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Relationship between the cholesterol ester transfer protein *Taq*IB polymorphism and the lipid-lowering effect of atorvastatin in patients with coronary atherosclerotic heart disease

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ABSTRACT. This study aimed to investigate the relationship between the cholesterol ester transfer protein (CETP) gene *Taq*IB polymorphism and the lipid-lowering effect of atorvastatin in patients with coronary atherosclerotic heart disease. Two hundred eighty-eight patients were divided into a control group, an acute coronary syndrome (ACS) group, and a stable coronary heart disease (CHD) group. Blood biochemical indices were determined using the enzyme method, and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis was performed to study the *Taq*IB polymorphism of the CETP gene. The ACS and stable CHD groups were treated with atorvastatin, and blood lipid levels were reexamined after three months. Plasma levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and lipoprotein(a) were all significantly higher in the ACS

and stable CHD groups compared to the control group ($P < 0.05$ or $P < 0.01$). After three months of treatment with atorvastatin, plasma levels of TC, LDL-C, triglycerides (TG) (only in patients with genotype B2B2), and lipoprotein(a) (only in patients with genotype B1B2) were all significantly decreased ($P < 0.05$ or $P < 0.01$). After treatment, the plasma level of TG was lower in patients with genotype B2B2 compared to patients with genotypes B1B1 or B1B2 (B1 carriers) ($P < 0.01$). Therefore, the CETP *Taq*IB polymorphism is associated with the lipid-lowering effect of atorvastatin in patients with CHD.

Key words: Cholesterol ester transfer protein; Gene; Atorvastatin; Coronary artery disease

INTRODUCTION

Coronary atherosclerotic heart disease has become one of the major diseases threatening human health. Acute coronary syndrome (ACS) is caused by incomplete or complete coronary obstruction due to the rupture of unstable atherosclerotic plaque in the coronary artery, and its clinical manifestations include unstable angina, acute myocardial infarction, and sudden death (Pillois et al., 2009; Ranjith et al., 2009). Intervention of risk factors for coronary heart disease (CHD) has increasingly attracted attention from medical workers. Dyslipidemia is a recognized important risk factor for CHD. Previous studies (Hsieh et al., 2007; Tsujita et al., 2007; Kimura, 2009; Estévez-González et al., 2010) have demonstrated that the cholesterol ester transfer protein (CETP) plays a vital role in lipid metabolism. Expression of the CETP gene determines its function, thereby affecting lipid metabolism and CHD occurrence and development. Statins can reduce the low-density lipoprotein cholesterol (LDL-C) level in blood, and thus increase the incidence and mortality rate of cardiovascular and cerebrovascular events. Therefore, whether subtle relationships exist among CETP, statins, and blood lipids deserves further investigation. Effects of CETP gene expression on the lipid-lowering effects of statins have not yet been reported. In this study, the blood lipid profiles of 99 patients with stable CHD, 147 patients with ACS, and 42 controls were observed. The relationship between the CETP *Taq*IB polymorphism and serum lipid levels was analyzed in patients with CHD, and the effect of the CETP *Taq*IB polymorphism on lipid-lowering effects of atorvastatin was investigated.

MATERIAL AND METHODS

Subjects

Two hundred eighty-eight patients who were admitted to our hospital between January 2011 and October 2012 were divided into a control group, an ACS group, and a stable CHD group. This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Tongji Hospital. Written informed consent was obtained from all participants. In the control group (42 cases, including 28 males and 14 females with an average age of 55.83 ± 13.05 years), all patients were admitted with chest pain as their chief complaint, but yielded negative coronary angiography results. These patients

had not taken lipid-lowering drugs, and hepatic and renal functions were normal. Patients with blood diseases were excluded.

