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IMPACT OF GENETIC DIVERSITY OF TLR4 (RS1927911) ON GLYCATED HEMOGLOBIN AND INFLAMMATORY LOAD IN IRAQI TYPE 2 DIABETIC PATIENTS

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ABSTRACT
Diabetes mellitus (DM) is a multifaceted metabolic disorder characterized by hyperglycemia, which has consequences that reduce quality of life and increase mortality rates. Toll-like receptor 4 (TLR4) is a key mediator of innate immune activation and has been implicated in the pathogenesis of type 2 diabetes mellitus (T2DM). Single-nucleotide polymorphisms (SNPs) in the Toll-like receptor 4 (TLR4) gene have been documented in type 2 diabetes mellitus (T2DM).
Aim: This study investigates the association between the rs1927911 SNP in the TLR4 gene and T2DM in the Iraqi population.
Methods: A case-control study recruited 300 type 2 diabetic Iraqi patients; 150 with dyslipidemia and 150 without served as the control group. Numerous metabolic and inflammatory analytes were determined by standard methods. Allele-specific polymerase chain reaction (AS-PCR) was used to genotype TLR4 at rs1927911.
Results: Fasting serum glucose (FSG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and C-reactive protein (CRP) were significantly higher in the patient group than in the control group. In contrast, HDL-C decreased significantly during a comparable assessment. Genotyping analysis revealed an insignificant association with dyslipidemia. However, under the dominant genetic model, individuals carrying the G allele (G/A + G/G) exhibited significantly lower HbA1c levels than those with the A/A genotype ($\beta = -2.15$, 95% CI: −3.51 to −0.80, $P = 0.002$), indicating that the A/A genotype was associated with elevated HbA1c concentration. Other associations with FSG, TG, TC, LDL-C, HDL-C, TNF, and CRP were not significant after adjustment.
Conclusion: The TLR4 rs1927911 polymorphism was not associated with diabetic dyslipidemia or inflammatory markers (TNF and CRP), but was significantly associated with HbA1c, suggesting a role in glycemic regulation rather than inflammation.

KEYWORDS: TLR4, rs1927911, T2DM, HbA1c, glycemic control

1. INTRODUCTION

DM is a term used to describe a variety of metabolic disorders characterised by chronic hyperglycemia. The underlying cause is either poor insulin secretion, various degrees of insulin resistance, or a combination of both (Yameny, 2025). The prevalence of type 2 diabetes mellitus (T2DM) has increased dramatically worldwide in recent years (Al-Barqaawi et al, 2022). According to the International Diabetes Federation, 589 million people were diagnosed with DM in 2024. This number is projected to rise to 853 million by 2050 (Genitsaridi et al., 2026).
Several studies have demonstrated that chronic inflammation is linked with an increased risk of developing complications in patients with T2DM. Oxidative stress resulting from hyperglycemia stimulates the production of pro-inflammatory mediators (Oguntibeju, 2019; Alsayed et al., 2021). Numerous environmental and lifestyle factors have been correlated with the development of T2DM. They include obesity, sedentary lifestyle, high caloric intake, physical inactivity, and ageing. Multiple genetic variants have been associated with T2DM, reflecting their contribution to T2DM susceptibility (DeForest & Majithia, 2022).
Toll-like receptor 4 (TLR4) is an essential component of the innate immune system. It is pivotal in initiating inflammatory responses. Activation of TLR4 signaling induces the synthesis of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α). The latter exacerbates insulin resistance, dyslipidemia, and vascular damage (Nikolaidis et al., 2025). Genetic polymorphisms in the TLR4 gene have been shown to affect receptor expression and signalling efficacy, resulting in changes in individual inflammatory responses (Uvarova et al., 2024).
The TLR4 gene is located on the long arm of chromosome 9 at 9q33.1, spanning base pairs 117704174 to 117723205. It contains regulatory and coding regions that impact receptor expression and signaling efficiency. Genetic polymorphisms within this gene may modify inflammatory responses and predisposition to metabolic disorders (Kumar et al., 2024). The rs1927911 polymorphism has been examined for its potential effects on TLR4 expression and inflammatory signaling. Polymorphisms at this locus may affect individual inflammatory responses in metabolic diseases (Zeng et al., 2023).
Several studies have evaluated TLR4 polymorphisms in relation to diabetes susceptibility and inflammatory disorders. Limited evidence is available regarding the independent association between rs1927911 and long-term glycemic control

in Middle Eastern populations, particularly among Iraqi patients (Fan et al, 2020; Ali & Salloom, 2026; Nikolaidis et al, 2025). Therefore, this study aimed to investigate the relationship of the TLR4 rs1927911 polymorphism with glycemic status and inflammatory load among Iraqi patients with T2DM.

