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Association of LDL Receptor Polymorphisms with Dyslipidemia in Type 2 Diabetes Mellitus: Insights from the Iraqi Population

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Abstract: **Background: Type 2 diabetes mellitus (T2DM) is a multifactorial disease often accompanied by dyslipidemia, a major cardiovascular risk factor. Genetic variations in the LDL receptor (LDLR) gene have been implicated in lipid metabolism abnormalities. This study investigates the association of LDLR polymorphisms with dyslipidemia in Iraqi T2DM patients.**

Methods: A case-control study was conducted with 420 type 2 diabetics: 210 patients with dyslipidemia (Cases) and 210 without served as a control group. Serum lipid levels were measured, and LDLR rs688 and rs2228671 SNPs were genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis.

Results: The variant genotype of the rs688 SNP was significantly associated with dyslipidemia in T2DM patients under the codominant (OR= 1.96, P= 0.018), dominant (OR= 1.62, P= 0.011) and recessive (OR= 1.96, P= 0.018) models. Also, the variant genotype of the rs2228671 SNP was significantly associated with dyslipidemia under the codominant (OR= 1.49, P= 0.043), dominant (OR= 1.62, P= 0.011) and recessive (OR=1.96, P=0.018) models. Carriers of the TT genotypes of the two SNPs exhibited lower HDL-c levels than those of the reference genotypes.

Conclusion: Carriers of the variant genotypes of the rs688 and rs2228671 SNPs have a 1.5-to 2-fold risk of dyslipidemia development relative to those with wild genotypes. The TT genotype is implicated in lowering high-density lipoprotein-cholesterol (HDL-c). The study explores the importance of identifying at-risk individuals and guiding personalized lipid-lowering interventions to reduce cardiovascular complications in T2DM.

Keywords: **LDL receptor, T2DM, Dyslipidemia, rs688, rs2228671.**

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a multifaceted disease, it represents a major global health challenge via increased mortality and morbidity and by placing significant economic pressure on healthcare systems [1]. The development of T2DM arises from both genetic factors and environmental exposures. It has been demonstrated that genetic factors contribute between 20% and 50% to the risk of developing T2DM which varies with environmental influences, highlighting the significant impact of genetic variations in this disease [2].

Patients with Diabetes Mellitus have abnormal lipid profiles. These can be characterized as increased levels of Triglycerides (TG); decreased levels of High Density Lipoproteins Cholesterol (HDL-C); and excessive numbers of Small Dense Low-Density Lipoproteins (LDL). Ischemic Heart Disease (IHD) is accelerated in patients who suffer from these abnormalities as demonstrated through numerous studies [3,4]. Lipoproteins have crucial functions in lipid metabolism through their transport of both cholesterol and TG [5]. Blood lipid level maintenance depends on the interaction between lipoproteins and

their receptors including the LDL receptor (LDLR) [6,7]. Dysfunctional LDLR-mediated lipid clearance due to genetic or functional defects causes dyslipidemia which then raises the risk of cardiovascular diseases (CVD) [8].

The gene responsible for encoding LDL receptors that enable LDL particle internalization by cells via endocytosis resides at 19p13.2 on chromosome 19 [9]. Lipid metabolism is affected by SNPs at positions rs688 and rs2228671 in the LDLR gene [10]. The rs688 SNP changes the splicing of exon 12 mRNA which may cause LDL receptors to become dysfunctional [11]. A study shows that the rs2228671 influences LDL-C concentration and cardiovascular disease (CVD) risk [12]. The researchers explore the mechanisms by which genetic variation contributes to develop dyslipidemia across multiple disorders [13]. There is evidence that genetic variation impacts lipid profiles and the risk for metabolic diseases [14]. There is only limited research on how LDLR polymorphisms affect dyslipidemia in Iraqi patients who have T2DM [15].

The current study examines the relationship of two LDLR gene polymorphisms (rs688 & rs2228671) to dyslipidemia in an Iraqi population that have been diagnosed as having Type 2 diabetes mellitus (T2DM). It will also look at how LDLR gene variations may influence the development of dyslipidemia in T2DM patients.

