Cholesteryl Ester Transfer Protein Gene and Effectiveness of Lipid Lowering of Atorvastatin

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Abstract: Cholesteryl ester transfer protein (CETP) plays a key role in lipid metabolism. Thus, variations in the CETP gene may be clinically relevant.

Newly started atorvastatin users (n=212) were genotyped for CETP genetic variants (TaqIB and I405V). Homozygotes for B1 allele of TaqIB polymorphism had lower plasma high density lipoprotein cholesterol (HDL-C) compared with B1B2 or B2B2 genotypes (p=0.03, for each). Homozygotes for I allele of I405V polymorphism had lower plasma HDL-C compared with IV or VV genotypes (p=0.001, for each). In the whole population, the B1 carriers increased HDL-C levels by 4% after atorvastatin treatment, compared with B2 carriers, where a 4% decrease occurred (p=0.03). Also homozygotes for B1 allele decreased triglyceride levels to a lesser, though not significant, degree compared to B1B2 or B2B2 genotypes.

CETP TaqIB or I405V polymorphisms seem to modify the lipid lowering response to atorvastatin treatment. This knowledge may help design more effective hypolipidaemic treatment.

Keywords: Atorvastatin, cholesteryl ester transfer protein, genetic polymorphisms, lipid profile.

INTRODUCTION

Cholesteryl ester transfer protein (CETP) plays a major role in modifying lipoprotein particles by mediating the transfer of cholesteryl esters from high-density lipoprotein (HDL) particles to apolipoprotein B-containing lipoproteins in exchange for triglycerides (TG) [1]. The CETP gene encompasses 16 exons, on chromosome 16q12-16q21; several CETP polymorphisms have been identified including I405V and TaqIB which are associated with reduced CETP mass and increased HDL cholesterol (HDL-C) [2]. I405V results in a single amino acid change at codon 405 in exon 14; in several studies, the I405V allele was associated with lower CETP levels [2]. TaqIB has been shown to be a silent base change affecting the 277th nucleotide in the first intron of the gene [3]. The B2 allele (absence of the *Taq*I restriction site) at this polymorphic site has been associated in normolipemic subjects with increased HDL-C levels and decreased CETP activity and levels [4].

HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors (statins) are the main drugs used to reduce plasma low density lipoprotein cholesterol (LDL-C) levels. Also, statins can be administrated to subjects with high triglyceride (TG) and low HDL-C levels (a dyslipidaemic combination which often coexists) [5, 6]. There is considerable variation in the response to statin treatment [7]. Although most subjects derive a 30% to 50% reduction in LDL-C cholesterol with statin therapy, there is wide variation in the dose response. Environmental and genetic factors may contribute to this variability. In line with our previous work [8], we assessed whether 2 common polymorphisms of CETP (I405V and TaqIB) influence the lipid response after treatment with atorvastatin.

SUBJECTS AND METHODS

Subjects

Ad hoc power analysis showed that in order to detect two-sided differences higher than 20% in one of the main outcome variables (TG) before and after treatment with atorvastatin, achieving statistical power equal to 90% at a significance level less than 0.05, we had to recruit at least 190 individuals for each group. Due to unexpected conditions, more people entered the study, potentially increasing its statistical power. We genotyped 212 Greek unrelated hypercholesterolaemic subjects (141 men and 71 women) aged

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56.8 (±12.9) years with primary hypercholesterolemia. Additional inclusion criteria included a stable medication (patients with coronary artery disease were on cardioselective β-blockers and aspirin, patients with hypertension were on angiotensin converting enzyme inhibitors) regimen and diet for at least 4 weeks prior to study screening. Subjects with a history of stroke, renal diseases, and diabetes mellitus were excluded from the study. The subjects were assigned to atorvastatin treatment for at least 6 months. The dose of atorvastatin (10-40 mg/day) was adjusted according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) treatment goal for LDL-C based on risk category (LDL-C <130 mg/dl, < 100 mg/dl or < 70 mg/dl; < 3.4 mmol/l, < 2.6 mmol/l or < 1.8 mmol/l) [9].

