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Original Article

Lipoprotein lipase gene *HindIII* polymorphism and risk of myocardial infarction in South Indian population

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ABSTRACT

Introduction: Studies have reported an association between lipoprotein lipase (LPL) gene and myocardial infarction in some populations. Therefore, the present study aimed to investigate the association of the *HindIII* polymorphism of the (LPL) gene with myocardial infarction and to explore its potential role in susceptibility in a South Indian population.
Subjects and methods: We included a total of 412 subjects (202 myocardial infarction patients and 210 age- and sex-matched controls). Demographic and clinical characteristics were collected. Lipid profiles were estimated. DNA was isolated and the LPL gene *HindIII* polymorphism was determined by polymerase chain reaction.
Results: Comparison of the lipid profiles between patients and controls showed that patients had statistically high significant values ($p = 0.0001$). The H^+ H^+ genotype of the LPL gene is associated with myocardial infarction. H^+ H^+ vs. H^- H^- was $\chi 2 = 19.4$, OR 3.1, CI 95% 1.8–5.2, $p < 0.0001$.
Conclusion: Our study strongly suggests that the LPL gene HindIII Hþ Hþ genotype is an independent risk factor for first MI.

1. Introduction

Myocardial Infarction (MI), also known as heart attack, is the irreversible necrosis of heart muscle secondary to prolonged ischemia. This usually results from an imbalance in oxygen supply and demand, which is most often caused by plaque rupture with thrombus formation in a coronary vessel, resulting in an acute reduction of blood supply to a portion of the myocardium. The classical symptoms of MI are shortness of breath, chest pain anxiety typically radiating to the left arm or left side of the neck, palpitations and vomiting. The important risk factors are previous history of vascular disease

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such as atherosclerosis, angina-heart attack or stroke and age – especially in men over 40 and women over 50 years.[1]

Lipoprotein lipase (LPL) plays a important role in lipid metabolism by hydrolyzing triglycerides in circulating lipoproteins, which constitutes the rate-limiting step in removal of triglyceride-rich lipoproteins, such as chylomicrons (CM) and very low-density lipoproteins (VLDL) from the circulation.[2] Lipoprotein lipase is multifunctional enzyme, recently shown to serve as a ligand for low-density lipoprotein (LDL) receptor-related protein and to influence the hepatic secretion and uptake of VLDL and LDL cholesterol.[3]

The LPL gene, located in region 8p22, is composed of 10 exons, 9 introns and contains some restriction fragment length polymorphisms (RFLPs).[4–6] Modifications in gene structure may affect LPL activity, resulting in lipid metabolism changes, such as slow hydrolysis of CM and VLDL, increased half life of LDL and CM, lower production of high density lipoproteins (HDL)[7,8] and increased LPL activity.[9] The *HindIII* (rs320) polymorphism is one of the most common LPL gene polymorphisms. It is an intronic base transition of thymine (T) to guanine (G) at position +495, which abolishes the restriction site for the enzyme *HindIII*. Several studies have shown that the common allele (H^+) is significantly associated with high triglycerides (TG) levels and low HDL levels compared to the rare allele (H^-).[10–16] The LPL H^+ H^+ genotype presented elevated TG levels.[17] Another study demonstrated that this genotype has a higher risk of myocardial infarction (MI) in patients over 90 years old, while H^- allele carriers are protected against MI.[18]

Hence, the present study was aimed at assessing the association of the *HindIII* polymorphism of the LPL gene in MI patients of a South Indian population. In addition to this, classical risk factors and lipid profiles have been studied in all the subjects.

2. Methods

The study was carried out on 202 MI patients (male:female = 181:21) admitted to Osmania General Hospital, ICCU, Cardiology Division, Hyderabad, Andhra Pradesh, India. The patients were 54–68 years of age. **The inclusion criteria for the current study was the patients with acute myocardial infarction who underwent coronary angiography, where as the patients with past history of coronary artery and vascular diseases, pulmonary, renal, hepatic disease were excluded from our study. For the present study, the selection of MI patient study group were free of diabetes. The reason is that Diabetes is a major risk factor for MI and it is well proven that LPL gene *HindIII* gene polymorphism is associated with lipid levels in diabetic patients. The present study was aimed to find out the association between LPL *HindIII* polymorphism and abnormal lipid levels in MI patients.** On the basis of typical ECG changes, elevated cardiac markers and clinical history, the diagnosis was confirmed as MI by the cardiologists. The study was approved by the Ethical Committee and written informed consent was obtained from all the subjects. Blood samples were collected from patients after 13–15 h of fasting. Simultaneously, blood samples were collected from 210 healthy, age- and sex-matched (male: female = 184:26) controls (blood donors from the same hospital) aged between 56 and 67 years and all controls were non-hypertensive.

