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Effect of CETP Polymorphism on Atorvastatin Lipid-Regulating Effect and Clinical Prognosis of Patients with Coronary Heart Disease

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Background: The aim of this study was to investigate the influence of genetic polymorphism of cholesteryl ester transfer protein (CETP) gene polymorphism –629C/A on the therapeutic effect of atorvastatin and clinical outcome in Han Chinese patients with coronary heart disease (CHD).

Material/Methods: From October 2011 to December 2012, 348 patients with angiographically confirmed CHD were recruited. CETP gene polymorphism was determined by polymerase chain reaction-restricted fragment length polymorphism (PCR-RFLP) method. Serum level of CETP was determined with enzyme-1inked immunosorbent assay (ELISA). Lipid 1evel in all patients was determined at baseline and after 12 months of treatment with 20 mg/d of atorvastatin. All the patients were followed-up at least 12 months. Major adverse cardiac events, including death, non-fatal infarction, revascularization, and stroke (MACE), were recorded.

Results: The frequency of the –629A allele was 0.412. Compared with CC or CA genotypes, individuals with AA genotype had lower CETP levels (P=0.026) and higher high-density lipoprotein cholesterol (HDL-C) levels (P=0.035). After 12 months of atorvastatin therapy, carriers with CC genotype had greater reduction of low-density lipoprotein cholesterol (LDL-C) (P<0.001), reduced LP (a) (P=0.005), and elevated HDL-C (P=0.045) compared with CA or AA genotypes. The incidence of MACE after a mean follow-up of 17.3±5.2 months was 8.8%. The cumulative MACE-free survival rates were 90.1%, 85.2%, and 71.1% for CC, CA, and AA genotypes, respectively.

Conclusions: Our results suggest that the AA variant of the –629A allele of CETP gene had higher HDL-C levels and reduced CETP levels, but patients with CC genotype appeared to have benefited more from statin therapy with reduction in LDL-C and LP (a) levels. Long-term clinical prognosis was, however, not affected by the 3 genotypes.

MeSH Keywords: Cholesterol, HDL • Genetics • Lipid A

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Background

The discovery of statins has promoted significant advances in serum cholesterol research and been invaluable in the primary and secondary prevention of coronary heart disease (CHD). In addition, the actions of statins can effectively decrease total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL), as well as increasing high-density lipoprotein cholesterol (HDL); therefore, significantly reducing the incidence of cardiovascular events and mortality [1]. However, individuals react differently to statins, with individual reactions to this drug treatment resulting from the combined effect of genetic and environmental factors [2]. Studies have shown that genetic polymorphisms of enzymes, transport proteins, and receptors involved in statin metabolism and lipid metabolism have important effects on the effectiveness of statin therapy [3–7]. Cholesteryl ester transfer protein (CETP) is an important protein involved in CHD pathogenesis, and its major physiological functions are the coordination of lipid exchange and transport among different lipoproteins and mediation of HDL cholesterol ester transfer to ApoB-rich very-low-density lipoprotein cholesterol (VLDL), while simultaneously mediating the TG transfer in the opposite direction, regulation of plasma HDL concentrations, components and particle sizes, and reduction of HDL particle size [8,9]. In addition, CETP plays important roles in completing and promoting cholesterol reverse transport processes [10,11].

The human CETP gene is located in the 16q12–21 area, close to lecithin, and the cholesterol acyltransferase (LCAT) gene has a total length of 25 kb, including 16 exons [12]. Its variations could affect serum CETP levels and eventually affect lipid metabolism. The –629C/A polymorphism was first discovered by Dachet et al. [13] in 2000. It is located in the CETP gene promoter area and can affect promoter activity. The nuclear transcriptional factor Spl/Sp3 can specifically bind the -629A allele and inhibit its transcription activity. The –629A allele carriers have decreased serum CETP activities and significantly increased HDL-C levels [14,15]. Wang et al. [14] found that the CC genotypes had higher CETP levels but significantly lower levels of HDL-C than the AA genotypes in the Chinese population. Wu et al. [15] reported that the CETP–629C/A polymorphic *loci* in the Chinese Han population did not significantly affect the serum HDL-C levels; however, it did affect serum LDL-C and ApoAII levels. The effect of CETP–629C/A polymorphic *loci* on the effectiveness of statins and long-term prognosis of CHD patients is not clear. We studied the CETP gene –629C/A polymorphism and analyzed its effect on the lipid regulating effect of statins and the long-term prognosis in a Chinese population.