Subjects were further divided according to their baseline HDL-C levels into groups: 1. Low HDL group [HDL-C <40 mg/dl (<1 mmol/l)] and 2. High HDL group [HDL ≥40 mg/dl (≥1 mmol/l)]. All subjects were started on atorvastatin as the only lipid lowering drug. Exclusion criteria were heavy drinking as well as liver and renal disease. Our Institutional Review Board approved the study.

DNA Analysis and Determination of Blood Lipids and Glucose

The CETP (TaqIB, I405V) polymorphisms were detected by using Polymerase Chain Reaction and Restricted Fragment Length Polymorphism analysis as previously described [10,11]. The measurement of total, LDL-C, HDL-C and TG was performed as described elsewhere [10]. Briefly, total cholesterol, TG and HDL-C levels were measured using enzymatic colorimetric methods, on a Roche Integra Biochemical analyzer, with commercially available kits (Roche Diagnostics Gmbh, Hannheim, Germany). The serum LDL-C levels were calculated using the Friedewald formula in subjects with TG levels < 400 mg/dl.

Statistical Analysis

All continuous variables are shown as median and interquartile range (25th, 75th percentile) since they all (except for age and BMI) deviated from normality. However, for facilitation reasons, age and BMI are also treated as non-normally distributed variables. All categorical variables are presented as relative (percentage) frequencies. The Kruskal-Wallis H statistic was used to compare the continuous variables among the 3 genotype groups, while the Mann-Whitney U test was used to compare the continuous variables between the 2 groups of carriers. Wilcoxon signed-rank test was used to evaluate the differences before and after treatment. The Pearson's chi-square test was used to evaluate any association between categorical variables and genotypes/alleles. The differences in total cholesterol, TGs, HDL-C and LDL-C before and after atorvastatin treatment were also described as % difference, based on the following rule: % difference = [(variable after-variable before)/variable before]*100. All tests were 2-sided at a significance level of p <0.05. Data were analyzed using STATA™ (Version 9.0, Stata Corporation, College Station, TX 77845, USA).

Results

Genotype and Allele Frequencies in the Whole Cohort

The genotype frequency of the TaqIB and I405V polymorphisms was B1B1 31.9%, B1B2 54.3%, B2B2 13.8% and II 45.0%, IV 40.8%, VV 14.2%, respectively. The B1 and B2 alleles were found at frequencies of 58.9% and 41.1%, respectively, while the I and V alleles were found at 65.5% and 34.5%, respectively.

Baseline Lipid Profile According to Genotype in the Whole Cohort

TaqIB Polymorphism

Homozygotes for B1 allele had lower plasma HDL-C compared with B1B2 and B2B2 genotype (p=0.03, for each, Table **1**). Accordingly, the B2 allele was associated with higher HDL-C levels compared with B1 allele (p=0.02, Table **2**). Total cholesterol, LDL-C and TG levels did not vary significantly among TaqIB genotypes (Table **1**).

I405V Polymorphism

The IV genotype was associated to higher HDL-C levels compared with II genotype (p=0.001). The V allele was associated woth higher HDL-C levels compared with I allele (p=0.04) (Table **2**).

Table 1.   Baseline Lipid Profile of the Study Cohort Based on TaqIB or I405V Genotypes

	CETP TaqIB				CETP I405V			
	B1B1 (n=67)	**B1B2 (n=114)**	**B2B2 (n=29)**	**p**	**II (n=95)**	**IV (n=86)**	**VV (n=30)**	**p**
Age (years)	59(21)	59(18)	54(23)	0.51	56(21)	59(19)	61(18)	0.25
BMI (kg/m2)	26(3)	27(5)	26(4)	0.57	27(4)	26(5)	27(4)	0,48
TC (mg/dl)	271(68)	294(66)	285(94)	0.06	280(69)	294(60)	272(75)	0.09
TG (mg/dl)	175(101)	144(122)	153(179)	0.46	167(123)	144(139)	147(99)	0.29
HDL-C (mg/dl)	40(15)	45(19)	49(24)	0.04	41(17)	48(21)	45(18)	0.004
LDL-C (mg/dl)	188(49)	195(88)	205(81)	0.62	185(81)	190(67)	194(88)	0.52

