysis, the negative correlation coefficient for HDL-C suggests that a high HDL-C level is protective against atherosclerosis. However, an increased risk of atherosclerosis is associated with both high levels of LDL-C and the predominance of the B1B1 genotype, as shown by the positive correlation coefficient for the two variables.

Conclusion

In conclusion, the study indicates that the human Cholesteryl ester transfer protein TaqIB polymorphism and HDL-C were significantly associated with Coronary artery disease (CAD). Specifically, the B1B1 genotype and the correlated low levels of HDL-C appear to be significant predictors of coronary atherosclerosis. This underscores the potential importance of the CETP gene in HDL-C metabolism and its role in the development of CAD.

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