Material and Methods

Subject

The present study was reviewed and approved by the Ethics Study Board of Fudan University. Informed written consent was obtained from all subjects or from their guardian before enrollment. The study subjects were CHD patients from October 2011 to December 2012. All of the patients are of Han descent. There were 348 cases, including 266 male patients and 82 female patients treated for acute coronary symptoms and stable angina, with an average age of 58.9±7.4 years. The inclusion criteria were: coronary angiography results showed that among the left anterior descending arteries, left circumflex arteries, and right coronary arteries, and there was at least 1 artery stenosis with a diameter ≥50%. The patients had no liver, kidney, or endocrine diseases that would affect lipid metabolism, and there was no consanguinity among the subjects. Patients with history of lipid-regulating medications or long-term use of hormone drugs were excluded. The clinical characteristics of the study subjects were collected and analyzed, including information on their height, weight, waistline, systolic blood pressure, diastolic blood pressure, body mass index (BMI), fasting blood glucose (FBG), serum cholesterol, and history of coronary artery disease.

Methods

Cholesterol measurement

After signing the consent form, fasting venous blood samples were collected from the patients after 12 h of fasting. Serum was isolated from the blood samples, and the serum cholesterol levels were quantified. The patients were given 20 mg of atorvastatin (Pfizer Inc. NY, USA) orally once every night. After treatment for a year, the enzymatic method was performed using a Toshiba 120FR automated chemistry analyzer to check the serum cholesterol levels. Throughout the period in which the patients were medicated, the ingestion of other lipid-regulating drugs or drugs metabolized by cytochrome P4503A4 was avoided.

CETP concentration measurement

Two milliliters of fasting peripheral venous blood was collected, and serum was isolated from the blood samples and stored at –80°C. The enzyme-linked immunosorbent assay (ELISA) was used to measure the CETP levels. The kits were purchased from the Shanghai R&D Company, and the manufacturer's recommendations were strictly followed. The samples were analyzed with a Thermo (USA) automated microplate reader.

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Genotype analysis

Five milliliters of fasting venous blood was collected. After ethylenediaminetetraacetic acid (EDTA) anticoagulation, the leukocytes were isolated. A kit from Tiangen Biotech Co., Ltd. was used to extract the DNA. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis was used to study the CETP-629 C/A polymorphism. The PCR-amplified target fragment length was 222 bp with the forward primer 5'-LTTCTTGGCCCCAGCTGTAGG-3' and reverse primer 5'-GAAACAGTCCTCTATGTAGACTTTCCTTGATATGCATAAAAT ACCACTGG-3' (synthesized by Sangon Biotech Co., Ltd.). The amplified product was digested with endonuclease *Van*91I (Fermentas Canada) and then analyzed for the genotypes by 3.5% agarose gel electrophoresis. The mutation on –629C/A can produce the endonuclease *Van*91I enzyme site. Two fragments at sizes of 175 bp and 47 bp were produced after the digestion. There are 3 genotypes of CETP–629C/A: CC genotype (222 bp wild-type), CA genotype (222 bp, 175 bp, and 47 bp heterozygous mutations), and AA genotype (175 bp and 47 bp homozygous mutations).