Continuous variables are shown as median and interquartile range. Kruskal-Wallis H statistic was used to compare the continuous variables among the three genotype groups. CETP: cholesteryl ester transfer protein, BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides.
For TC, HDL and LDL, to convert from mg/dl to mmol/l divide by 38.8. For TG, to convert from mg/dl to mmol/l divide by 88.6

Table 2.   Baseline Lipid Profile of the Study Cohort Based on TaqIB or I405V Alleles

	CETP TaqIB			CETP I405V		
	B1	**B2**	**p**	**I**	**V**	**p**
Age (years)	59(20)	57(20)	0.43	57(20)	60(19)	0.09
BMI (kg/m2)	27(4)	26(4)	0.91	27(4)	27(4)	0.82
TC (mg/dl)	280(66)	294(68)	0.04	287(70)	285(65)	0.33
TG (mg/dl)	165(115)	144(128)	0.39	163(126)	144(112)	0.11
HDL-C (mg/dl)	42(19)	48(19)	0.02	43(20)	48(19)	0.04
LDL-C (mg/dl)	190(61)	197(81)	0.41	190(77)	194(74)	0.26

All continuous variables are shown as median and interquartile range. Mann-Whitney U statistic was used to compare the continuous variables among the three genotype groups. CETP: cholesteryl ester transfer protein, BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides. B1: variant allele-carrying genotypes (B1B1, B1B2), B2: variant allele-carrying genotypes (B2B2, B1B2), I: variant allele-carrying genotypes (II, IV) , V : variant allele-carrying genotypes (VV, VI). For TC, HDL and LDL, to convert from mg/dl to mmol/l divide by 38.8. For TG, to convert from mg/dl to mmol/l divide by 88.6.

Baseline lipid profile according to genotype in Low HDL group and High HDL group.

TaqIB Polymorphism

The B1 allele was more frequent in Low HDL group than in High HDL group (64.1% vs 53.4%, p=0.05), while the B2 allele frequency was higher in High HDL group compared with Low HDL group (46.6% vs 35.9%, p=0.05).

In Low HDL group, B1B2 subjects or B2 allele carriers had higher total cholesterol than B1B1 subjects (p=0.03) or B1 allele carriers (p=0.01).

In High HDL group, no significant associations were found between the TaqIB polymorphism and baseline lipid profile.

I405V Polymorphism

The II genotype was more frequent in Low HDL group compared to High HDL group (54.7% vs 37.3%, p=0.02), while the IV genotype frequency was higher in High HDL group compared with Low HDL group (48.2% vs 31.3%, p=0.03).

Effect of Atorvastatin on Lipid Profile in the Whole Cohort and Both Groups

Total cholesterol, LDL-C and TG levels were significantly decreased after atorvastatin administration (-34.4%, -41.2% and -28.5%, respectively; p<0.001 for each). The HDL-C slightly increased though not significantly 2.8% (p=0.46).

The changes in total cholesterol, HDL-C, LDL-C and TG levels were:-37.0% (p<0.001), +12.9% (p<0.001), -40.1% (p<0.001), -38.1% (p<0.001), respectively in the Low HDL group and -30.9% (p<0.001), -8.3% (p=0.001), -43.2% (p<0.001), -15.2% (p<0.001), respectively in the High HDL group.

Effect of Atorvastatin Treatment According to Genotype of the Whole Cohort

The B1 carriers increased HDL-C levels by 4% after atorvastatin treatment, compared with B2 carriers, where a

4% decrease was found (p=0.03). Also homozygotes for B1 allele decreased TG levels in a lesser, though not significant, degree compared with B1B2 or B2B2 genotypes [20.6%, 35.8% or 29.1%, respectively (all 3 decreases significant: p<0.001, p=0.40 for in-between comparison)].

