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Association of Mutations and Polymorphisms in the Lipoprotein Lipase Gene with Coronary Heart Disease in Iraqi Patients at Tikrit Hospital, 2024

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ABSTRACT. Background: Diabetes mellitus (DM) is a multifactorial metabolic disorder characterized by chronic hyperglycemia and disturbances in carbohydrate, fat, and protein metabolism due to defects in insulin secretion, action, or both. Previous investigations have explored the relationship between lipase gene polymorphisms, particularly those affecting cholesteryl ester transfer, and DM risk, though results remain controversial. This study aimed to evaluate whether specific lipase gene variants are associated with lipid profile abnormalities in Iraqi diabetic patients and to examine potential links with coronary artery disease (CAD). **Methods:** A meta-analysis of existing studies clarified the association between the lipase gene TaqIB polymorphism and high-density lipoprotein

cholesterol (HDL-C) levels in DM patients. A cross-sectional study was conducted with 160 Iraqi participants (90 DM patients and 70 controls). Serum lipids, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and very-low-density lipoprotein cholesterol (VLDL-C), were measured and compared between groups.
Results: DM patients exhibited significantly higher TC, TG, LDL-C, and VLDL-C levels ($P<0.0001$) and markedly lower HDL-C ($P<0.0001$) than controls. The study group was predominantly male (75.55%), possibly reflecting healthcare-seeking trends. Among examined single nucleotide polymorphisms, the rs708272 (g.5454G>A) variant influenced HDL-C levels. Moreover, the LPL HindIII H+H+ genotype and H+ allele, along with the Ser447X XX genotype, were significantly linked to CAD risk, whereas the PvuII polymorphism showed no association.
Conclusions: Specific lipase gene polymorphisms may contribute to dyslipidemia in DM and serve as potential biomarkers for CAD risk in the Iraqi population. Further research is needed to confirm these findings in this cohort.

Key words: Lipase polymorphism; Coronary heart disease; Cholesterol; Triglyceride; RFLP.

INTRODUCTION

Lipoprotein lipase is a key enzyme in the regulation of lipid fuel disposal (Goldberg IJ, 2019) and it provides fatty acids for tissue utilization by catalyzing the hydrolysis of triacylglycerol circulating in triglyceride-rich lipoproteins (Auer RC, 2016). Anchored to the surface of the capillary endothelium by glycosaminoglycan, lipoprotein lipase hydrolyzes plasma chylomicrons and VLDL to remnant particles (Toth PP, 2016). As such, lipoprotein lipase is the rate-limiting enzyme responsible for the removal of plasma triglyceride-rich lipoproteins from the circulation (Murthy VJP, 1996). Although expressed in most tissues of the body, in particular, skeletal and heart muscle and adipose tissue, lipoprotein lipase is also expressed and secreted by macrophages (Kim MS, 2012). Lipoprotein lipase is important for the transfer of phospholipids and Apo lipoproteins to HDL and, thus, is critical for the formation of this particle (Blanchette-Mackie EJ, 1989). Apo lipoprotein C-II is an essential cofactor for the activation of lipoprotein lipase activity, whereas Apo lipoprotein C-III inhibits activity (Beigneux AP, 2019).

A number of polymorphisms in the lipoprotein lipase gene have been associated with varying degrees of plasma lipoprotein levels and the severity of coronary artery disease (Auwerx J, 1992). Low levels of lipoprotein lipase activity, as seen with a partial deficiency of lipoprotein lipase, have been associated with the progression of coronary atherosclerosis (Kumari A, 2021). Decreased lipoprotein lipase activity and the resultant elevated triglyceride levels and reduced HDL cholesterol levels increase the risk of ischemic heart disease (Gunn KH, 2020). Low HDL cholesterol levels reduce reverse cholesterol transport. Elevated triglyceride levels indicate that lipoprotein remnants and partially delipidized lipoproteins of differing size and composition, such as VLDL, IDL, chylomicron remnants, and lipoprotein B-containing particles (LP-B:C, LP-B:C:E, and LP-A-II:B:C:D:E), are present in the plasma (Rodrigues B, 1997).

