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Association of Mutation and Polymorphism in Lipoprotein Lipase Gene with Coronary Heart Disease in Some Iraqi Patient

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Abstract: Prior research has assessed the correlations between the likelihood of acquiring diabetes mellitus and the polymorphism in the cholesterol ester transfer protein (LIPASE GENE). Chronic hyperglycemia and abnormalities in the metabolism of carbohydrates, fats, and proteins due to deficiencies in insulin production, action, or both are characteristics of the metabolic condition known as diabetes mellitus (DM), which has several etiologies. However, the conclusions are still up for debate. This study sought to determine whether lipid profile abnormalities in Iraqi diabetic patients were associated with the LIPASE GENE. Methods, To shed light on the relationships between the LIPASE GENE TaqIB polymorphism, HDL-C levels, and diabetes mellitus, we performed a meta-analysis of the literature. Findings: This study included 160 Iraqi participants, 90 of whom had diabetes mellitus, and 70 of whom served as controls. Table 1 displays the population study's blood lipid data. TC, TG, LDL-C, and VLDL-C were all considerably greater (P<0.0001) in the patient group than in the control group, with the exception of HDL-C, which was lower (P<0.0001). In this study, there were more men (75.55%) than women (24.4%) with type 2 diabetes. The large percentage of men in this research may result from the demographics of the hospital's patients, who tend to seek medical care more frequently than women to have more free time because most of them are retired. Included in the correlation between HDL-C concentration and lipase polymorphism. The LIPASE GENE gene has been shown to have a variety of single nucleotide polymorphisms. The influence of the rs708272 (g.5454G>A) polymorphism on HDL-C focus has been explained. This study aimed to evaluate the LIPASE gene site polymorphism and its effect on blood lipids in Iraqi patients with lipid problems. Since a few evaluations listed the LIPASE GENE polymorphism's association with the HDL level we decided to use it because we couldn't locate any Iraqi studies that addressed this polymorphism.

Keywords: Lipase Polymorphism, Coronary Heart Disease, Cholesterol, Triglyceride, RFLP.

Introduction

By accelerating the breakdown of triacylglycerol circulating in triglyceride-rich lipoproteins, lipase, a crucial enzyme in controlling lipid fuel disposal, supplies fatty acids for tissue usage. Glycosaminoglycan anchors lipoprotein lipase to the capillary endothelium surface, hydrolysing VLDL and plasma chylomicrons to leave residual particles. Therefore, the rate-limiting enzyme that eliminates plasma triglyceride-rich lipoproteins from the

bloodstream is lipoprotein lipase. Although lipoprotein lipase is found in most bodily tissues, including skeletal, cardiac, and adipose tissue, macrophages also express and release it. Lipoprotein lipase is essential for producing HDL because it facilitates the transfer of phospholipids and Apo lipoproteins to HDL. While Apo lipoprotein C-III suppresses lipoprotein lipase activity, Apo lipoprotein C-II is a necessary cofactor for activating lipoprotein lipase activity.

The severity of coronary artery disease and different plasma lipoprotein levels have been linked to many polymorphisms in the lipoprotein lipase gene. Low levels of lipoprotein lipase activity have been associated with the development of coronary atherosclerosis, as evidenced by partial deletion of lipoprotein lipase. Reduced lipoprotein lipase activity boosts triglyceride and reduces HDL cholesterol, increasing the risk of ischemic heart disease. Reverse cholesterol transfer is decreased by low HDL cholesterol levels. Increased triglyceride levels suggest the presence of lipoprotein remnants and partly delipidized lipoproteins of varying size and composition in the plasma, including VLDL, IDL, chylomicron remnants, and particles containing lipoprotein B (LP-B: C, LP-B:C: E, and LP-A-II:B:C:D: E).

Apo lipoprotein C-III, a marker of triglyceride-rich lipoprotein metabolism and the clearance of chylomicron and VLDL particles, is an independently significant predictor of the progression of coronary atherosclerosis, according to data from two sizable serial coronary angiographic clinical trials. Some pathologic diseases, including diabetes, chylomicronemia, obesity, and atherosclerosis, are associated with aberrant expression of LPL. Chromosome 8p22 contains the LPL gene. This gene has been identified to have more than 100 mutations.