Association of the I405V or TaqIB Variants with Effectiveness of Atorvastatin in Low and High HDL Group

B2 carriers from Low HDL group had greater decrease of total cholesterol compared with B1 carriers (-120 (44) mg/dl vs -100(58) mg/dl, p=0.02), Table **3**. Also, B2 carriers from the Low HDL group had greater decrease of TG compared with B1 carriers (-45% vs. -37%, p=0.02).

In the High HDL group, LDL-C showed greater decrease in subjects with II genotype compared with those with IV genotype [-108 mg/dl (-47.2%) vs -79 mg/dl (-37.1%), p=0.006].

DISCUSSION

We evaluated whether the common CETP TaqIB or I405V gene polymorphism was associated with differentiation of the plasma lipid profile and involvement of the atorvastatin effectiveness on lipid lowering. Our results show that TaqIB polymorphism modulated the effectiveness of atorvastatin reduction on lipid values, especially on HDL-C and TG (to a lesser degree). Also, in the Low HDL group the effectiveness of reduction of total cholesterol and TG varied according to TaqIB polymorphism. In the High HDL group the % reduction of LDL-C varied according to I405V polymorphism.

The gene frequencies for the TaqIB and I405V polymorphisms in our study cohort were similar to those reported in other Caucasian [3, 12, 13] and dyslipidaemic populations [14]. For example, the population in the Regression Growth Evaluation Statin Study (REGRESS) had similar TaqIB allele frequencies with our population (B1: 59% vs 58.9% and B2: 41% vs 41.1%, respectively) [15]. In another study involving Greek dyslipidaemic individuals, the V allele frequency was 33% and in Greeks with coronary artery disease 32% [8, 16], all similar to the present study (34.5%).

Table 3. **Differences (in mg/dl) in Lipid Profile of the Whole Study Cohort According to I405V or TaqIB Alleles after Atorvastatin Treatment in Low and High HDL Groups**

	Low HDL group					
	CETP TaqIB			CETP I405V		
	B1	**B2**	**P**	**I**	**V**	**p**
TC	-100(58)	-120(44)	0.02	-103(66)	-112(41)	0.38
TG	-50(103)	-118(157)	0.05	-61(150)	-82(140)	0.63
HDL-C	5(10)	3(8)	0.22	4(9)	2(17)	0.25
LDL-C	-55(85)	-79(89)	0.28	-52(94)	-85(52)	0.12
	High HDL group					
	CETP TaqIB			CETP I405V		
	B1	**B2**	**p**	**I**	**V**	**P**
TC	-89(52)	-89(59)	0.93	-90(58)	-88(52)	0.60
TG	-22(75)	-35(65)	0.59	-33(77)	-21(56)	0.56
HDL-C	-4(12)	-5(14)	0.25	-4(12)	-5(14)	0.42
LDL-C	-78(52)	-88(58)	0.89	-84(52)	-86(49)	0.58

All continuous variables are shown as median and interquartile range. Mann-Whitney U statistic was used to compare the continuous variables among the two allele groups. CETP: cholesteryl ester transfer protein, BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides, diff: Difference between value after and value before atorvastatin treatment.
B1: variant allele-carrying genotypes (B1B1, B1B2), B2: variant allele-carrying genotypes (B2B2, B1B2), I: variant allele-carrying genotypes (II, IV) , V : variant allele-carrying genotypes (VV, VI). For TC, HDL and LDL, to convert from mg/dl to mmol/l divide by 38.8. For TG, to convert from mg/dl to mmol/l divide by 88.6.

Concerning the baseline lipid profile, the VV and B2B2 genotypes have been reported to present with higher HDL-C levels [2, 8]. Similarly, in the present study, the B2B2 genotypes, as well as the B2 allele, were associated with higher HDL-C levels. The IV (rather than the VV) genotype and V allele was associated with higher HDL-C levels. However, no such association was found for the VV genotype which could be attributed to the low number of subjects with this genotype.

