Human Lipoprotein Lipase *Hin*dIII Polymorphism in Young Patients With Myocardial Infarction

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We investigated the possibility that the DNA *Hin*dIII polymorphism of human lipoprotein lipase (LPL) is associated with the severity of coronary artery disease (CAD) determined by angiography in young patients who survived a myocardial infarction (MI). Conflicting studies have explored the relationship linking CAD severity to the *Hin*dIII restriction site polymorphism at the LPL gene locus, and to our knowledge, no data are available from Italy. The patients were aged less than 45 years (mean age, 40.1 ± 3.9 years); 83 were male and four were female. The 87 case-patients had a Q-wave or non–Q-wave infarction (67.3% and 32.7%, respectively); the MI was anterior (50.5%), lateral (41.7%), or inferior (7.8%). Analysis of coronary angiograms showed the absence of critical stenosis in 13.8% and the presence of monovessel disease in 50.6% and multivessel disease in 35.6% of the case-patients. The allelic frequency of the *Hin*dIII H(−) and H(+) allele was 0.37 and 0.63, respectively. There was a striking association between the *Hin*dIII polymorphism and the number of diseased vessels. The patients with *Hin*dIII(+/+) genotypes were significantly more likely to have double- or triple-vessel disease and less likely to have no significantly diseased vessels. In this study, we demonstrated that the homozygous form of the LPL *Hin*dIII(+) allele increases the risk of multivessel disease by a factor of 4 in an Italian group of young MI survivors. This association was independent from the smoking status and a positive family history for CAD and hypertension, which are known to predict CAD severity. The discrepancies in the results of these studies are difficult to explain. The lack of homogeneity in the study populations (age at which CAD occurred, number of enrolled patients, and geographical origin) and differences in the assessment of CAD severity may account for these conflicting results.

HUMAN LIPOPROTEIN LIPASE (LPL) is a critical enzyme involved in the clearance of triglyceride-rich lipoproteins from the circulation via its role in the hydrolysis of triglycerides from very–low-density lipoproteins (VLDLs) and chylomicrons.[1,2] Moreover, LPL influences the exchange of apolipoproteins and phospholipids between VLDL and high-density lipoprotein (HDL).[3] Thus, LPL may influence the plasma concentration of all major lipoprotein classes and is likely involved in the development of atherosclerosis.

The LPL gene is located on chromosome 8p22 and spans about 30 kilobases (kb) and contains 10 exons[4,5]; the first nine of its 10 exons code for a protein of 475 amino acids. After a posttranslational cleavage, the protein in the mature form is 60,000 daltons.[6] Some common sequence variants have been reported to have a modest effect on LPL catalytic function.[7-9] In addition to these mutations, the *Hin*dIII LPL gene polymorphism.[10] a common restriction fragment length polymorphism in intron 8 of the LPL gene, has been widely studied. The H+ allele of the *Hin*dIII polymorphism has been associated with higher levels of plasma triglycerides and lower levels of HDL-cholesterol in healthy individuals.[11-12] The data on the relationship between the *Hin*dIII polymorphism and coronary artery disease (CAD) are conflicting,[13-17] but the H+ allele of *Hin*dIII polymorphism is associated with a significantly higher risk of CAD.[18] Factors predicting the occurrence of premature CAD may not be the same as those predicting CAD severity. Conflicting studies have explored the relationship linking CAD severity to the *Hin*dIII restriction site polymorphism at the LPL gene locus,[14,16,19] and to our knowledge, no data are available from Italy.

Since a relatively high mean age for the first episode of myocardial infarction (MI) may be a selection bias when a putative risk factor is heritable and the genetic effect decreases with age, we decided to study patients aged less than 45 years at their first episode of MI. We investigated the possibility that the DNA polymorphism of LPL *Hin*dIII is associated with the severity of CAD determined by angiography in young patients who survived a MI.