According to a few studies, PvuII, Ser447X, and HindIII polymorphisms were linked to an increased risk of CAD These findings were debatable, though. According to some research, there is no correlation between these LPL gene variations and the risk of CAD20. These findings link the development of atherosclerosis to the ineffective elimination of triglyceride-rich lipoproteins by lipoprotein lipase. Decreased removal of chylomicrons and VLDL particles prolongs circulatory residence time and, therefore, increases the exposure of the arterial wall to these atherogenic particles. Low lipoprotein lipase activity may also contribute to atherosclerosis by promoting postprandial lipemia.

Due to their higher frequency and impact on atherosclerosis susceptibility, the LPL gene, Asp9Asn, Asn291Ser, and S447X are the most significant mutations identified. Although the LPL D9N and LPL N291S polymorphisms have been linked to a poor lipid profile, there has been little evidence linking them to cardiovascular disease. D9N and N291S have been associated in a meta-analysis with an increase in triglycerides of 20% and 31%, respectively, and S447X was associated with reduced plasma triglyceride and increasing HDL-C28. The study aimed to determine risk factors and the association of lipid profiles with the LPL gene in patients with coronary artery disease and the healthy Sudanese population.

Methodology

Subjects selection

The total number of the study sample was 180 subjects, 100 individuals were patients with coronary disease and 80 individuals were healthy have been selected as a control, age ranged from 17 to 55 years, and gender was matched in both groups, volunteers were recruited by the private clinic from Iraqi population at large.

Sample collection

During the time of clinical examination, 6 ml of blood samples were collected from each subject and divided into two parts: In the first part, 2 ml of blood was collected in EDTA tubes for DNA extraction, while in the second part, 4 ml was taken in a normal test for separation of the blood serum.

Laboratory measurements

Enzymatic colorimetric techniques were used to assess serum lapse activity [29]. Enzymatic colorimetric techniques [(30)] were used to quantify the lipid profile's TC, HDL-C, and TG levels, while Friedewald's formula [(31)] was used to estimate the LDL and VLDL.

Determination of lipase gene polymorphism

This case-control study aimed to investigate the lipid profiles and risk variables of CHD patients in Sudan and their correlation with the lipoprotein lipase gene. All participants gave their informed permission.A systematic questionnaire was used to gather comprehensive demographic data and CVD risk variables. The MINDRAY BS-200 analyzer (MINDRAY, Shenzhen, China) examined the lipids. Genomic DNA was extracted from the blood by kits, and PCR-RFLP was applied to detect D9N, N291 and S447X lipoprotein lipase genotypes, using TaqI, RsaI and Mnl1 restriction enzyme, respectively. SPSS v.18 was used for statistical studies.

Results

Serum lipid results of the population study

In this study, 180 Iraqis were recruited, 80 served as controls and 100 had CHD. Serum lipase values from the population study and lipid profile (TC, TG, LDL-C, and VLDL-C) were considerably higher ($P<0.0001$) in the patient group than in the control group ($P<0.0001$), except HDL-C. One of the reasons influencing the development of dyslipidemia in patients with coronary heart disease is the resulting abnormalities of lipoprotein metabolism. Diabetic dyslipidemia involves not only quantitative but also qualitative and kinetic abnormalities of lipoproteins, which are intrinsically atherogenic[32].

Hypertriglyceridemia, along with prolonged postprandial hyperlipidemia and elevated remnant particle levels (caused by increased production of triacylglycerol-rich lipoproteins and decreased catabolism of triacylglycerol-rich lipoproteins), as well as decreased HDL-cholesterol levels due to an increased rate of HDL catabolism[33], are the main (characteristic) quantitative abnormalities. The most common qualitative anomalies that may contribute to atherogenicity

include glycation of Apo lipoproteins[34], a rise in the size of big VLDL particles (VLDL1), a higher percentage of tiny, dense LDL particles, an increased vulnerability of LDL to oxidation, and an increase in the triacylglycerol content of both HDL and LDL. The encouragement of lipid deposition inside artery walls may be implied by the longer LDL plasma residence time caused by a reduced turnover rate, even when LDL levels may be normal in individuals with CHD illness. Some factors, such as insulin resistance and possibly some adipokines (e.g. adiponectin) and hyperglycemia, are involved in the pathophysiology of diabetic dyslipidemia[35].