Information has been collected using a questionnaire on age, sex, height, weight (for calculating body mass index), cigarette smoking, exercise schedule, alcohol consumption and hypertension. Exercise criteria were defined by an individual doing 1 h daily in the form of brisk walking or gym activity. Hypertension was defined according to JNC-VII guidelines. Accordingly, hypertension was defined as a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg, based on the average of two blood pressure measurements, or a patient's self reported history of hypertension. Smokers were defined as those reporting daily smoking. Ex-smokers and occasional smokers were classified as non-smokers. Since patients were found to drink alcohol in different forms and many were reluctant to admit the exact amount consumed, we defined alcohol usage as consumption of at least three alcoholic drinks in a week.

To do the genotyping of LPL *HindIII* Polymorphism, 5 ml venous blood was collected in a plain test tube and serum was separated. In the region of intron 8, the LPL gene containing *HindIII* polymorphism was amplified using the following primers: forward primer 5′-GATGTCTACCTGGATAA TCAAAG-3′and the reverse primer was 5′-CTTCAGCTAGAC ATTGCTAGTGT- 3′. PCR reaction was carried out in a 50-uL reaction volume containing 100 ng of genomic DNA, 0.4 mmol/L of each primer, 0.2 mmol/L dNTPs (Invitrogen, USA), 2 mmol/L $MgCl_2$ in 10% PCR buffer and 1 U of DNA polymerase. PCR involved an initial 5-min denaturation at 96 °C, initial denaturing at 94 °C for 1 min, annealing at 57 °C for 1 min and extension at 72 °C for 1 min, with a final extension at 72 °C for 7 min, total 35 cycles were kept. The PCR amplified 355-bp product was digested with 2.5 U of *HindIII* (MBI Ferments) at 37 °C for 4 h, and the fragments were separated on an ethidium bromide stained 2% agarose gel; the replacement of a thymine (T) with a guanine (G) base at position +495 abolished the *HindIII* cleavage by converting the recognition sequence for *HindIII* (AAGCTT) into AAGCGT. The presence of a 225-bp band and a 140-bp band represents the homozygous mutant H^+ H^+ genotype; 365-bp, 225-bp and 140-bp bands represent the heterozygous H^+ H^- genotype; and 365-bp bands represent the homozygous H^- H^- genotype. Total cholesterol (TCL), triglycerides (TGL), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were estimated using a semi-automatic analyzer

Table 1 – Demographic characteristics of the study population.

Characteristics	Controls $n = 210$(%)	MI patients $n = 202$(%)
AGE (Mean ± SD)	61.3 ± 4.6	63.2 ± 3.96
Sex ratio (Male: Female)	184:26	181:21
BMI (Kg/m^2) (Mean ± SD)	22.4 ± 2.5	28.1 ± 1.7
Smokers	11 (5.2)	65 (32.1)
Alcoholic	17 (8.0))	75 (37.1)
Exercise	117 (55.7)	16 (32.3)
Hypertension	0	66 (29.5)

MI = myocardial infarction; SD = standard deviation; BMI = body mass index.

Table 2 – Comparison of lipid profiles between MI patients and controls.

Parameters	Controls (Mean ± SD)	Patients (mean ± SD)	t value	p value
TCL (mg/dl)	168.3 ± 24.0	239.8 ± 29.0	27.3	0.0001
TGL (mg/dl)	137.8 ± 1.5	177.3 ± 11.6	48.9	0.0001
LDL (mg/dl)	98.5 ± 11.9	173.6 ± 28.4	35.2	0.0001
HDL (mg/dl)	42.3 ± 5.3	33.8 ± 3.6	18.3	0.0001
VLDL (mg/dl)	27.3 ± 1.3	36.6 ± 1.9	58.1	0.0001

Values represent mean ± standard deviation. MI = myocardial infarction; TCL = total cholesterol; TGL = triglycerides; LDL = low-density lipoprotein; HDL = high-density lipoprotein; VLDL = very-low-density lipoprotein.

(ERBA, CHEM-7, and Transasia Biomedicals, India) using commercial kits (ERBA).

2.1. Statistics

Analysis of variance (ANOVA) test was performed for lipid profiles among controls and MI patients using SPSS software, 15.0 Windows version. For all cases, $p < 0.05$ was considered significant. Hardy–Weinberg law of equilibrium was tested for the LPL gene polymorphism in controls and MI patients, the genotype frequencies were in agreement with the law. The association between genotypes of MI patients and controls was examined by using the odds ratio (OR) with 95% confidence interval (CI) and chi-square analysis. Allelic frequencies for the *HindIII* polymorphic site were estimated by gene counting. Multivariate logistic regression analysis was done for adjusting the confounding factors with LPL genotypes.