The ACS group (147 cases, including 105 males and 42 females with an average age of 56.69 ± 12.51 years) comprised 88 cases of unstable angina and 59 cases of acute myocardial infarction. The inclusion criteria were as follows: the time of persistent chest pain was more than 20 minutes; dynamic ST-T changes appeared in the electrocardiogram (ECG); the levels of markers for myocardial injury (creatine kinase and its isoenzyme MB, myoglobin, and troponin) were increased by more than three times (more than two or three of the above events occurred simultaneously). Furthermore, coronary angiography results revealed ≥70% diameter stenosis in at least one of the left anterior descending coronary artery, left circumflex artery, and right coronary artery, with visible unstable plaque or thrombus projection. The blood flow was lower than grade 2 in thrombolysis in myocardial infarction (TIMI) with or without culprit vessels. No patients had taken lipid-lowering drugs or had a history of long-term hormone use.

In the stable CHD group (99 cases, including 69 males and 30 females, with an average age of 73.66 ± 15.45 years), the inclusion criteria were as follows. Patients had a history of exertional angina. Newly diagnosed CHD patients were suspected to have CHD based on ECG, treadmill, blood biochemistry, and echocardiography examination, with a positive coronary arteriography result and negative markers for myocardial injury. No patients had taken lipid-lowering drugs.

The height, weight, and waistline of all patients were measured, and the body mass index (BMI) [weight (kg) / height^2 (m^2)] was calculated.

Blood biochemical indices

In the ACS group, patients lay in repose, and elbow venous blood was taken within 24 h after disease onset. In the stable CHD and control groups, elbow venous blood was taken in early morning with supine position. Three milliliters venous blood was used for separation of serum. Total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and lipoprotein(a) were detected using the ADVIA1650 automatic biochemical analyzer (kits were provided by COLAB Company, Germany). Fasting blood glucose (FPG) was detected using the hexokinase method. For the ACS and stable CHD groups, 2 mL fasting venous blood was anticoagulated using edetate disodium (EDTA). After shaking, standing, and demixing, samples were stored at -20°C until used for analysis of CETP *Taq*IB genotypes.

Analysis of CETP *Taq*IB genotypes

After thawing fasting venous blood, the hemolysis method using low-permeability buffer was applied for extraction of genomic DNA from white blood cells. CETP *Taq*IB gene fragments were amplified using polymerase chain reaction (PCR) with primer 1 (5'-CACTAGCCCAGAGAGAGGAGTGC-3') and primer 2 (5'-CTGAGCCCAGCCGCACA CTAA-3'), respectively. PCR conditions were as follows: 300 mM Tris-HCl, 75 mM ammonium sulfate, 12.5 mM $MgCl_2$, pH 10.0, degeneration at 95°C for 30 s, annealing at 62°C for 30 s, and extension at 72°C for 60 s for 35 cycles. The amplified product was digested with *Taq*I enzyme, and then 2% agarose gel electrophoresis was conducted for identification of CETP *Taq*IB genotypes (Figure 1).

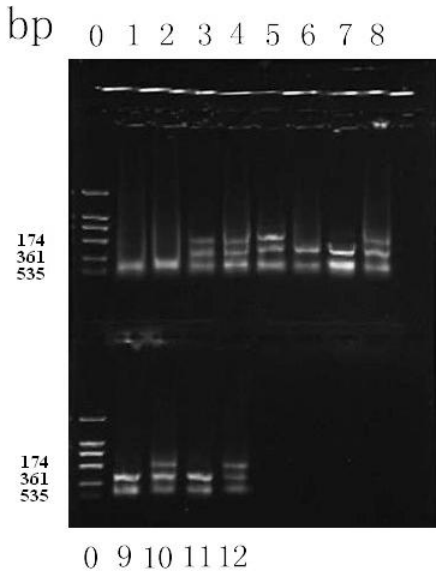

Figure 1. Enzyme electrophoresis of CETP *Taq*IB. *Lane 0* = marker; *lanes 1* and *2* = one band (535 bp), defective heterozygote B2B2; *lanes 6*, *7*, *9*, and *11* = two bands (361 and 174 bp), mutant homozygote B1B1; *lanes 3*, *4*, *5*, *8*, *10*, and *12* = three bands (535, 361, and 174 bp), mutant heterozygote B1B2.

Treatment and follow-up

After admission, all patients in the ACS and stable CHD groups were treated with statin drugs to lower blood lipid levels. The specific scheme was as follows: 20 mg atorvastatin (Pfizer Inc., USA) was orally administered one time every night. After three months of treatment, outpatient follow-up was performed by telephone appointment, and blood lipid was reexamined using the methods described above.