Clinical prognosis

All the follow-ups were performed by our group and were conducted by telephone to determine the incidence of major adverse cardiac events (MACE), such as death, nonfatal myocardial infraction (MI), revascularization and stroke. Deaths were considered cardiac unless an unequivocal noncardiac cause was established. MI was defined as new Q waves and an increase in the creatine kinase MB concentration to greater than 5 times the upper limit of the normal range, if occurring within 48 h after the procedure, or as new Q waves or an increase in creatine kinase MB concentration to greater than the upper limit of the normal range, plus ischemic symptoms or signs, if occurring more than 48 h after the procedure. Stroke was defined as a sudden onset of vertigo, numbness, aphasia, or dysarthria resulting from vascular lesions of the brain, including hemorrhage, embolism, thrombosis, or rupturing aneurysm, and persisting for 24 h. Ischemia-driven target-vessel revascularization was defined as any repeat revascularization in the treated vessel in which there was stenosis of at least 50% of the diameter in the presence of ischemic signs or symptoms, or at least 70% stenosis in the absence of ischemic signs or symptoms. All events were adjudicated by an event adjudication committee blinded to patient groups.

Statistics analysis

The data are expressed as the means ± standard deviation. A comparison among the different genotype variables was analyzed using an analysis of variance (ANOVA). Qualitative data are expressed as a rate or ratio. The alleles were confirmed to be in accordance with Hardy-Weinberg equilibrium. A comparison among the different genotype variables was performed using the Pearson χ^2 test and Kruskal-Wallis test. The relationship between CETP concentrations and serum cholesterol levels was examined using Pearson correlation analysis. A comparison between the serum cholesterol levels at baseline and after medication among the different genotypes was analyzed using ANOVA. A comparison between the 2 groups was made using the least significant difference test or Dunnett's t test (heterogeneity of variance). The Kaplan-Meier survival curve log-rank test was used to study the effects of different genotypes on the survival rate. All statistical analyses were performed using SPSS 16.0 software, and the statistical tests were based on 2-tailed tests, with $P<0.05$ indicating significant differences.

Results

The difference between the CC, CA, and AA genotype distribution frequencies and expected frequencies was not significant, which is in accordance with Hardy-Weinberg equilibrium and suggests that the samples represented the population. The mutated gene frequency was 0.412, and the C allele frequency was 0.578

Comparison of the general information of the CETP gene –629C/A genotype

The differences in the age, sex, level of hypertension, number of diabetic patients, number of smoking patients, BMI, serum fasting blood glucose (FBG), and left ventricular ejection fraction, as well as the CETP levels among the 3 genotypes of CETP–629C/A were not significant ($P>0.05$). A comparison of the CC, CA, and AA genotypes and serum HDL-C levels showed an increasing trend, and the CETP and LDL-C concentrations showed a decreasing trend (Table 1).

The effect of CETP-629C/A genotypes on atorvastatin lipid-regulating effect among CHD patients

The differences in serum cholesterol among the different genotypes of the patients after lipid-regulating treatment for 12 months were recorded and are shown in Table 2. (1) The serum LDL-C level change rates among the 3 different genotypes were significantly different ($P<0.001$). A pairwise comparison showed that among the CA, AA, and CC genotypes, the CC genotype showed the most significant decrease in LDL-C levels, the CA genotype showed less of a decrease than the CC genotype, and the AA genotype showed the smallest decrease of the 3. (2) The differences in the serum lipoprotein (a) level change rates among the 3 different genotypes were significant ($P=0.021$). A pairwise comparison showed that among the CA, AA, and CC genotypes, the CC genotype had the most

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Table 1. Characteristics of subjects between genotypes.

Variables	CC genotype (n=83)	CA genotype (n=199)	AA genotype (n=66)	*P* value
Ages (years)	58.7±8.6	58.1±9.6	59.7±9.3	0.112
Male (%)	58 (69.9)	130 (65.3)	46 (69.7)	0.221
Hypertension (%)	40 (48.2)	96 (48.2)	31 (47.0)	0.543
Diabetes (%)	20 (24.1)	44 (22.1)	17 (25.8)	0.112
Smoking (%)	44 (53.0)	113 (56.8)	38 (57.6)	0.226
BMI (kg/m^2)	26.8±5.6	27.1±4.7	27.2±5.7	0.549
FBG (mmol/ L)	6.5±2.5	6.4±2.4	6.5±1.7	0.421
TC (mmol/L)	4.9±1.4	4.9±1.7	4.8±1.9	0.776
TG (mmol/L)	1.9 ±1.0	1.8±0.7	1.9±0.9	0.119
HDL-C (mmol/ I)	1.0±0.2	1.2±0.3	1.4±0.2	0.035
LDL-C (mmol/ L)	3.8±0.9	3.4±1.0	2.9±0.8	0.024
ApoA I (g/L)	1.1±0.2	1.1±0.3	1.1±0.4	0.125
ApoB (g/L)	1.2±0.5	1.4±0.4	1.2±1.0	0.665
CETP (mg/mL)	3.4±1.2	2.7±1.8	2.2±1.5	0.026
EF (%)	60.0±8.2	60.3±8.5	61.4±8.7	0.743
Average degree of stenosis (%)	90.1±8.2	89.7±9.2	88.2±8.3	0.153