Consistent with these findings are data from 2 large serial coronary angiographic clinical trials indicating that Apo lipoprotein C-III, a marker of triglyceride-rich lipoprotein metabolism and the clearance of chylomicron and VLDL particles (allan CM, 2017) is an independently significant predictor of the progression of coronary atherosclerosis (amps L, 1990) . The abnormal expression of LPL is part of some pathophysiological processes, such as diabetes, chylomicronemia, obesity, and atherosclerosis (Voss CV, 2011). The LPL gene is located on chromosome 8p22. Over 100 mutations have been found in this gene (Jensen MK, 2009). A few studies have reported that the polymorphisms of HindIII, Ser447X and PvuII were associated with the risk of CAD (Jensen MK, 2009; Wion KL, 1987; Sayad A, 2012). However, these results were also controversial (Tanguturi PR, 2013; Abu-Amero KK, 2003). Some studies found no association between these gene variants of LPL and the risk of CAD (Al-Jafari AA, 2012). These data implicate the inefficient removal of triglyceride-rich lipoproteins by lipoprotein lipase in the progression of atherosclerosis (Izar MC, 2009). Decreased removal of chylomicrons and VLDL particles prolongs circulatory residence time and, therefore, increases the exposure of the arterial wall to these thermogenic particles (Van Bockxmeer FM, 2001). Low lipoprotein lipase activity may also contribute to atherosclerosis by promoting postprandial lipemia (Abdel Hamid MM, 2015; Bahrami M, 2015). LPL gene, Asp9Asn, Asn291Ser, and S447X are the most important mutations described because of their greater frequency and influence on susceptibility to atherosclerosis (Corella D, 2002). The LPL D9N and LPL N291S variants have been associated with an adverse lipid profile, but the association with cardiovascular disease has been less consistent (Socquard E, 2006) D9N and N291S have been associated in a meta-analysis with an increase in triglycerides of 20% and 31%, respectively (Nicklas BJ, 2000), and S447X was associated with reduced plasma triglyceride and increasing HDL-C (Chen Q, 2008). The study aimed to determine risk factors and the association of lipid profiles with LPL gene in patients with coronary artery disease and healthy Sudanese population.

MATERIAL AND METHODS

Study population

The study included a total of 180 participants, comprising 100 individuals diagnosed with coronary disease and 80 healthy individuals selected as controls. The age range of the participants was between 17 and 55 years, and both groups were matched in terms of gender. Volunteers were recruited from the Iraqi population through a private clinic.

Sample collection

At 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 has been collected in EDTA tubes for DNA extraction, while in the second part 4 ml was taken in a normal test for separation of the serum.

Laboratory measurements

Serum lapse activity was measured by enzymatic colorimetric methods (Bankaitis VA, 2020). Lipid profile TC, HDL-C and TG levels were measured by enzymatic colorimetric methods (Handley SA, 2024), and the LDL and VLDL was estimated by Fried Ewald formula (Khongwichit S, 2023).

Determination of lipase gene polymorphism

This case control study was designed to study risk factors, lipid profile in CHD patients and their association with lipoprotein lipase gene in Sudan. Informed consent was obtained from all participants. Detailed demographic and risk factors for CVD were collected using a structured questionnaire. Lipids were analyzed by MINDRAY BS-200 analyzer (MINDRAY, Shenzhen, China). Genomic DNA was extracted from blood by kits and PCR-RFLP was applied to detect D9N, N291 and S447X lipoprotein lipase genotype, using TaqI, RsaI and Mnl1 restriction enzyme, respectively. Statistical analyses were performed using SPSS v.26.

RESULT AND DISCUSSION

Serum lipid results of the population study

In this study, 180 Iraqi participants were recruited, 100 patients with CHD and 80 as a control. Table 1 shows serum lipase results of the population study and lipid profile, (TC, TG, LDL-C, and VLDL-C) were significantly higher (P<0.0001) except HDL-C was lower in the patient group compared to the control group (P<0.0001). The resulted shown abnormalities of lipoprotein metabolism are the one of factors contributing to dyslipidemia risk in patients with CHD disease, and diabetic dyslipidemia includes not only quantitative but also qualitative and kinetic lipoprotein abnormalities that are inherently thermogenic (Ukkola O, 2021). The primary (characteristic) quantitative abnormalities are hypertriglyceridemia, accompanied by prolonged postprandial hyperlipidemia and increased levels of remnant particles (related to the increased production of triacylglycerol-rich lipoproteins and a reduction in the rate of catabolism of triacylglycerol-rich lipoproteins), and decreased HDL-cholesterol levels secondary to an increased rate of HDL catabolism (AshokKumar M, 2010). The most frequent qualitative abnormalities, which are potentially thermogenic, include an increase in large VLDL particle size (VLDL1); a greater proportion of small, dense LDL particles; an augmented susceptibility of LDLs to oxidation; an increase in triacylglycerol content of both LDL and HDL; and glycation of Apo lipoproteins (Abd El-Aziz TA, 2011). Although levels of LDL may be normal in patients with CHD disease, LDL plasma residence time is increased due to a slower turnover rate, and this may infer the promotion of lipid deposition within artery walls. Some factors, such as insulin resistance and possibly some adipokines (e.g. adiponectin) and hyperglycemia are involved in the pathophysiology of diabetic dyslipidemia (Tripathi R, 2011).