Statistical analysis

Data are reported as means ± SD. Statistical analysis was performed using the SPSS 17.0 statistical software. The Student's *t*-test was used to analyze differences before and after lipid lowering therapy with atorvastatin, and single factor analysis of variance (ANOVA) was conducted for comparing blood lipid profiles among multiple groups. $P < 0.05$ was considered to be statistically significant.

RESULTS

Related indices comparison

As shown in Table 1, before lipid-lowering therapy with atorvastatin, the plasma levels of TC, LDL-C, and lipoprotein(a) were significantly higher in both the ACS and stable CHD groups compared to the control group ($P < 0.05$ or $P < 0.01$). There was no significant

difference in either TG or HDL-C levels among the three groups. Waistlines were significantly larger in the ACS group compared to the control group ($P < 0.05$), FPG levels were markedly higher in the ACS and stable CHD groups compared to the control group ($P < 0.05$), and there was no significant difference in BMI among the three groups.

Table 1. Comparisons of related indexes among 3 groups.

Group	Control group	ACS group	Stable CHD group
N	42	147	99
TC (mM)	4.18 ± 0.75	4.67 ± 1.08*	4.64 ± 0.87*
TG (mM)	1.48 ± 1.03	1.59 ± 0.98	1.69 ± 1.56
HDL-C (mM)	1.07 ± 0.33	1.04 ± 0.29	1.05 ± 0.26
LDL-C (mM)	2.60 ± 0.64	3.12 ± 0.93**	3.00 ± 0.77**
Lipoprotein(a) (mg/L)	259.92 ± 105.15	347.74 ± 172.37**	348.89 ± 201.08*
BMI (kg/m^2)	23.92 ± 3.23	24.09 ± 2.95	24.02 ± 3.01
Waistline (cm)	86.10 ± 9.99	88.52 ± 8.66*	87.97 ± 9.02
FPG (mM)	5.52 ± 1.10	6.86 ± 2.48*	6.22 ± 2.01*

*$P < 0.05$ and **$P < 0.01$ compared with control group.

CETP *Taq*IB genotype effects

As shown in Table 2, HDL-C levels in patients with genotype B1B2 were significantly higher compared to those in patients with genotype B1B1 ($P = 0.005$). There was no statistical difference in any blood lipid index between B1B2 and B2B2 patients.

Table 2. Effects of CETP TaqIB genotypes on blood lipid levels.

Lipid profile index	CETP TaqIB genotype		
	B1B1	B1B2	B2B2
N	82	73	21
TC (mM)	4.68 ± 0.93	4.52 ± 0.89	4.64 ± 0.99
TG (mM)	1.66 ± 1.02	1.44 ± 1.05	1.68 ± 1.27
HDL-C (mM)	0.99 ± 0.23	1.10 ± 0.32**	1.10 ± 0.27
LDL-C (mM)	3.12 ± 0.79	2.93 ± 0.75	3.07 ± 0.79
Lipoprotein(a) (mg/L)	358.35 ± 191.30	344.64 ± 175.68	355.38 ± 213.32

**$P < 0.01$ compared with B1B1; DNA specimens of 176 patients in ACS group and stable CHD group were obtained for determination of genotype.

Atorvastatin effects

After three months of lipid-lowering therapy with atorvastatin, the plasma levels of TC, LDL-C, TG (only in B2B2 patients), and lipoprotein(a) (only in B1B2 patients) all decreased significantly ($P < 0.05$ or $P < 0.01$) (Table 3).

Association between allele and lipid-lowering effects of atorvastatin

After 3 months of treatment with atorvastatin, only the plasma level of TG in B2B2 patients significantly decreased ($P < 0.05$). Furthermore, the plasma level of TG in B2B2 patients was lower than that in B1B1 and B1B2 patients (B1 carriers) after treatment ($P = 0.009$).

Table 3. Effects of atorvastatin on blood lipid levels.