Table 1. Comparison between lipid levels of patients and control group

Parameter	Patients (No. 90)	Control (No. 70) Mean ± SD	*P* value
Lipase (UI/L)	162.3± 10.625	90.1± 11.279	0.001**
HDL-C (mg/dL)	41.236 ± 10.792	51.5 ± 7.964	0.001**
TC (mg/dL)	168.512 ± 5.378	147.9 ± 2.352	0.001**
LDL-C (mg/dL)	103.025 ± 5.374	71.2 ± 8.722	0.001**
VLDL-C (mg/dL)	27.409 ± 9.510	31.985 ± 5.638	0.002**
TG (mg/dL)	137.479 ± 7.302	74.8 ± 10.603	0.001**

Genotypes and alleles frequency:

By PCR-RFLP analysis of the lipase polymorphism, three types of genotypes (B1B1, B1B2, B2B2) have been obtained as show in (Fig 2).

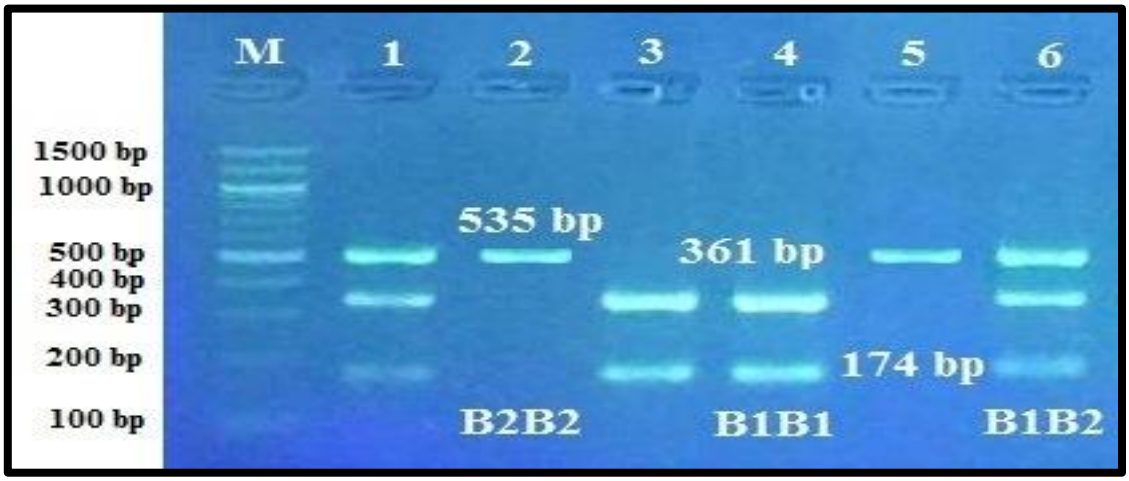

Figure 1. Showing LIPASE GENE gene polymorphism of PCR-RFLP products. Lane (M) 100 bp DNA ladder, lane (3 & 4) B1B1 homozygote (361 & 174 bands), lane (1 & 6) B1B2 heterozygote (535, 361 & 174 bp bands), lane (2 & 5) B2B2 homozygote (535 bp band).

53.1% of the population was male, 22% had a family history of coronary heart disease, 42.6% had high blood pressure, 41.6% had diabetes, 18.2% smoked, and 5.3% drank alcohol. The cultural denial of drinking and smoking in our culture, particularly among women, may be the cause of the low rates of these behaviors[36]. TC and LDL-C values are lower in patients than in controls. Reduced TC, LDL, and triglycerides were substantially linked to African ancestry[37]. LPL D9N, N291S, and S447X carriers had respective allele frequencies of 4.2%, 30.7%, and 7.1% (Table 1).In various populations, the N291S carrier of frequency ranged from 2% to 5%[38]. In contrast, S447X was 18% in CAD patients and 23% in control[39]. The incidence of p.Asp9Asn variation in the Tunisian

population was 10.37% in CAD patients compared to 3.66% in controls, while the frequency of p.Ser447X variation was 8.8% in CAD patients compared to 13.7% in controls[40]. Lipid profiles of D9N, N291S carriers (patient) and non-carriers (control) did not significantly (P <0.05) differ from one another.