2. MATERIALS AND METHODS

2.1 Study Design

A case-control study was conducted to assess the relationship between polymorphisms in the LDLR gene (rs688 and rs2228671), with dyslipidemia among T2DM patients in Iraq. The study included 210 Iraqi patients with T2DM and dyslipidemia, and a comparison group of 210 Iraqi T2DM patients without dyslipidemia. The study was conducted in the Biochemistry Department, Faculty of Medicine, University of Kufa from Dec. 2023 to Jul. 2024. The Department of Biochemistry's Scientific Committee at the Faculty of Medicine approved the study protocol.

2.2 Study Population

The patient group included 210 T2DM with dyslipidemia; their ages were from 30 to 73, with a mean of 51.5 ± 11.5 years. Patients with other diseases were excluded. The control group contained 210 T2DM patients with normal serum lipid concentrations (without dyslipidemia), free from diseases other than T2DM. Their ages were from 31 to 70, with a mean age of 50.8 ± 10.7 years. Each participant was given a written informed consent before inclusion in the study.

2.3 Sample Collection

Blood samples of approximately 5 ml venous blood were obtained from all participants. two ml of this sample was placed in a EDTA tube for DNA extraction. The other 3ml was then placed in plain tubes. These plain tube samples were allowed to clot at 37^{o}C. After clotting had occurred the samples were centrifuged at 2000 x g for ten minutes. The serum portion was then divided into three equal portions and frozen at -20^{o}C for subsequent lipid profile analysis.

2.4 Serum Lipid Analysis

The level of TC, TG, and HDL-c concentrations was measured using standard enzymatic methods. LDL-c and VLDL-c concentrations were counted indirectly using the Friedewald formula [16].

2.5 Genotyping of LDLR Polymorphisms

Genomic DNA was isolated from EDTA-treated blood samples using a commercial kit called ReliaPrep™ Blood gDNA (Promega). The two polymorphisms in the LDLR gene; rs688 and rs2228671 were analyzed for genotype by PCR with restriction endonuclease digestion to analyze the PCR products (polymerase chain reaction-restriction fragment length polymorphism or PCR-RFLP) . For the rs688 polymorphism PCR primers were used as follows:

- Forward: 5’-CTCACATGTGGTTGGAGCTG-3’
- Reverse: 5’-CGTTCATTGGCTTGAGTG-3’

The resulting 200 bp amplicons were digested using the HincII restriction enzyme and analyzed on 1.5% agarose gels stained with diamond dye. Genotypes were classified as follows: CC (200 bp), TT (185 bp and 15 bp), and CT (200 bp, 185 bp, and 15 bp).

For the rs2228671 polymorphism, the primers used for PCR amplification were:

- Forward: 5'-CTCTCAGTGGGCGACAGACG-3'
- Reverse: 5'-CAACATGGCGAGACCCTGTC-3'

The 194 bp amplicons were digested with the BstUI restriction enzyme and analyzed on 1.5% agarose gels. Genotypes were determined as CC (194 bp), TT (174 bp and 20 bp), and CT (194 bp, 174 bp, and 20 bp).

2.6 Statistical Analysis

The chi-square test (χ^2) was used to compare genotype and allele frequencies between the patients and control groups. Odds ratios (ORs) with 95% confidence intervals (CIs) were counted to evaluate the relative risk that associated with each genotype and allele. One-way analysis of variance (ANOVA) has also been used to evaluate the mean difference among genotypes regarding lipid levels. A P-value ≤ 0.05 denoted statistical significance. The tests were run using SPSS software version 25.0 (SPSS Inc., Chicago, IL).

3. RESULTS

The current research assessed anthropometric parameters, serum lipid profiles, LDLR gene polymorphisms (rs688 and rs2228671), and their association with serum lipid concentrations. These results reveal significant insights into the interplay between genetic and metabolic factors in T2DM.

3.1 Anthropometric Parameters and Serum Lipid Profile

Type 2 diabetic patients with dyslipidemia had a mean age of (51.5 ± 11.5 years) and BMI of (29.3 ± 3.4 kg/m²) similar to the control group (50.8 ± 10.7 years, BMI of (28.5 ± 4.1 kg/m²), with no statistically significant differences. Serum lipid profiles showed significant elevations of TG, TC, LDL-c, and VLDL-c levels in type 2 diabetics with dyslipidemia, alongside reduced HDL-c levels, compared to those without dyslipidemia ($P < 0.05$ for all).