3. Results

The demographic and clinical characteristics of the 210 controls and 202 MI patients are represented in Table 1. The mean age of the controls and patients were 61.3 ± 4.6 and 63.2 ± 3.96 years respectively. The sex ratios were comparable in both groups. The Body Mass Index was **higher in** MI subjects, as compared to controls. Smokers and alcoholics were predominant among patients. Only 32.3% were involved in exercise among MI subjects against 55.7% among controls. Hypertensive individuals were excluded among controls, where as 29.5% among MI patients.

The comparison of lipid profiles between controls and patients are showed in Table 2. The TCL, TGL, LDL and VLDL levels were significantly high in patients in comparison with controls ($p = 0.0001$), where as the HDL levels were significantly high in controls than in patients ($p = 0.0001$). The association of LPL genotypes with lipid levels between MI patients and controls are summarised in Tables 3 and 4.

The distribution of LPL genotypes and allelic frequencies of the study groups are presented in Table 5. The genotypic association between patients and controls were shown in Table 6. The $H^+ H^+$ vs. $H^- H^-$ was $\chi 2 = 19.4$, OR 3.1, CI 95% 1.8–5.2, $p < 0.0001$; $H^+ H^+$ vs. $H^+ H^-$ was $\chi 2 = 1.4$, OR 1.3, CI 95% 0.8–2.0, $p > 0.22$; $H^+ H^+$ vs. $H^- H^- + H^+ H^-$ was $\chi 2 = 5.7$, OR 0.64, CI 95% 0.4–0.9, $p < 0.01$. H^+ allele was significantly associated with MI: H^+ vs. H^- was $\chi 2 = 23.8$, OR 2.0, CI 95% 1.5–2.6, $p < 0.0001$.

Multivariate logistic regression analysis was done for adjusting the confounding factors with LPL genotypes. After adjusting the all confounding factors we observed that Homozygous ($H^+ H^+$) mutation shows 33 times and Heterozygous ($H^+ H^-$) genotype shows 6 times risk of MI as compared with Homozygous ($H^- H^-$) genotype.

4. Discussion

LPL plays a central role in the metabolism of lipoproteins and associated with the development of atherosclerosis and coronary heart disease (CHD). LPL gene mutants have been extensively described in human. Number of studies have been focused on the influence of LPL *HindIII* polymorphism on plasma TG, TC, HDL-C and apolipoproteins levels; however the results are inconsistent.[19–21] Although LPL *HindIII* (rs320) polymorphism is not expected to have any direct functional effect on LPL activity, some of data have demonstrated that H+ allele is associated with higher TG, lower HDL-C level, hyper triglyceridemia, the severity of atherosclerosis and an increased risk of coronary artery disease (CAD).[22]

We examined the impact of genetic variants of the LPL gene on plasma lipid levels in South Indian population. To our knowledge, this is the first study of its kind in South Indians, a population with very high rates of premature CAD.[23]

The present study investigated the role of this polymorphism in the development of MI. The frequencies of the

Table 3 – Association of LPL genotypes with lipid levels in MI patients.

Parameters	Genotypes				
	$H^- H^-$	$H^- H^+$	$H^+ H^+$	F value	p value
TCL (mg/dl)	215.8 ± 29.1	237.1 ± 29.8	266.7 ± 28.1	45	0.001
TGL (mg/dl)	172.4 ± 11.9	179.7 ± 11.2	180.0 ± 11.7	5.6	0.004
LDL (mg/dl)	168.2 ± 29.1	170.1 ± 27.6	182.5 ± 28.5	5.3	0.005
HDL (mg/dl)	35.6 ± 3.2	34.2 ± 3.7	31.6 ± 3.9	18.2	0.001
VLDL (mg/dl)	32.6 ± 2.1	39.3 ± 1.8	37.9 ± 2.0	80	0.0001

Values represent mean ± standard deviation. MI = myocardial infarction; TCL = total cholesterol; TGL = triglycerides; LDL = low-density lipoprotein; HDL = high-density lipoprotein; VLDL = very-low-density lipoprotein.

Table 4 – Association of LPL genotypes with lipid levels in controls.