Table 2. Serum lipid levels of the patients according to gender

Parameter	Male (No. 77)	Female (No. 23) Mean ± SD	*P* value
Lipase (UI/L)	175.2± 11.423	158.1± 11.351	0.001**
HDL-C (mg/dL)	32.604 ± 10.822	37.409 ± 10.751	0.031**
TC (mg/dL)	162.980 ± 6.104	188.045 ± 42.777	0.049**
LDL-C (mg/dL)	92.936 ± 5.827	132.663 ± 8.893	0.001**
VLDL-C (mg/dL)	39.767 ± 5.11	27.8364 ± 5.507	0.003**
TG (mg/dL)	137.129 ± 6.189	139.181 ± 5.435	0.847

The findings of this study revealed that diabetic patients had significantly higher levels of total cholesterol (p=0.888) than non-diabetic subjects. This increase could be attributed to either a rise in the plasma concentration of VLDL and LDL, which could be caused by increased hepatic production of VLDL or a decrease in the removal of VLDL and LDL from the bloodstream[41]. According to the study, diabetic patients have significantly higher levels of LDL (p=0775) and triglycerides (p=0.327). This could be because overproduction of VLDL raises plasma levels of triglycerides, which are then exchanged by cholesterol ester transfer protein. Result in decreased HDL cholesterol levels; it might also be caused by an insulin shortage, which leads to poor glucose utilization, hyperglycemia, and the release of fatty acids from adipose tissue. Adipose tissue fatty acids are released for energy purposes, and extra fatty acids build up in the liver where they are transformed into triglycerides[42]. The combination of increased TGs (VLDL-TG), reduced clearance of TG-rich lipoproteins, and decreased high-density lipoproteins (HDL)[43] was the most common change in the lipid profile.

Table 3. Serum lipid levels of the patients and control according to LIPASE GENE polymorphism

Parameter	B1B1 (No. 49) Mean ± SD	B1B2 (No. 25) Mean ± SD	B2B2 (No. 26) Mean ± SD	*P* value
Lipase (UI/L)	163.3± 10.421	166.1± 11.266	176.2± 10.867	0.001**
HDL-C (mg/dL)	32.999 ± 4.486	34.2631±11.94	31.227 ±11.633	0.682
TC (mg/dL)	166.973 ± 5.966	169.988 ± 4.903	174.023 ± 5.347	0.888
LDL-C (mg/dL)	105.325 ± 5.844	96.720 ± 5.926	105.965 ± 9.628	0.775
VLDL-C (mg/dL)	35.656 ± 3.704	40.366 ± 6.612	38.682 ± 5.848	0.417
TG (mg/dL)	139.658 ± 7.761	143.3012 ± 5.267	122.246 ± 3.125	0.327

Table 4 shows results of the genotype and allelic frequencies in (%) and number of patients having each genotype of study population. The distribution of genotype in case and control group was accomplished in the Hardy-Weinberg equilibrium. The results demonstrate that there is a substantial differential (p value 0.001) between frequency of genotypes and alleles of LIPASE GENE polymorphism in the patient and control groups. In comparison to the control, patients with the B2B2 genotype (22.86%) had significantly lower

levels, whereas those with the B1B1 (8.57%) and B1B2 (68.57%) genotypes had higher levels. Additionally, we found that the patient's B1 allele frequency was higher than that of the control group, but the B2 allele frequency was lower (P <0.05).