3.2 Genotyping Results

The analysis of LDLR gene polymorphisms revealed that the TT genotype of the rs688 SNP was more prevalent in the dyslipidemic diabetic group (17.1%) compared to controls (9.5%) with a significant association under the recessive model (OR= 1.96, 95% CI: 1.15–3.34, P = 0.018). Additionally, the dominant model (CT+TT) showed increased frequency in the dyslipidemic diabetic group (64.3% vs 52.9%, OR= 1.62, 95% CI: 1.13–2.31, P= 0.011). The minor allele frequency (MAF) of rs688 SNP was also higher in the patients group (34.3%) than in controls (30.5%, P = 0.017). For rs2228671 SNP, the TT genotype was significantly associated with dyslipidemia (27.1% vs 20.0%, OR= 1.49, 95% CI: 1.00–2.27, P= 0.043). The combined GT+TT genotypes were more frequent in the dyslipidemic diabetic group (72.4% vs 61.4%, OR = 1.62, P = 0.011), and MAF was higher in these patients (34.3% vs 30.5%, P = 0.017).

Table 1: Anthropometric and biochemical features of patient and control individuals

	Cases	Control	P value
	Mean ± SD		
Number	210 (140 M/70 F)	210 (137 M/73 F)	
Age (y)	51.5 ± 11.5	50.8 ± 10.7	0.52
BMI (kg/m^2)	29.3± 3.4	28.5± 4.1	0.11
Triglycerides (mg/dL)	157.5± 30.7	130.3± 28.4	0.001
Cholesterol (mg/dL)	198.6± 27.4	162± 28.8	0.001
HDL-c (mg/dL)	44.5± 7.5	49.7± 6.4	0.031
LDL-c (mg/dL)	112.8± 23.9	96.4± 20.6	0.025
VLDL-c (mg/dL)	30.4± 5.4	28.6± 5.3	0.035

Table 2: Adjusted genotype and allele frequencies of LDLR gene polymorphism in CAD patient and control groups

	Cases (n=210)	Control (n=210)	OR (95%CI)	P value
rs688				
Codominant				
CC	75 (35.7%)	99 (47.1%)		
CT	99 (47.1%)	91 (43.3%)	1.18 (0.83–1.67)	0.418
TT	36 (17.1%)	20 (9.5%)	1.96 (1.15–3.34)	0.018
Dominant				
CC	75 (35.7%)	99 (47.1%)		
CT+TT	135 (64.3%)	111 (52.9%)	1.62 (1.13–2.31)	0.011
Recessive				
CC+CT	174 (82.9%)	190 (90.5%)		
TT	36 (17.1%)	20 (9.5%)	1.96 (1.15–3.34)	0.018
MAF	72 (34.3%)	64 (30.5%)	1.34 (0.91–1.97)	0.017
rs2228671				
Codominant				
GG	58 (27.6%)	81 (38.6%)		
GT	94 (44.8%)	86 (41.0%)	1.18 (0.83–1.68)	0.416
TT	57 (27.1%)	42 (20.0%)	1.49 (1.00–2.27)	0.043
Dominant				
GG	58 (27.6%)	81 (38.6%)		
GT+TT	152 (72.4%)	129 (61.4%)	1.62 (1.13–2.31)	0.011
Recessive				
GG+GT	152 (72.4%)	129 (61.4%)		
TT	57 (27.1%)	42 (20.0%)	1.96 (1.15–3.34)	0.018
MAF	72 (34.3%)	64 (30.5%)	1.34 (0.91–1.97)	0.017

3.3 Phenotype Analysis

Serum lipid levels were analyzed concerning rs688 and rs2228671 SNP genotypes under the codominant model. For rs688 SNP, HDL-c levels were significantly lower in carriers of the CT (44.74 ± 8.65 mg/dL) and TT (45.70 ± 8.52 mg/dL) genotypes compared to those of the CC (47.69 ± 8.22 mg/dL, P = 0.033) genotype. For rs2228671 SNP, carriers of the TT genotype showed significantly reduced HDL cholesterol levels (44.18±8.23 mg/dL) compared to those of the CT (45.79 ± 8.43 mg/dL) and CC (48.07 ± 7.83 mg/dL, P = 0.021) genotypes. Other parameters did not explore significant relevant variations to the two analyzed SNPs.