Table 2. Changes of lipids levels after treatment of atorvastatin in different genotype ($^{\Delta}$change %, $\bar{x}$±s).

Variables	CC genotype (n= 83)	CA genotype (n=199)	AA genotype (n=66)	P value
TC (mmol/ L)	–18.6±17.1	–14.5±12.8	–10.3±15.1	0.175
TG (mmol/ L)	1.2±36.3	7.3±32.5	–7.7±33.1	0.324
HDL-C (mmol/L)	14.7±24.8	10.4±24.3	6.7±29.7	0.455
LDL-C (mmol/L)	–35.4±25.7	–18.8±35.2**	–8.1±31.5**	<0.001
VLDL-C (mmol/L)	–2.8±38.0	6.1±44.3	–2.7±38.7	0.221
LP(a) (g/L)	–31.4±30.7	–13.4±41.7*	–2.6±43.1**	0.005
ApoA I (g/L)	14.4±22.9	10.7±24.1	19.1±21.3	0.153
ApoB (g/L)	6–2.27±35.2	–1.19±27.5	–1.77±28.2	0.870

$^{\Delta}$change% – [(lipids level after treatment of atorvastatin – lipids level before treatment)/(lipids level before treatment)] ×100%.
Compared to CC genotype, * P<0.05, ** P<0.01.

significant decrease in LP (a) level, the CA genotype showed a smaller decrease than the CC genotype, and the AA genotype showed the smallest decrease of the 3. (3) The CC genotype showed the most significant increase in HDL-C levels, the CA genotype showed less of an increase than the CC genotype, and the AA genotype had the smallest increase of the 3. However, none of the differences were significant. (4) Among the 3 genotypes, the levels of TC, TG, VI.DL-C, ApoAI, and ApoB showed no significant differences.

Clinical prognosis follow-up

During the follow-up period, there were 30 cases (8.62%) with MACE. Among these cases, there were 4 deaths (1.15%), 8 nonfatal myocardial infarctions (2.3%), 14 revascularizations (4.02%), and 4 strokes (1.15%). The MACE-free survival rates among the 3 genotypes were 92.4% for the CC genotype, 85.3% for the CA genotype, and 65.0% for the AA genotype. Although there were gradient change trends, such as the CC genotype

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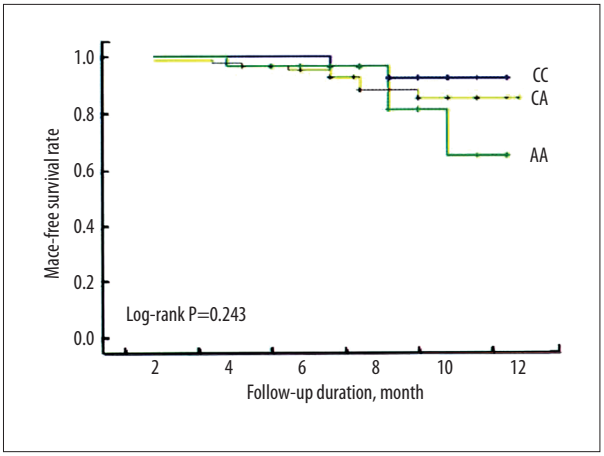

Figure 1. Mace-free survival rate.

having a better prognosis than the CA and AA genotypes, the difference was not significant (P=0.243), as shown in Figure 1.