SUBJECTS AND METHODS

Subjects

Ninety patients (n = 90) aged less than 45 years were recruited from the Coronary Care Unit (S. Giovanni Battista Hospital and Maria Vittoria Hospital, Turin, and Hospital of Savigliano) with a diagnosis of MI according to the criteria of the World Health Organization.[20] None of the patients had a previous MI. All patients underwent coronary angiography. Each angiogram was classified as revealing no coronary lesion with more than 50% luminal stenosis or as showing one, two, or three major epicardial coronary arteries with more than 50% luminal obstruction.

Demographic data were obtained from each subject, including age, sex, smoking history, blood pressure, diabetes status, and personal and family history of CAD. A positive family history was established if the case-patients had a first-degree relative with CAD at the age of 55 years or less for men or age 65 years or less for women. Hypertension was defined as a systolic or diastolic blood pressure higher than 140/90 mm Hg or the use of antihypertensive agents, according to the Joint National Committee criteria.[21] Subjects were classified as smokers if they currently smoked or had smoked within the previous 10 years.

Blood samples for determination of plasma lipid, lipoprotein, and apolipoprotein concentrations were drawn at least 3 months after the MI (mean ± SD, 3.5 ± 0.5 months; range, 3 to 5)

Lipids and Apolipoproteins

Venous blood samples obtained after an overnight fast were collected in a vacutainer tube containing EDTA and centrifuged for 30 minutes at 2,500 rpm at 4°C in a J6B centrifuge (Beckman, Palo Alto, CA). Plasma

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was stored at −20°C until processed. Total cholesterol and triglyceride levels were measured enzymatically. HDL-cholesterol was determined after precipitation of apolipoprotein B (apo B)–containing lipoproteins with heparin and manganese chloride.[22] Low-density lipoprotein (LDL)-cholesterol was calculated according to the method of Friedewald et al.[23] Plasma apo B and apo AI were determined by the turbidimetric method (Poli Diagnostici, Milan, Italy). The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared.

Isolation and Amplification of Genomic DNA

Genomic DNA was prepared from 100 μL frozen whole blood collected in EDTA with the QIAamp Blood Kit (Qiagen-Genenco M-Medical, Firenze, Italy). Primer sequence analysis and polymerase chain reaction (PCR) amplification were performed according to published data.[24] Genomic DNA was amplified by PCR using primers flanking the part of the genomic DNA that contains the T → G substitution in intron 8 of the LPL gene; the T → G substitution creates a *Hin*dIII restriction enzyme cleavage site. PCR products were digested overnight in the proper buffer at 37°C with *Hin*dIII (New England Biolabs, Beverly, MA), and the digestion product was subjected to electrophoresis through a 10% nondenaturing polyacrylamide gel and stained with silver stain. The genotypes were named according to the presence or absence of the enzyme restriction site: H−/H−, H−/H+, or H+/H+ are homozygous for the absence of the site, heterozygous for the presence and absence of the site, and homozygous for the presence of the site, respectively. The whole blood or DNA of three patients was not available for this study.

Statistical Analysis

Data are expressed as the mean ± SD. Triglyceride values were logarithmically transformed due to their skewed distribution when a parametric test was used. The relation between the *Hin*dIII genotype or the number of diseased coronary arteries and plasma lipids and apolipoproteins was assessed by analysis of covariance using the BMI as a covariant. Allele frequencies between groups were compared by the gene-counting method and χ^2 test. The χ^2 test was also used for comparison of noncontinuous variables among groups.

Logistic regression models that included *Hin*dIII polymorphism (categorized according to the presence of the H− allele: H-positive [either H−/H− or H−/H+] or H-negative [H+/H+]), smoking status (smokers *v* nonsmokers), family history of CAD (present *v* absent), hypertension (present *v* absent), and dyslipidemia (defined as total cholesterol ≥220 mg/dL, LDL-cholesterol ≥130 mg/dL, HDL-cholesterol ≤37 mg/dL, or triglycerides ≥170 mg/dL) were used to identify determinants of CAD severity, and the odds ratio (OR) is presented with the 95% confidence interval (95% CI). Cutoff levels for lipids, apoproteins, and apolipoproteins correspond to the mean ± 2 SD for these levels in a large group of healthy individuals at the Central Laboratory of the Molinette Hospitals; the same cutoff levels are used in our laboratory.

