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Research paper

Study of common variants of the apolipoprotein E and lipoprotein lipase genes in patients with coronary heart disease and variable body mass index

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ABSTRACT

OBJECTIVE: In the present study, we evaluated the influence of lipoprotein lipase (LPL) and apolipoprotein (apo) E polymorphisms on lipid concentrations of 178 Greek men of similar age with coronary heart disease (CHD), but varying body mass index (BMI). DESIGN: Patients were divided according to their BMI (in kg/m²) into three groups: lean (BMI=20-24.9), overweight (BMI=25-29.9), and obese (BMI ≥30). Polymorphisms of LPL (HindIII, S447X) and apo E (ε2, ε3, ε4), and lipid parameters were studied. RESULTS: There was a negative correlation between BMI and high-density lipoprotein cholesterol (HDL-C) concentration (r=-0.272, p<0.001), as has already been described. Lean homozygotes for the HindIII(+) allele had higher HDL-C levels compared to lean homozygotes for the HindIII(-) allele (p=0.012). No correlation was found between S447X or apo E polymorphisms and BMI or plasma lipids in any group. Overweight men with the ε3/ε3 and SS genotypes had higher triglycerides concentration compared with overweight men with ε3/ε3 and SX (p=0.002). CONCLUSIONS: The HindIII polymorphism alone may influence HDL-C concentration in lean men, in contrast to S447X alone, which has no influence on any lipid parameters. However, the S447X and apo E polymorphisms may have a synergetic effect and alter plasma triglyceride concentration in overweight men.

Key words: Apolipoprotein E, Body mass index, Coronary heart disease, Lipids, Lipoprotein lipase, Polymorphism

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INTRODUCTION

Coronary heart disease (CHD) is a multifactorial disease caused by a combination of genetic and environmental factors. Among them, abnormal plasma lipid concentrations are the major risk factors for CHD. On the other hand, obesity, being a chronic

disease, leads to metabolic abnormalities and increased mortality because of the accumulation of body fat.[1] In obese subjects, the main lipid disorder is increased triglyceride (TG) levels, due to increased free fatty acid released by adipose tissue, leading to increased very low-density lipoprotein cholesterol (VLDL) production by the liver.[2,3] Genes whose expression products are involved in lipoprotein metabolism as lipoprotein lipase (LPL)[4] and apolipoprotein (apo) E[5,6] are considered excellent candidates for studying susceptibility to CHD. In particular, LPL plays a key role in lipoprotein metabolism by hydrolyzing TGs from VLDLs and chylomicrons and also by removing lipoproteins from the circulation.[7-9] Furthermore, LPL is implicated in atherogenesis since it influences both the interaction between atherogenic lipoproteins and cell surface and the receptors on the vascular wall.[10-12] Several studies have described more than 60 different mutations of the LPL gene leading to a reduction in enzyme synthesis and activity. One of the most frequent polymorphisms of LPL, the S447X polymorphism with an incidence of 17-22% in Caucasian populations,[13,14] seems to be favorable for the catabolism of VLDLs, decreasing fasting concentrations of TGs.[15-17] In particular, the S allele has been associated with higher TG levels,[18] while the X allele has been linked to anti-atherogenic lipid profiles and a modest reduction in coronary disease risk.[19] On the other hand, the S447X polymorphism was not correlated with the incidence of CHD.[20] Another common LPL gene polymorphism is the HindIII polymorphism. As regards HindIII alleles, the common allele (+) is significantly associated with high TG levels and low high-density lipoprotein cholesterol (HDL-C) levels compared with the rare allele (-).[21-23] Furthermore, the LPL (+/+) genotype has demonstrated a higher risk of myocardial infraction.[24] Apo E, as a component of TG-rich lipoproteins which was first discovered in 1970,[25] is an amphipathic glycoprotein mediating the distribution of lipids and cholesterol among cells, expressed mainly by the brain and liver.[26] Apo E is polymorphic and presents three common alleles: ε2, ε3, and ε4. It seems that ε2 carriers are characterized by lower low-density lipoprotein and apo B levels but higher HDL-C and apo A-I levels than ε3 carriers, while the opposite has been found for ε4 carriers compared with ε3 carriers.[27-31] Therefore, we evaluated the polymorphisms of LPL (HindIII, S447X) and apo E (e2, e3, e4) and their influence on lipid values in Greek men with CHD grouped by their body mass index (BMI). Additionally, we studied the synergetic effect of LPL and apo E on lipid values.

SUBJECTS AND METHOLOGY

Subjects

One hundred and seventy-eight (178) unrelated Greek men with angiographically documented CHD were divided into three groups: lean (BMI=20-24.9 kg/m^2), overweight (BMI=25-29.9 kg/m^2), and obese (BMI $\geq$30.0 kg/m^2). All subjects were included irrespectively of concomitant risk factors, namely smoking, arterial hypertension, dyslipidemia, and diabetes mellitus. The lipid values of patients who were on hypolipidemic treatment were taken from the patient's file in the pre-treatment period (not during the first days after acute myocardial infarction). The Ethics Committee of the Onassis Cardiac Surgery Center approved the protocol of this study. All patients included in the study provided written informed consent.