Discussion

Our results suggest that among the Chinese Han population, the CETP–692A/C polymorphism was correlated to serum cholesterol levels and atorvastatin lipid-regulating effects, but not to a clinical prognosis. The CETP–629C→A mutation can lead to decreased CETP levels and less activity and may eventually lead to a blockage of cholesteryl ester transfer from HDL to VLDL and LDL, accumulation of cholesteryl ester in the HDL particles, increase in HDL particle size, and increase in HDL levels in plasma. A partial explanation for the increased HDL-C is the increase in large particles of HDL-C.

Statins can become clinical first-line treatments because they decrease LDL-C and significantly decrease cardiovascular risks. Different individual reactions to statins among patients are caused by a combined effect of genetic and environmental factors. Single-nucleotide polymorphisms (SNPs) of the genes involved in statin and lipid metabolism, such as ApoAI, ApoE, CETP, LDL receptor, HMGCR, and lipoprotein lipase, could be the major genetic factor affecting the individual lipid-regulating effects [3]. Currently, studies on the effect of the CETP polymorphism on the effectiveness of statins are still in the initial stages and lack consistent conclusions. van Venrooij et al. [16] found that after adjusting for the effects of confounding factors, such as alcohol consumption and smoking, the –629C/A polymorphism CC genotype carriers (80 mg/d group) can benefit more from statins. Poduri et al. [2] provided 265 CHD patients with 20 mg/d atorvastatin daily and performed follow-up investigations for 1 year. They found that patients with the –629 AA genotype had higher baseline LDI-C level; however, patients with the –629CC genotype had more significantly increased HDL-C levels (P<0.05). Blankenberg et al. [18] performed a study of 1211 CHD patients and performed a follow-up for 4.1 years. They found that 411 patients (34%) had received treatment with statins, and the results showed that the patients with the –629 AA genotype had higher HDL-C levels and lower CETP activity. The cardiovascular mortality of the CC, CA, and AA genotypes were 10.8%, 4.6%, and 4.0% (P<0.0001), respectively. In addition, patients with the –629 AA genotype showed better lipid-regulating effects.

We found that in the study population, the CETP–629C/A polymorphism is correlated to atorvastatin lipid-regulating effects in CHD patients. After treatment for 12 months, the CC genotype patients had the most decreased LDL-C levels, whereas the serum lipoprotein level was the most significant in the CC genotype. The regulating effects of TC, TG, VLDL, ApoAI, and ApoB were not affected by the CETP polymorphism. During the follow-up period, the MACE-free survival rates of the 3 genotypes were 92.4% for the CC genotype, 85.3% for the CA genotype, and 65.0% for the AA genotype. Although there were gradient change trends, such as the CC genotype having a better prognosis than the CA and AA genotypes, the difference was not significant. In addition, the lipid-regulating effects of statins on the CHD patients were also affected by age, sex, body weight, and height, as well as lifestyle habits such as smoking. Our study compared age, sex, level of hypertension, number of diabetic patients, number of smoking patients, BMI, serum glucose, and CETP levels among the 3 CETP–629C/A polymorphism genotypes. The differences were not significant (all P>0.05); therefore, we did not adjust for confounding factors in the analysis. We have shown from the serum cholesterol levels that genetic factors can affect an individual's lipid-regulating effect of statins. The –629C/A polymorphism was correlated to decreased LDL-C and LP (a) levels caused by atorvastatin lipid-regulating treatment. Patients with the CC genotype showed better lipid-regulating effects. However, multi-center clinical trials with larger sample sizes are required to determine whether this gene polymorphism can become a predicting factor in the long-term prognosis of atorvastatin lipid-regulating treatment.

Conclusions

Carriers with the -629A allele of CETP gene had higher HDL-C levels and reduced CETP levels and patients with CC genotype appeared to have benefited more from statin therapy with reduction in LDL-C and LP (a) levels. Long-term clinical prognosis was, however, not affected by the CETP polymorphism.

Competing interests

The authors declare no competing interests exist.

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