RESULTS

Baseline Clinical and Metabolic Characteristics

The patients were aged less than 45 years (mean age, 40.1 ± 3.9 years) and 83 were male and four were female. The 87 case-patients had a Q-wave or non–Q-wave infarction (67.3% and 32.7%, respectively); the MI was anterior (50.5%), lateral (41.7%), or inferior (7.8%). Analysis of the coronary angiograms showed the absence of critical stenosis in 13.8% and the presence of monovessel disease in 50.6% and multivessel disease in 35.6% of the case-patients. Three patients had type 2 diabetes and one patient had type 1 diabetes. There was no significant difference between lipid, lipoprotein, and apolipoprotein levels in patients with none, one, two, or three diseased coronary arteries; individuals with more than two diseased vessels had higher levels, albeit not significant, of total cholesterol, triglycerides, LDL-cholesterol, and apo B compared with those with other degrees of CAD (Table 1). The apo B/LDL-cholesterol ratio in the lipid profile increased with the magnitude of vessel disease, but the results did not reach statistical significance.

LPL Hin*dIII Polymorphism*

The allelic frequency of the *Hin*dIII H(−) and H(+) allele was 0.37 and 0.63, respectively. There was a striking association between the *Hin*dIII polymorphism and the number of diseased vessels. Patients with *Hin*dIII(+/+) genotypes were significantly more likely to have double- or triple-vessel disease and less likely to have no significantly diseased vessels (Table 2). The OR was calculated as a measure of the association of the *Hin*dIII(+/+) genotype with more severe CAD. The OR indicated a significant increase in the risk of multivessel disease when patients with two or more diseased vessels were compared with patients with none or at least one diseased vessel (OR 4.43; 95% CI, 1.73 to 11.33; $P = .0014$). The *Hin*dIII(+/+) genotype was significantly associated with multivessel disease compared with both the +/− and −/− genotypes ($\chi^2 = 6.05$, $P = .013$ and $\chi^2 = 7.97$, $P = .0048$, respectively), whereas the +/− genotype was not more likely to be associated with multivessel disease compared with the −/− genotype ($\chi^2 = 1.01$, $P = .31$). We did not find any association between smoking status (OR 1.84; 95% CI, 0.53 to 6.28; $P = .32$), family history of CAD (OR 1.74; 95% CI, 0.70 to 4.27; $P = .22$), hypertension (OR 0.87; 95% CI, 0.31 to 2.45; $P = .80$), or dyslipidemia (OR 0.63; 95% CI, 0.24 to 1.66; $P = .35$) and the risk of multivessel disease.

Using logistic regression analysis, the *Hin*dIII(+/+) geno-

Table 1. Lipids, Lipoproteins, and Apolipoproteins According to the Number of Diseased Coronary Arteries

Parameter	No. of Vessels With >50% Stenosis				
	0 (n = 12)	1 (n = 44)	2 (n = 19)	3 (n = 12)	*P*
Total cholesterol	230.5 ± 39.9	216.9 ± 43.9	214.2 ± 44.9	254.5 ± 74.7	.13
Triglycerides	141.7 ± 75.5	144.6 ± 78.5	176.6 ± 119.0	222.1 ± 248.6	.27
HDL-cholesterol	53.6 ± 6.4	47.6 ± 8.9	48.8 ± 8.9	53.4 ± 6.1	13
LDL-cholesterol	147.8 ± 38.6	141.8 ± 40.8	129.9 ± 35.5	156.8 ± 77.8	.48
Apo AI	100.5 ± 12.1	87.2 ± 18.6	95.0 ± 24.2	96.7 ± 12.2	.21
Apo B	117.8 ± 33.5	114.6 ± 30.2	112.6 ± 35.4	141.1 ± 51.3	.13
Apo B/LDL-cholesterol	0.81 ± 0.16	0.86 ± 0.30	0.88 ± 0.19	0.92 ± 0.36	.74