Blood lipid profile	B1B1	B1B2	B1 carriers	B2B2
N	56	42	98	10
TC (before treatment) (mM)	4.83 ± 0.96	4.66 ± 0.90	4.73 ± 0.92	4.77 ± 1.12
TC (after treatment) (mM)	4.25 ± 1.03**	3.73 ± 1.00**	3.96 ± 1.01**	3.70 ± 0.83**
ΔTC (mM)	-0.57 ± 1.00	-0.92 ± 1.06	-0.72 ± 1.03	-1.07 ± 0.71
N	56	42	98	10
TG (before treatment) (mM)	1.73 ± 1.09	1.58 ± 1.16	1.61 ± 1.10	2.12 ± 1.95
TG (after treatment) (mM)	1.82 ± 1.40	1.60 ± 0.93	1.77 ± 1.01	1.21 ± 0.82*
ΔTG (mM)	0.10 ± 1.11$^{\Delta\Delta}$	0.03 ± 1.11$^{\Delta}$	0.07 ± 1.10$^{\Delta\Delta}$	-0.92 ± 1.33
N	54	42	96	9
HDL-C (before treatment) (mM)	0.96 ± 0.22	1.01 ± 0.28	0.97 ± 0.24	1.08 ± 0.35
HDL-C (after treatment) (mM)	0.97 ± 0.24	1.01 ± 0.38	0.98 ± 0.20	1.78 ± 0.21
ΔHDL-C (mM)	0.01 ± 0.25	0.00 ± 0.34	0.01 ± 0.28	0.10 ± 0.22
N	54	42	96	9
LDL-C (before treatment) (mM)	3.27 ± 0.79	3.06 ± 0.76	3.20 ± 0.77	3.11 ± 0.95
LDL-C (after treatment) (mM)	2.65 ± 0.78**	2.23 ± 0.69**	2.42 ± 0.70**	2.23 ± 0.78**
ΔLDL-C (mM)	-0.63 ± 0.83	-0.82 ± 0.87	-0.71 ± 0.85	-0.89 ± 0.70
N	25	21	46	4
Lipoprotein (a) (before treatment) (mg/L)	398.64 ± 250.85	394.72 ± 178.23	396.53 ± 212.49	465.51 ± 324.39
Lipoprotein (a) (after treatment) (mg/L)	387.46 ± 193.89	333.14 ± 163.73**	355.26 ± 198.73	306.50 ± 182.01
ΔLipoprotein (a) (mg/L)	-11.28 ± 184.78	-61.57 ± 86.98	-34.24 ± 149.04	-159.00 ± 165.54

*P <0.05 and **P < 0.01 compared with before treatment; $^{\Delta}$P < 0.05 and $^{\Delta\Delta}$P < 0.01 compared with B2B2 group. Δ, difference value after treatment with before treatment. Lipid lowering therapy with atorvastatin was performed on all patients in stable CHD group and ACS group; Number of patients was reduced due to loss to follow-up after 3 months of therapy.

DISCUSSION

It is currently believed that CHD is caused by multiple genetic factors combined with environmental factors (Tsujita et al., 2007; Kimura, 2009), and that lipid metabolism disorder can lead to the occurrence of CHD (Kolovou et al., 2011). The present study demonstrated that the plasma levels of TC, LDL-C, and lipoprotein(a) were significantly higher in the ACS and stable CHD groups compared to the control group. These blood lipid profiles have been confirmed with several independent lines of evidence (Kimura et al., 2011). The plasma level of HDL-C was lower in the ACS group than the stable CHD group, and was much lower than that of the control group. This indicates that HDL-C has a stabilizing effect on lipid plaque.