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

Parameter	Patients (No. 90) Mean ± SD	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

PCR-RFLP analysis of the lipase gene polymorphism identified three genotypic variants: B1B1, B1B2, and B2B2, the PCR-RFLP products illustrate the polymorphism of the lipase gene. Lane (M) contains a 100 bp DNA ladder, lanes (3 & 4) correspond to the B1B1 homozygote (361 & 174 bp bands), lanes (1 & 6) represent the B1B2 heterozygote (535, 361 & 174 bp bands), and lanes (2 & 5) show the B2B2 homozygote (535 bp band) (Figure 1).

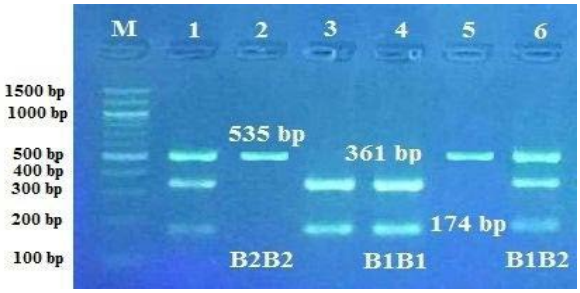

Figure 1. The LIPASE GENE gene polymorphism of PCR-RFLP products.

By PCR-RFLP analysis of the lipase polymorphism, three types of genotypes (B1B1, B1B2, B2B2) have been obtained. Where 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).

Among the population 53.1% were male, 22% had family history of CHD, 42.6% hypertension, 41.6% diabetes, 18.2% smoking and 5.3% alcohol. The low smoking and alcohol consumption may be due to cultural denial of smoking and alcohol in our community especially among females (AbdEl-Aziz TA, 2023). Patients show lower TC and LDL-C levels compared to controls. African ancestry was significantly associated with decreased TC, LDL and triglycerides (Daoud MS, 2013). Allele frequency of LPL D9N, N291S and S447X carrier was 4.2%, 30.7% and 7.1%, respectively (Table 1). The carrier of frequency of N291S was ranging from 2% to 5% in different populations (Tanguturi PR, 2013). While for S447X was 18% in patients with CAD and 23% in the control (Ferencak G, 2003). In Tunisian population the frequency of p.Asp9Asn variation was 10.37% in CAD patients versus 3.66% in controls, and for p.Ser447X was 8.8% in CAD patients versus 13.7% in controls (Li Y, 2014). No significant ($P < 0.05$) association in lipid profiles was found between carriers (patient) and non-carriers (control) of D9N, N291S (Table 2).

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

Parameter	Male (No. 77) Mean ± SD	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 result of this study showed significant increase in the levels of total cholesterol (p=0.888) in diabetic patients compared to non-diabetic subjects, this increase it may be due to an increase in the plasma concentration of VLDL and LDL, which may be due to increase hepatic production of VLDL or decreased removal of VLDL and LDL from the circulation (Clee SM, 2000). The study suggest significant increased level of LDL (p=0775) in diabetic patients and higher level of triglycerides (p=0 .327) in diabetic patients may due to overproduction of VLDL lead to increased plasma levels of triglyceride which, via an exchange process mediated by cholesterol ester transfer protein, result in lower levels of high density lipoprotein HDL-cholesterol, also may be due to insulin deficiency which results faulty glucose utilization causes hyperglycemia and mobilization of fatty acids from adipose tissue. The fatty acids from adipose tissue are mobilized for energy purpose and excess fatty acid is accumulated in the liver, which are converted to triglyceride (Preiss-Landl K, 2002). The most frequent alterations of lipid profile were combination of elevated TGs (VLDL-TG), decreased clearance of TG-rich lipoproteins and decreased high-density lipoproteins HDL (Zhang Y, 2016) (Table 3).

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 conducted in the Hardy-Weinberg equilibrium. The results show that there is a significant difference (p value 0.001) between frequency of genotypes and alleles of LIPASE GENE polymorphism in the patient and control groups. Patients with B2B2 genotype (22.86%) were significantly lower while both the B1B1 (8.57%) and B1B2 (68.57%) genotypes were higher compared with the control. Also we observed that there is an increasing in the B1 allele frequency on the contrary B2 allele in the patient compared to the control group (P <0.05).

Table 3. Serum lipid levels in 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. Genotype and allele frequency distribution in patients and controls group.