Table 4. Distribution of genotypes and alleles frequency of the patients and controls group

	Patients No. (100)		Control No. (80)				
Genotypes	**No.**	**%**	**No.**	**%**	***P* value**	**OR**	**(95% CI)**
B1B1	49	49	13	9.57		7.27	2.48-21.92
B1B2	25	25	49	68.67	**0.0001****	0.51	0.23-1.16
B2B2	24	24	18	33.86		1 Ref.	-
Alleles	**No.**	**%**	**No.**	**%**	***P* value**		
B1	125	66.63	60	43.85		2.665	1.679 to 4.216
B2	65	33.37	80	56.15	**0.0002****	1 Ref.	-

Discussion

And S447X "genotype (Table 1). D9N and N291S mutations were related with increased plasma TG[44]. The S447X variation was linked to a decreased risk of CHD[45], greater HDL, and lower TG. Heterozygote carriers of the p.Asp9Asn mutation showed a substantial drop in HDL[46] and an increase in total cholesterol in the healthy Tunisian population. In conclusion Heart conditions are common in Iraq and share risk factors with other countries. The lipoprotein lipase polymorphism was not associated with the incidence of CHD. In this study, we first performed a meta-analysis of the association between LPL polymorphism and CAD risk. It was found that the LPL HindIII polymorphism was positively correlated with CAD risk. In contrast, the LPL PvuII polymorphism exhibited no connection with CAD risk Conversely, there was no correlation between the LPL PvuII polymorphism and the incidence of CAD. The relationship between the LPL Ser447X polymorphism and the risk of CAD requires more investigation. The LPL gene, located on chromosome 8p22, is more than 30 kb long and consists of 10 exons and 9 introns. Its 475 amino acid proteins, including a 27 amino acid signal peptide, are translated from its cDNA. Restrictions fragment length polymorphisms (RFLPs) in the LPL gene[47] have shown a number of sequence variants, including BamHI, PvuII, HindIII, BstNI, and Ser447X sites.

The HindIII, Ser447X, and PvuII polymorphisms were the most prevalent among these variants and might be linked to significant changes in plasma lipids. The HindIII, Ser447X, and PvuII gene ploymorphisms have been shown in recent research to reduce plasma LPL activity. Moreover, reduced HDL-C and increased TG levels in patient samples were linked to lower plasma LPL activity, which may increase the risk of CAD [48]. The HindIII polymorphism can impact RNA splicing[49] and is situated in intron 8, 495 bp from the splice-donor location. The HindIII polymorphism's H-allele may result in improved lipid binding[50] or increased enzyme activity.

The Ser447X polymorphism is found at position 1959 in intron 9, where guanine (G) takes the place of cytosine (C). The last two amino acids, serine and glycine, at position 447 of protein [51], are suppressed as a result of this polymorphism. Intron 6 has the PvuII polymorphism, which is 1.57 kb away from the SA site. The C497-T mutation may obstruct

proper messenger RNA[52] splicing, since the area containing the PvuII site is similar to the splicing site in its similarity to the consensus sequence needed for 39-splicing and the development of the lariat structure.The relationship between the LPL polymorphism and CAD has been explored for thirty years. However, the findings to yet have been uneven. Large-scale case control studies examining the relationship between LPL polymorphism and CAD risk do not yet exist. In order to investigate the relationship between LPL polymorphism and CAD risk, we conducted a meta-analysis. Between 2000 and 2015, we examined seven studies, comprising 1853 cases and 1171 controls, to examine the relationship between the HindIII polymorphism and the risk of CAD. The results of the investigation showed a substantial correlation between the risk of CAD and the HindIII H+H+ genotype and the H+ allele genotype[53].

For thirty years, researchers have studied the connection between CAD and the LPL polymorphism. Still, the results have been inconsistent. There are currently no extensive case control studies investigating the connection between LPL polymorphism and CAD risk. We performed a meta-analysis to look into the connection between LPL polymorphism and CAD risk. In order to investigate the connection between the HindIII polymorphism and the risk of CAD, we looked at seven studies from 2000 to 2015, which included 1853 cases and 1171 controls. The study's findings demonstrated a strong association between the HindIII H+H+ genotype and the H+ allele genotype with the risk of CAD.

Conclusion

In summary, we discovered a substantial correlation between the incidence of CAD and the LPL polymorphisms HindIII H+H+ genotype and H+ allele genotype. Additionally, there was a strong correlation between the Ser447X XX genotype and the risk of CAD. However, more studies are needed to confirm these findings. In contrast, the PvuII polymorphism had no association with the risk of CAD. We have concluded that LPL HindIII polymorphism might serve as a potential biomarker" for CAD risk.

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