Table 2. *Hin*dIII Polymorphism According to the Number of Diseased Coronary Arteries

*Hin*dIII LPL Genotype	No of Vessels With >50% Stenosis							
	0		1		2		3	
	No.	%	No.	%	No	%	No.	%
H−/H−	3	25	11	25	1	5	1	8
H−/H+	6	50	18	41	5	27	3	25
H+/H+	3	25	15	34	13	68	8	67
Allelic Frequency								
H(−)	0.50		0.45		0.18		0.21	
H(+)	0.50		0.55		0.82		0.79	

NOTE. For genotype H+/H+ *v* H−/H− and H−/H+, $\chi^2 = 10.54$, $df = 3$, $P = .0014$.

type was still independently predictive of multivessel disease when smoking status, positive family history of CAD, hypertension, and dyslipidemia were included (Table 3).

Lipid values for H−/H−, H−/H+, and H+/H+ genotypes are reported in Table 4. Patients carrying the *Hin*dIII(+/+) genotype have higher levels of triglycerides and apo B compared with those who are heterozygous or homozygous for the H− allele. We could not demonstrate variations in the apo B/LDL-cholesterol and HDL_2-/HDL_3-cholesterol ratio. There was no relationship between the LPL *Hin*dIII(+) allele and low HDL-cholesterol, and we did not find any dose-dependent relationship between the presence of the *Hin*dIII(+) allele and high triglyceride levels.

DISCUSSION

Conflicting studies have explored the relationship linking CAD severity to the *Hin*dIII restriction site polymorphism at the LPL gene locus, and to our knowledge, no data are available from Italy. Since a relatively high mean age for the first episode of MI may be a selection bias when a putative risk factor is heritable and the genetic effect decreases with age, we decided to study patients aged less than 45 years at their first episode of MI. Mattu et al,[14] in a sample of 235 patients aged 55 years and 92 age-matched controls, found significant associations of the H+/H+ genotype and H(+) allele with the severity of CAD defined using the Brandt scoring system. In a group of 86 young MI survivors aged 40 years and 93 age-matched healthy individuals from Sweden, Peacock et al[17] reported that patients carrying the H(−) allele had the highest atherosclerosis scores in association with the X447 allele of the functional variant LPL serine447stop.[17] They used a semiquantitative method elaborated in their laboratory to quantify the severity of CAD. In a recent study from Australia, Wang et al[19] examined the relationship between CAD severity and two common LPL gene polymorphic markers. In a sample of 475 white patients aged 65 years or younger, they found that the *Hin*dIII polymorphism was not associated with the number of diseased coronary vessels but had an additive effect with the *Pvu*II polymorphism. The investigators determined the severity of disease according to the number of epicardial arteries with stenosis greater than 50%.

In our patients, there was no significant difference in lipid, lipoprotein, and apolipoprotein levels between patients with none, one, two, or three diseased coronary arteries. Individuals with more than two diseased vessels had higher levels, albeit not significant, of total cholesterol, triglycerides, LDL-cholesterol, and apo B and a higher apo B/LDL-cholesterol ratio compared with the other degrees of CAD (Table 1). In the lipid profile, the apo B/LDL-cholesterol ratio is a way to estimate the size of LDL particles, of which the smallest and most dense are the most atherogenic.

In this study, we demonstrated that the homozygous form of the LPL *Hin*dIII(+) allele increases the risk of multivessel disease by a factor of 4 in an Italian group of young MI survivors. This association was independent of the smoking status, a positive family history for CAD, hypertension, and dyslipidemia, which are known to predict CAD severity.[25] The discrepancies in the results of these studies are difficult to explain. The lack of homogeneity in the study populations (age at which CAD occurred, number of enrolled patients, and geographical origin) and the differences in the assessment of CAD severity may account for these conflicting results.