4. DISCUSSION

The current findings highlight the association between LDLR polymorphisms (rs688 and rs2228671) and dyslipidemia in T2DM. Dyslipidemia is marked by elevated TG, TC, LDL-c, and VLDL-c levels with reduced HDL-c levels. It is a major cardiovascular risk factor influenced by insulin resistance, chronic inflammation, and genetic predispositions. The analysis of LDLR gene polymorphisms provides novel insights into their role in impaired lipid metabolism and increased susceptibility to dyslipidemia in T2DM.

Table 3: Serum Lipid Concentrations in Carriers of Different Genotypes of LDLR Gene Polymorphism Analysed Under Codominant Model

	(Mean ± SD)			P value
rs688				
	CC (n=75)	**CT (n=99)**	**TT (n=36)**	
Cholesterol	183.16 ± 21.71	185.54 ± 22.31	184.58 ± 21.42	0.725
Triglycerides	147.17 ± 19.12	153.42 ± 20.25	154.09 ± 19.53	0.156
HDL-c	47.69 ± 8.22	44.74 ± 8.65	45.70 ± 8.52	0.033*

VLDL-c	29.45 ± 6.23	30.59 ± 6.34	30.59 ± 6.41	0.182
LDL-c	106.02 ± 23.33	110.10 ± 24.51	108.30 ± 24.24	0.513
rs2228671				
	CC (n= 75)	**CT (n= 94)**	**TT (n= 31)**	
Cholesterol	182.02 ± 20.31	185.34 ± 20.50	185.63 ± 21.11	0.413
Triglycerides	148.77 ± 19.42	150.00 ± 18.70	155.89 ± 19.24	0.321
HDL-c	48.07 ± 7.831	45.79 ± 8.43	44.18 ± 8.23	0.021*
VLDL-c	29.74 ± 6.74	29.92 ± 6.32	31.06 ± 5.92	0.283
LDL-c	104.12 ± 22.23	109.63 ± 22.53	110.48 ± 24.62	0.182

4.1 Anthropometric Parameters and Serum Lipid Profile

The elevated concentrations of TG, TC, LDL-c, and VLDL-c, along with reduced HDL-c levels in type 2 diabetic patients with dyslipidemia, can be attributed to several factors: insulin resistance is a hallmark of T2DM, it disrupts lipid metabolism that leads to increased hepatic lipogenesis, decreased clearance of circulating TG-rich lipoproteins, and elevated production of VLDL particles. T2DM is considered a chronic low-grade inflammation, which promotes lipoprotein remodelling and degradation of HDL-c particles, further reducing their levels [17]. LDLR polymorphisms could directly influence lipid profiles by impairing LDL clearance from circulation. This may partly explain the elevated LDL-c levels in dyslipidemic diabetics [18]. While anthropometric parameters such as BMI were comparable, dietary patterns, physical activity, and other environmental factors could exacerbate dyslipidemia in susceptible individuals [19].

Numerous significances could be recognized from the current findings. Dyslipidemia in T2DM patients is a significant risk factor for CVD. Elevated LDL-c, TC, and TG levels and low HDL-c contribute to atherogenesis and the progression of atherosclerotic plaques. They are appropriate for early detection and intervention; identifying the dyslipidemic profile in diabetic individuals is crucial for stratifying cardiovascular risk and implementing therapeutic measures, such as lipid-lowering medications or dietary interventions [20]. Persistently elevated LDL-c and VLDL-c levels promote endothelial dysfunction and plaque formation, accelerating the progression of macrovascular complications such as coronary artery disease and stroke in T2DM [7]. Dyslipidemia may also exacerbate microvascular complications, such as diabetic retinopathy and nephropathy, by contributing to oxidative stress and inflammation. Both dyslipidemia and insulin resistance form a vicious cycle where lipid abnormalities further impair glucose metabolism, complicating glycemic control [21].

The current investigation is consistent with previous reports examining serum changes in serum lipid concentrations in T2DM. Hao et al. found that dyslipidemia is more common among individuals with diabetes, especially those aged 55–64; over a four-year follow-up, lipid profiles showed improvement in diabetic and prediabetic patients [22]. Wu et al. demonstrated a positive and non-linear relationship between TG/HDL-c ratio and pre-DM in Chinese non-obese people with a standard range of LDL-c [23].