Parameters	Genotypes				
	$H^- H^-$	$H^- H^+$	$H^+ H^+$	F value	*p* value
TCL (mg/dl)	164.6 ± 21.6	166.1 ± 26.2	174.2 ± 24.2	3.2	0.04
TGL (mg/dl)	134.8 ± 1.4	135.6 ± 1.2	143.0 ± 1.9	25	0.01
LDL (mg/dl)	95.8 ± 12.1	97.3 ± 11.8	102.4 ± 12.0	5.8	0.03
HDL (mg/dl)	44.2 ± 4.9	42.8 ± 5.4	40.1 ± 5.6	10.9	0.03
VLDL (mg/dl)	25.3 ± 1.1	28.6 ± 1.5	28.0 ± 1.3	28	0.01

Values represent mean ± standard deviation. TCL = total cholesterol; TGL = triglycerides; LDL = low-density lipoprotein; HDL = high-density lipoprotein; VLDL = very-low-density lipoprotein.

Table 5 – Distribution of LPL genotypes and allelic frequencies of the study population.

Study group	LPL genotypes			Total	Allelic frequencies		Total
	$H^- H^-$	$H^- H^+$	$H^+ H^+$		H^-	H^+	
Controls	72 (34.3)	68 (32.4)	70 (33.3)	210	0.51	0.49	420
Patients	32 (15.9)	72 (35.6)	98 (48.5)	202	0.34	0.64	404

LPL: Lipoprotein lipase gene; Percentages provided in parentheses.

$H^+ H^+$ genotype and H^+ allele were significantly higher in patients compared with controls, indicating the association of LPL gene *HindIII* polymorphism with the disease. The results of the present study were in accordance with observations of earlier investigators, which support that $H^+ H^+$ genotype associated with myocardial infarction.[24]

Several researchers have identified a significant association between the H+ allele and MI[25], while others have shown an association with CAD.[26,27] We also got the results with a strong association between the H+ allele and MI .The ECTIM case–control study reported an increased odds ratio (2.1) for MI with *HindIII* ($H^+ H^+$) compared with *HindIII* ($H^- H^-$) genotypes. A higher frequency of the H^+ allele is reported in patients with Alzheimer's disease (AD) compared to a control group, suggesting an increased risk of AD in H^+ allele carriers indicating that LPL gene *HindIII* polymorphism showed association with Alzheimer disease.[28]

Thorn et al, (1990) observed a higher frequency of the H+ allele in patients with atherosclerosis and a recent study showed an association with higher levels of TG, lower levels of HDL, atherosclerosis severity and increased risk of CAD.[29] A study of elderly Russian MI patients and elderly controls (>90 years) showed a protective effect of the H–allele.[18] A lipid profile with high TG and low HDL is a risk factor for atherosclerosis, which was associated with the H+ allele in several populations and it also proved that polymorphic *HindIII* site in the LPL gene is functional because it affects the binding of a transcription factor and it also has an impact on LPL expression.[29]

In the present study, 202 patients and 210 controls were included and our selection criteria were specific for patients with a first MI without previous history of vascular disease. However, patients with cancer, neurological and all kidney diseases were excluded from the study. The classical risk factors and lipid profiles were significantly high in patients in comparison with controls, which is consistent with previous studies.[19] We have observed that the LPL gene *HindIII* $H^+ H^+$ genotype frequency was significantly associated with MI patients in South Indian population. Similar results on MI in Brazil and Russian population have been observed.[24] Infact, studies on the LPL gene *HindIII* polymorphism are very limited in India. Moreover, there are no reports on the LPL gene *HindIII* polymorphism in MI from an Indian population.

To the best of our knowledge, this is the first study to investigate the association of the LPL gene *HindIII* polymorphism in MI in a South Indian population. However, it warrants further study in a larger cohort to confirm the association of this gene polymorphism.

Table 6 – Distribution of LPL genotypes between MI patients and controls for statistical significance.

Genotypes & alleles (Patients vs. controls)	Chi-square (χ^2)	Odds ratio	CI 95%		*p* value
			L. limit	U. limit	
$H^+ H^+$ vs. $H^- H^-$	19.4	3.1	1.8	5.2	0.0001
$H^+ H^+$ vs. $H^+ H^-$	1.4	1.3	0.8	2.0	0.22
$H^+ H^+$ vs. $H^- H^-$ + $H^+ H^-$	5.7	0.64	0.4	0.9	0.01
H^+ vs. H^-	23.8	2.0	1.5	2.6	0.0001

LPL = Lipoprotein lipase gene; MI = myocardial infarction; CI = confidence interval; L = lower; U = upper.

5. Conclusion

Our data strongly suggest that the LPL gene *HindIII* $H^+ H^+$ genotype is a independent risk factor for first MI.

Conflicts of interest

All authors have none to declare.

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