The precise mechanisms by which the *Hin*dIII LPL gene polymorphism may influence the severity of atherosclerotic lesions are still unclear. Several hypotheses may explain the association of LPL *Hin*dIII gene polymorphism and CAD severity. The relationship between the *Hin*dIII(+) allele and lipid levels is consistent with the apparent association with CAD severity. Most studies indicate that the *Hin*dIII(+) allele is

Table 3. Multiple Logistic Regression Analysis for Multivessel Disease (2 to 3 diseased vessels *v* 0 to 1 diseased vessel)

Parameter	OR	95% CI	*P*
*Hin*dIII polymorphism*	5.10	1.86-13 89	.002
Smoking status	1.94	0.50-7.49	32
Positive family history of CAD	1.81	0.60-4.90	.24
Hypertension	1.10	0.34-3.46	.86
Dyslipidemia	0.69	0.24-2.02	.51

*H+/H+ *v* H−/H− and H−/H+.

Table 4. Lipids, Lipoproteins, and Apolipoproteins According to LPL *Hin*dIII Genotype

Parameter	*Hin*dIII Genotype			*P*
	H−/H−	H−/H+	H+/H+	
Total cholesterol	224.8 ± 49.4	215.3 ± 39.6	227.4 ± 55 9	.62
Triglycerides	148.7 ± 58.9	130 1 ± 46.6	190.5 ± 166.4	.09
HDL-cholesterol	48 4 ± 9.5	49 4 ± 8.3	49.7 ± 8.6	.79
LDL-cholesterol	143.1 ± 47.8	140.9 ± 37 8	141.4 ± 50.5	.99
Apo AI	85.9 ± 19.4	93 3 ± 16.8	93.3 ± 20.8	.23
Apo B	113.9 ± 30.4	111.1 ± 31.7	124.5 ± 39.4	.24
Apo B/LDL-cholesterol	0.88 ± 0.46	0.80 ± 0.18	0.90 ± 0.25	.27
HDL_2/HDL_3-cholesterol	0.33 ± 0.17	0.27 ± 0.10	0.35 ± 0.14	.07

associated with high triglycerides[11,12,14,16,17] and low HDL-cholesterol.[12,13,16] In our study, patients carrying the +/+ genotype (Table 4) showed a trend for higher triglyceride and apo B levels, whereas we could not demonstrate variations in HDL-cholesterol levels and the HDL_2-/HDL_3-cholesterol and apo B/LDL-cholesterol ratio. Both plasma triglyceride[26] and apo B[27] levels have been shown to predict the severity of CAD. The mutation responsible for the *Hin*dIII restriction fragment length polymorphism occurs at a site of the LPL gene that renders this mutation unlikely to be functionally relevant. The *Hin*dIII polymorphism is probably a neutral marker in linkage disequilibrium with one or several functional sites. The results of the European Atherosclerosis Research Study suggest that the *Hin*dIII site is in strong linkage disequilibrium with the functional variant LPL serine447stop (S447X), and the effect on lipid levels associated with the H(−) allele is explained in large part by the effect associated with the X447 and not by the H polymorphism.[28] Moreover, the H+S447 haplotype was associated with significantly higher postprandial triglyceride levels versus the H-X447 haplotype.[28] Given the central role of LPL in the catabolism of triglyceride-rich particles, the LPL gene is a strong candidate for the regulation of postprandial lipemia. Delayed postprandial triglyceridemia has been shown to be an important determinant of atherosclerosis[29] and CAD risk.[30] In conclusion, we found a striking association between the *Hin*dIII polymorphism and the number of diseased vessels: patients with *Hin*dIII(+/+) genotypes were significantly more likely to have double- or triple-vessel disease and less likely to have no significantly diseased vessels. Moreover, we demonstrated that the homozygous form of the LPL *Hin*dIII(+) allele increases the risk of multivessel disease by a factor of 4 in an Italian group of young MI survivors. This association was independent of the smoking status, positive family history for CAD, and hypertension, which are known to predict CAD severity.

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