Despite the proven efficacy of statins as a primary and secondary prevention for cardiovascular disease, a significant proportion of patients do not achieve LDL-C goals [17]. This could be due to the interindividual variability in the response to statin treatment [18]. In the REGRESS study, pravastatin reduced total cholesterol, LDL-C, and TG levels and increased HDL-C to a similar extent in all 3 TaqIB genotypes [15]. However, in animals study de Haan *et al.* [19] reported that atorvastatin increased HDL-C by reducing hepatic CETP expression in E3L.CETP mice (APOE*3-Leiden mice crossbred with mice expressing human CETP). This fact supported the hypothesis that CETP gene polymorphisms could play an important role in the lipid lowering effectiveness of atorvastatin. Also, van Venrooij *et al.*, who evaluated the cohort (n=217) from Diabetes Atorvastatin Lipid Intervention (DALI) study (frequency of B1 allele similar to our study 57.1%), reported that in carriers with the B1B1 genotype, HDL-C levels increased, whereas in B2B2 carriers, atorvastatin had no effect on HDL-C [20]. Poduri *et al.* [21] found association with reduced LDL-C lowering by atorvastatin and gene polymorphisms involved in lipid metabolism (including CETP gene) in an Indian population.

They compared the wild-allele homozygote genotype vs variant allele carrying heterozygote and homozygote genotypes and found that variant allele-carrying genotype of TaqIB showed greater increase in HDL-C concentrations following atorvastatin therapy and variant allele carrying I405V showed lower reduction in total cholesterol levels. Contrary to our findings, patients involved in their study had coronary artery disease, were mostly men and had median total cholesterol of 204(35) mg/dl and HDL-C of 35(9) mg/dl, while subjects in our study were dyslipidaemic, 30% were women and had total cholesterol 286(69) mg/dl and HDL-C 44(20) mg/dl. Furthermore, Mohrschladt *et al.* did not find any differences between TaqIB and statin treatment [22]. In a previous study of ours, the TaqIB had no influence on response to treatment with simvastatin opposite to I405V polymorphism, where I allele carriers responded better [8]. In the present study, carriers of B1 allele increased HDL-C levels after atorvastatin therapy, while the carriers of B2 alleles decreased the HDL-C levels. One explanation is that carriers of the B2 allele had higher HDL-C levels at baseline [42(19) mg/dl vs 48(19) mg/dl, respectively]. In the Low HDL group the B2 carriers responded better to statin therapy (greater reduction of total cholesterol and TGs). Moreover, in the High HDL-C group the II genotype was associated with greater % reduction of LDL-C and B1B1 genotype with lower reduction of HDL-C after atorvastatin treatment. Possible explanation for this discrepancy may be that another statin was used (atorvastatin instead of simvastatin). Overall, subjects with low HDL-C levels at baseline seem to benefit to a greater extent than those with high HDL-C levels at baseline after atorvastatin treatment. The HDL-C level was significantly increased (+12.9%) and TGs were significantly

decreased (-38%) in group with low HDL-C compared with -8.3% and -15.2%, respectively in the group with high HDL-C. The different response to hypolipidaemic drugs according the HDL-C baseline levels was suggested by our research group since 1995 [7, 23, 24]. At that time, this was only a clinical observation. However, the response to statin treatment is not solely influenced by a single gene polymorphism. Furthermore, the pharmacogenetic studies on association between genes and lipid lowering response to statins are limited [25]. Many factors could contribute to an individual's response such as side effects, gender, age, body mass index, diet, environmental, CETP mass and activity (CETP genotypes may influence both by approximately 5% to 10%) [26], as well as gene-gene interaction. Gene assessment also has cost and time implications which are disadvantages in routine clinical practice. Nevertheless, these disadvantages may become less relevant as technology develops.

CONCLUSIONS

The results favour the hypothesis that CETP polymorphisms modify the effect of statin treatment and may help to identify subjects who will benefit more from statin therapy. Thus, the prospective identification of subjects who have a diminished or increased response to statins, may improve the risk-to-benefit ratio of statin therapy. However, this is a small study. To clarify the genes contribution to the statin lipid lowering effect more studies involving higher number of individuals are required.

DECLARATION OF INTEREST

This study was conducted independently; no company or institution supported it financially.

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