Genotyping

After the recruitment of the study population, LPL and apo E genotyping was performed. The analysis of the HindIII (+/+, +/-, -/-) and S447X (SS, SX, XX) genotypes was prepared as described by Humphries et al.[32] The analysis of apo E genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4) was performed as described by Hixson and Vernier.[33] The analyses of the biochemical parameters were performed as described in a previous study.[34]

Statistical Analysis

Categorical variables are presented as relative frequencies. Numerical variables were tested for normality of their distribution and are presented as mean values plus or minus one standard deviation, unless otherwise stated. The statistical evaluation was based on the calculation of the chi-square criterion using Yates' correction for continuity. Comparisons of patients' quantitative characteristics among BMI groups were performed by ANOVA or the Kruskal-Wallis test, whichever appropriate, while comparison between two groups was performed with the use of the independent samples t-test or Mann-Whitney U test, whichever appropriate. Spearman's correlation

coefficient was calculated for the correlation between BMI and HDL-C. All reported P-values are from two-sided tests. P-values less than 0.05 were considered to be statistically significant.

STATA 6 software was used for the calculations (STATA Corp. College Station, Texas, USA).

RESULTS

All clinical characteristics and lipid values are presented in Table 1.

BMI and lipid values

There was a negative correlation between BMI and HDL-C concentration (Spearman's correlation coefficient r=-0.272, p<0.001).

Genotype and allele distribution

There was no difference in genotype or allele distribution among groups (Table 2 and Table 3).

Table 2. The distribution (in %) of LPL and apo E genotypes by BMI

	Lean n=50	Overweight n=94	Obese n=34	Overall n=178
LPL				
S447X				
SS	72.0	79.8	79.4	77.5
SX	26.0	19.1	20.6	21.3
XX	2.0	1.1	0.0	1.1
HindIII				
+/+	34.0	47.9	47.1	43.8
+/-	52.0	42.6	44.1	45.5
-/-	14.0	9.6	8.8	10.7
Apo E				
ε2/ε3	6.0	7.4	8.8	7.3
ε2/ε4	2.0	1.1	2.9	1.7
ε3/ε3	82.0	76.6	61.8	75.3
ε3/ε4	8.0	13.8	23.5	14.0
ε4/ε4	2.0	1.1	2.9	1.7

Table 1. Clinical characteristics of all groups. Comparisons of patients' quantitative characteristics among BMI groups were performed by ANOVA or the Kruskal-Wallis test, as appropriate

	Lean n=50	Overweight n=94	Obese n=34	P
Age (years)	64±10	61±10	63±9	0.130
BMI	23±1	27±1	32±2	<0.001
Smoking (current, n%)	28	26	47	0.059
TC (mg/dl)	236±48	233±58	225±49	0.670
TG (mg/dl)	152±94	175±121	179±74	0.451
HDL-C (mg/dl)	44±11	37±9	36±10	<0.001
LDL-C (mg/dl)	163±45	158±48	152±45	0.613
Apo A (mg/dl)	119±24	116±25	110±25	0.299
Apo B (mg/dl)	93±30	98±26	99±38	0.633
Glucose (mg/dl)	129±63	133±60	135±68	0.909
SBP (mm Hg)	148±22	151±26	154±23	0.555
DBP (mm Hg)	80±11	82±11	83±12	0.553
No. of arteries	2.4±0.7	2.1±0.9	2.3±0.7	0.180
Previous MI (n %)	66	61	53	0.427
Diabetes mellitus (n %)	24	31	38	0.374
Hypertension (n %)	70	72	79	0.619

Apo: apolipoprotein; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; DBP: diastolic blood pressure; No of arteries: number of stenosed coronary arteries more than 50% of lumen diameter; MI: myocardial infarction; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides.
Continuous variables are presented as mean (±) one standard deviation, while qualitative variables are presented as relative frequencies.

Table 3. The distribution (in %) of LPL and apo E alleles by BMI

	Lean n=50	Overweight n=94	Obese n=34	Overall n=178
LPL				
S447X				
S	85.0	89.4	89.7	88.2
X	15.0	10.6	10.3	11.8
HindIII				
+	60.0	69.1	69.1	66.6
-	40.0	30.9	30.9	33.4
Apo E				
ε2	4.0	4.3	5.9	4.5
ε3	89.0	87.2	77.9	86.0
ε4	7.0	8.5	16.2	9.6

Correlations

Lean homozygotes for the HindIII(+) allele (n=17) had higher HDL-C concentration compared with lean homozygotes for the HindIII(-) allele (n=7) [in mg/dl; 46 (95% CI for mean 40-51) vs 34 (95% CI for mean 29-39), p=0.012]. No difference was found between the apo E or S447X polymorphisms and plasma lipids in any group.

No any association between the LPL polymorphism and number of stenosed arteries was found.