Genotypes	Patients No. (100)		Control No. (80)		*P* value	OR	(95% CI)
	No.	%	No.	%			
B1B1	49	49	13	9.57		7.27	2.48-21.92
B1B2	25	25	49	68.67	**0.001****	0.51	0.23-1.16
B2B2	24	24	18	33.86		1 Ref.	-
Alleles	**No.**	**%**	**No.**	**%**	***P* value**	**OR**	**(95% CI)**
B1	125	66.63	60	43.85	**0.002****	2.665	1.679 to 4.216
B2	65	33.37	80	56.15		1 Ref.	-

The S447X genotype is shown in Table 1. The D9N and N291S variants have been linked to elevated plasma triglyceride (TG) levels (Ani A, 2010). In contrast, the S447X variant is associated with lower TG levels, higher HDL levels, and a reduced risk of coronary heart disease (CHD) (Ehrhardt N, 2014). Among a healthy Tunisian population, individuals carrying the p.Asp9Asn substitution in a heterozygous state exhibited a significant increase in total cholesterol and a decrease in HDL (Péterfy M, 2012). This suggests that heart diseases are common in Iraq and share similar risk factors with other regions. However, lipoprotein lipase polymorphism was not found to be associated with CHD incidence. In this study, we first performed a meta-analysis for 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 had no association with CAD risk. Further research on the association between LPL Ser447X polymorphism and CAD risk is still needed.

The LPL gene spans over 30 kb, comprising 10 exons and nine introns on chromosome 8p22. Its cDNA is translated to a 475 amino acid proteins, including a 27 amino acid signal peptide. Several sequence variations, including BamHI, PvuII, HindIII, BstNI and Ser447X sites, have been identified by restriction fragment length polymorphisms (RFLPs) in the LPL gene (Roberts BS, 2018). Among these variations, the HindIII, Ser447X and PvuII polymorphisms were the most common and may be associated with profound alterations in plasma lipids. Recently, some studies have reported that the HindIII, Ser447X and PvuII gene plolymorphisms decreased plasma LPL activity. Furthermore, decreased plasma LPL activity was associated with elevated TG and low HDL-C levels in patient samples, which can contribute to CAD risk (Qi L, 2017). The HindIII polymorphism is located in intron 8, 495 bp from the splice-donor site, and it can affect RNA splicing (Hwang J, 2018). The H-allele of the HindIII polymorphism could cause either enhanced enzyme activity or more efficient lipid binding (Gunn KH, 2020). The Ser447X polymorphism is located in intron 9, where cytosine (C) is replaced by guanine (G), at position 1959. This polymorphism leads to the suppression of the final two amino acids, serine and glycine at position 447 of protein (Shi G, 2017). The PvuII polymorphism is located on intron 6, 1.57 kb from the SA site. The region containing the PvuII site resembles the splicing site in its homology to the consensus sequence required for 39-splicing and the formation of the lariat structure, suggesting that C497-T change may interfere with the correct splicing of messenger RNA (Kim GH, 2018).

The association between the LPL polymorphism and CAD has been researched for thirty years. However, the results to date have been inconsistent. Currently, there are no large scale case control studies for LPL polymorphism and CAD risk. Thus, we performed a meta-analysis to study the association between LPL polymorphism and CAD risk. To analyze the association between the HindIII polymorphism and CAD risk, we reviewed seven studies including 1853 cases and 1171 controls that were conducted from 2000 to 2015. The analysis revealed that the HindIII H^+H^+ genotype and the H^+ allele genotype were significantly associated with the risk of CAD. These results were consistent with previous reports that HindIII is the most common polymorphism of LPL associated with CAD risk. However, for the Ser447X polymorphism, the association with CAD was only found in the XX genotype; the other genotype had no significant association. The difference in the XX genotype may have been caused by publication bias because two studies reported no events in the XX genotype (Bhattacharya A, 2018).

However, this study has some limitations. First, the included studies were moderate due to our inclusion and exclusion criteria, potentially introducing random error. Second, results relied on unadjusted effect estimates, while a more precise analysis would account for factors like age, sex,

drinking, and smoking. Third, the absence of individual-level data limited further analysis of genetic variations and metabolic traits (Ghafer A, 2023; Hamad ST, 2023).

CONCLUSIONS

Our findings indicate that the LPL polymorphisms HindIII H+H+ genotype and H+ allele genotype are significantly linked to an increased risk of CAD. Additionally, the Ser447X XX genotype showed a significant association with CAD risk. However, further research is necessary to validate these results. Conversely, no correlation was observed between the PvuII polymorphism and CAD risk. Based on our analysis, the LPL HindIII polymorphism may serve as a potential biomarker for assessing CAD risk.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FINANCIAL DISCLOSURE

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