LDL-C and HDL-C contents have been shown to be closely related to the occurrence of CHD (Kuivenhoven et al., 1998; Lemieux et al., 2000; Krauss, 2001). In addition, CETP is a key enzyme in plasma lipoprotein that influences TG and HDL-C metabolism (Huang et al., 2011). Therefore, improvement of CETP activity can lead to increased TG, LDL-C, and very low-density lipoprotein cholesterol (VLDL-C) levels, and decreased HDL-C levels. The activity and transport functions of CETP are affected by genetic and environmental factors (Ghasabeh et al., 2007; López-Ríos et al., 2011). The action mechanism of CETP on atherosclerosis is complex. CETP defects or decreased activity leads to increased HDL-C levels and enlargement of LDL particles, which prevents the occurrence of atherosclerosis (Kuivenhoven et al., 1998). At the same time, decreased CETP activity may result in the accumulation of large particles of HDL and in the reduction of neogenic small and dense HDL particles. Therefore, the capacity for uptaking cholesterol from peripheral cells is decreased, which affects reverse cholesterol transport and leads to atherosclerosis (Lemieux et al., 2000; Stancáková et al., 2006). The pathological, physiological, and clinical significance of

CETP can be more accurately evaluated by investigating the relationship between CETP and atherosclerosis from a molecular biology perspective. CETP gene expression plays a decisive role in lipid transport and lipoprotein composition. To date, more than 10 novel genotypes have been found resulting from genetic polymorphisms and mutations of the CETP gene (Wu et al., 2006), and the *Taq*IB polymorphism is particularly universal (Hassanzadeh et al., 2009). Based on allele differences, the *Taq*IB polymorphism can be divided into three genotypes: B1B1, B1B2, and B2B2, corresponding to the mutant homozygote, heterozygote, and defective homozygote, respectively. Allele B1 is closely related to increases in plasma CETP levels and activity (Kuivenhoven et al., 1998), and is correlated with LDL-C levels.

In the present study, the HDL-C level was significantly higher in patients with the B1B2 genotype compared to patients with the B1B1 genotype. This is consistent with results of Kuivenhoven et al. (1998) that showed that plasma CETP activity was lower in B1B2 patients than in B1B1 patients, resulting in increased plasma HDL-C levels. Consequently, atherosclerosis could not easily occur. According to this principle, plasma HDL-C levels should be relatively higher in patients with genotype B2B2. However, no significant difference was found in any blood lipid index between B1B2 and B2B2 genotypes in the present study. One possible explanation is that the frequency of B2B2 in the population is smaller than that of the other two genotypes. Indeed, B2B2 was the least common genotype in the present sample, which might have influenced the results. Another possibility is that the expression intensity of the defective allele B2 is weaker than that of the mutant allele B1.

The protective effect of atorvastatin in patients with CHD has been confirmed in several studies (Boekholdt et al., 2005). In the present study, after three months of lipid lowering therapy with atorvastatin, the plasma level of HDL-C was increased in patients with all CETP *Taq*IB genotypes, but the difference was not significant, and there were no significant differences among the three genotypes. In addition, after treatment with atorvastatin, the plasma TG level was significantly decreased in B2B2 patients, and was lower than that of B1B1 and B1B2 patients (B1 carriers).

Due to the dependence of lipid transport and lipolysis processes on TG, the plasma TG level has become known as an important factor affecting the HDL-C level. When the concentration of TG in HDL increases to a certain degree, TG is hydrolyzed by hepatic lipase, resulting in a decrease in particle size and an increase in density. Consequently, it is rapidly cleared from plasma, leading to a reduction in the HDL-C level and an increase in the risk of CHD (Rajman et al., 1996; Hokanson et al., 1999).

The B2B2 genotype is associated with decreased CETP activity and increased HDL-C levels (Yilmaz et al., 2005; Xu et al., 2006; Yijiang et al., 2008). In patients with B2B2, the plasma TG level significantly decreased after lipid-lowering therapy with atorvastatin. The CETP gene contains 16 exons and 15 introns, and *Taq*IB is the first intron (Corbex et al., 2000). The *Taq*IB polymorphism plays a key role in regulating the expression of the whole gene, which is possibly because it is a target of statins for exerting its pharmacological function. This polymorphism can cause changes in the promoter region rather than in any one amino acid (Boekholdt and Thompson, 2003), and thus affects CETP activity directly and changes the cholesterol ester transport speed, leading to a series of changes in the blood lipid profile. Although the decrease in the TG level in patients with the B2B2 genotype after treatment with atorvastatin was demonstrated in the present study, the relationship among *Taq*IB, statins, and blood lipid still needs further investigation.

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