LPL plus apo E genotype distribution

Overweight patients with the apo ε3/ε3 and SS genotypes (n=61) had higher plasma TG concentration compared with overweight patients with the apo ε3/ε3 and SX genotypes (n=10) [in mg/dl; 189 (95% CI for mean 150-228) vs 121 (95% CI for mean 101-149), p<0.002).

DISCUSSION

These data demonstrate that the polymorphism of HindIII alters plasma HDL-C in lean subjects, in contrast to the S447X or apo E polymorphisms, which do not appear to have any effect on plasma lipids in any group. The presence of a specific combination of S447X and apo E polymorphisms alters plasma TG concentration in overweight men.

In the Bogalusa Heart Study,[35] the TG levels, adjusted for age and BMI were lower in carriers versus non-carriers of the X allele. We have found that TG levels were higher in the SS genotype versus the SX in homozygosity for the apo ε3 allele, and only in overweight subjects. Barg reported that carriers of the X allele have lower TG and higher HDL-C levels as well as a reduced risk of CHD.[36] Agirbasli M et al reported that the S447X variant of the LPL gene is inversely associated with severity of CHD and lower TG and HDL-C levels.[37] Also in a recent study, the LPL gene polymorphism was shown to be associated with the consumption of alcohol and unsaturated fat and to modulate serum HDL-C levels. Specifically, the X allele was positively associated with HDL-C concentrations (p<0.001).[38] Furthermore, the S447X polymorphism of the LPL gene may play a role in the risk of atherogenic sdLDL fraction.[39] The study of Shimo-Nakanishi et al[4] demonstrated that the HindIII polymorphism was associated with increased risk of atherothrombotic infarction; however, they did not find the HindIII allele to be significantly correlated with plasma levels of total cholesterol, TG, or HDL-C. By contrast, in the present study we found that in lean patients, homozygotes for the HindIII(+) allele had higher HDL-C than homozygotes for the HindIII(-) allele. Abd-El-Aziz et al presented a synergistic interaction between the H2H2 genotype of the LPL gene and the S2S2 genotype of the apo C3 gene which leads to increased severity of CHD.[40] Al-Jafari et al reported than the odds ratio of the HindIII genotype H(+/+) vs the H(-/-) genotype at 95% Confidence Interval were 4.6 (1.57-13.2) and p<0.005, hence showing no significant association with CHD.[41] Munshi et al reported that TGs were found to be elevated in individuals bearing the HindIII (+/+) genotype in comparison with the HindIII (-/-) genotype, but only in the presence of significantly lower HDL-C levels.[42] Additionally, Muñoz-Barrios reported that the genotype T/T of HindIII was associated with increase of total cholesterol (β =23.6 mg/mL; p=0.03),[43] while Rebhi et al referred to a significant association between the genotype of the HindIII polymorphism and lower HDL-C and TG levels.[44]

Reports on the association between lipid variables and the HindIII polymorphism have been controversial.[45] Several studies have reported a significant association between the HindIII(+) allele and higher TG or lower HDL-C levels,[46-48] findings not in line with

those of Heinzmann et al.[49] There are also controversial results regarding the LPL polymorphism and obesity. Vohl et al[50] suggested that the HindIII polymorphism might modulate the magnitude of the dyslipidemic state associated with visceral obesity. They found that visceral obesity was associated with increased TG concentrations in HindIII(+/+) homozygous men, suggesting that visceral obesity may lead to hypertriglyceridemia in the presence of the HindIII(+/+) genotype. In the HindIII(+/-) group, variation in the amount of visceral obesity was not associated with differences in TG concentration. Similar results were found by Jemaa et al.[51] They also reported that the plasma TG levels varied significantly among the HindIII genotypes [(+/+) had the highest TG levels] and that the HindIII polymorphism showed a significant association with HDL2-C. These associations were only observed in females and could not be explained by the variations in BMI and age.

In the present study we also found an association between the LPL polymorphism and serum HDL-C in lean subjects with CHD. This was the only association found concerning LPL polymorphisms alone. However, overweight subjects with the ε3/ε3 and SS genotypes had altered plasma TG concentration. These findings indicate that the apo E genotype and heterogeneity at the LPL gene locus may have an interactive effect on plasma lipid and lipoprotein levels in overweight subjects.

This type of study has several limitations. For example, certain apo E and LPL polymorphisms may cause premature death from CHD and therefore such patients may be under-represented in the study. Environmental factors such as lifestyle modifications may influence the expression of the apo E and LPL genotypes. Additionally, we did not find any significant differences in the obese group concerning lipid variables, probably due to the small number of patients carrying the less frequent genotypes, as is true of most populations. Furthermore, local factors (e.g. the Mediterranean diet) may also exert some influence.

In conclusion, our results suggest that the HindIII polymorphism alone may influence the HDL-C concentration in healthy-weight men with CHD, in contrast to S447X alone, which has no influence on any lipid parameters. However, the presence of both S447X and apo E polymorphisms probably has a synergetic effect and alters plasma TG concentration in overweight men. No other differences were found between LPL or apo E polymorphisms and BMI or plasma lipids in any group. Nevertheless, further prospective investigations in large populations among various races are required to confirm these findings.

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