4.2 Genotyping of LDLR gene for rs688 and rs2228671 SNPs

The TT genotype of rs688 in LDLR was significantly associated with dyslipidemia in type 2 diabetics, with an OR of 1.96 under the codominant model, suggesting a risk factor of 1.96 to develop this metabolic disturbance. However, the TT genotype of the rs2228671 SNP also exhibited a significant association of 1.96 OR with dyslipidemia under the recessive model, indicating a risk factor 1.96 to develop such a condition. These findings suggest that genetic variations in the LDLR gene may play a crucial role in the lipid metabolism of T2DM patients. The rs688 and rs2228671 SNPs resulted in lower function of the LDL receptor which leads to increased concentrations of circulating LDL cholesterol. Individuals who are homozygous for the T allele (TT genotype), as a result appear to be more likely to exhibit dyslipidemia. Further evidence supporting this includes the higher frequency of minor alleles and single nucleotide polymorphisms in individuals suffering from diabetes mellitus-related dyslipidemia [24]. This is enhanced by the argumentation of why individuals having the TT genotype were more dyslipidemic than others [25].

Recognizing the particular LDLR polymorphisms linked to dyslipidemia in T2DM has numerous important practical ramifications. Polymorphisms could be considered genetic markers for detecting dyslipidemia among patients with T2DM. Dysregulation in lipid metabolism may impair insulin sensitivity and glucose homeostasis. Increased circulated atherogenic lipids, such as LDL-c, can further reduce insulin action and worsen T2DM glycemic control [26]. Understanding the genetic basis of lipid metabolism abnormalities will be remarkable for developing the most effective treatment strategies in populations with genetic predisposition, such as the Iraqi population. Thus, individuals carrying the TT genotype of either

rs688 or rs2228671 SNPs may require more intensive lipid-lowering treatments. Also, these individuals need a more comprehensive plan to approach the prevention and treatment of cardiovascular diseases related to T2DM, taking genetic factors into account [27].

To relate the current findings to the previously published data, a comprehensive search for studies investigating the association of polymorphisms of the LDLR gene and dyslipidemia prevalence among T2DM patients has been made. Nevertheless, a few studies have been observed investigating the association of these polymorphisms with serum lipid profiles. Demirci et al. identified no association of LDLR rs688 polymorphism with diabetes [28]. Eroglu et al. identified a possible function of LDLR gene variants in lipid disorders in diabetics [29]. It seems necessary to emphasize the importance of further studies to elucidate dyslipidemia's genetic determinants in T2DM better.

4.3 Phenotype-Genotype relationship

The unique observed phenotype-genotype relationship is reduced HDL-c levels in individuals carrying the CT and TT genotypes of rs688 SNP and the TT genotype of rs2228671 SNP. Reduced levels of HDL-c may be attributed to several factors. rs688 and rs2228671 SNPs can create variants capable of undermining the efficacy of the receptor to enable the uptake and clearance of LDL from the circulatory system, leading to an imbalance in lipid metabolism [30]. Polymorphisms are also involved in lipoprotein remodeling, negatively influencing HDL-c levels [31]. The diminished activity of LDLR can indirectly affect the activity of lipid metabolizing enzymes like lecithin-cholesterol acyltransferase (LCAT) in the critical process of maturation of HDL particles. It might be one of the explanations for lowering HDL-c levels among carriers of the TT genotypes [32].

Reducing HDL-c to the variant allele of the two SNPs studied can have several implications. It is a risk factor for increased cardiovascular disease, which is the key determinant of morbidity and mortality in T2DM patients. The reduced levels of HDL-c can worsen the lipid profile in T2DM patients, resulting in more advanced dyslipidemia and contributing to atherosclerosis development [33]. These findings demonstrate the need for genotype-directed lipid-lowering therapy in patients with specific genotypes to prevent the onset of both dyslipidemia and cardiovascular morbidity.

5. CONCLUSION

Individuals with TT genotypes of rs688 and rs2228671 SNPs are associated with a 1.5-to 2-fold risk of developing dyslipidemia compared to individuals with wild genotypes. The TT genotype directs the lowering of the HDL-c level. The investigation envisages the possibility of genetic screening for vulnerable individuals and the justification for specific lipid-lowering therapy to avoid cardiovascular complications in T2DM.

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