2. METHODS

2.1. Study subjects

A case-control design was used in this investigation, including 300 individuals. The participants were divided into two groups: a control group of 150 T2DM patients without dyslipidaemia and a group of 150 T2DM patients with dyslipidaemia. Patients were selected from the Al-Najaf Center for Diabetes and Endocrinology, which is located in the Al-Najaf Governorate's Al-Sadr Medical City. The study period spanned from September 2025 to April 2026. The study was carried out at the Postgraduate Laboratory Department of Biochemistry, Faculty of Medicine, University of Kufa.
The case group included 150 T2DM patients with dyslipidaemia, with ages ranging from 35 to 65 years old. The diagnosis was made using the American Diabetes Association (ADA) criteria, which include fasting plasma glucose (FPG) ≥ 126 mg/dL and/or HbA1c ≥ 6.5%, along with other clinical signs and symptoms. The control group consisted of 150 T2DM patients without dyslipidemia. They were similar in age to the case group. Participants with renal dysfunction, liver disease, kidney disease, pregnancy, T1DM, smoking, thyroid condition, or autoimmune disease were excluded from this study. Biochemical and genetic tests were conducted in the Postgraduate Laboratory of the Biochemistry Department at the Faculty of Medicine, University of Kufa.

2.2. Sample collection and biochemical analysis

Body mass index (BMI) was calculated by dividing weight (in kilograms) by height squared (in meters). After a 12-hour overnight fast, 5 mL of venous blood was taken via peripheral venipuncture. The first part contained 2 mL of blood, which was placed in an EDTA tube for HbA1c measurement and gene analysis. For phenotypic characterization, 3ml was transferred to plain tubes, incubated at 37°C for 15 minutes for coagulation, centrifuged at 2000 ×g for 10-15 minutes, and stored at -20°C. The levels of FSG, TG, TC, and HDL-C were measured using an automated enzymatic colourimetric method. LDL-C levels were calculated using the Friedewald equation. The serum TNF-α and C-reactive protein concentrations were determined using a sandwich ELISA kit (Sunlong BioTech, China).

2.3. Genotyping analysis

A DNA purification mini kit (Magen kit) was used to extract DNA from blood samples. TLR4 was genotyped at rs1927911 by allele-specific PCR (AS-PCR). The designed primers were:
Reverse primer: GGATACAGAGAAGATGAGCATG,
Allele A: AAGGGTCAATGAGCCAAGA
Allele G: AAGGGTCAATGAGCCAAGG
Amplification was performed in two PCR tubes, yielding a final reaction volume of 20 µl per tube. Two PCR tubes were used in the amplification reaction. Tube one contained 5 µl FIREPOL(R) Master Mix (Solis BioDyne, Tartu, Estonia), 1 µl reverse primer, 1 µl allele A Primer, 8 µl nuclease-free water, and 5 µl genomic DNA solution as the template. The second tube contains the same solutions, but contains 1 µl of the allele G Primer. The PCR program consisted of an initial denaturation at 95 °C for 5 min, followed by 32 cycles of Denaturation at 95 °C for 30 sec, annealing at 57 °C for 30 sec, extension at 72 °C for 1 min, and a final extension at 72 °C for 7 min. The length of the amplicon is 309 bp for both alleles A & G. The PCR products were resolved by electrophoresis through a 1.5% agarose gel for 60 minutes at 75 V. Subsequently, the PCR Products were visualized by Safe Stain under UV light. 2.4. Statistical analysis
Continuous variable data were presented as mean ± standard deviation (SD). The t-test was applied to compare the T2DM patients with dyslipidemia group with the T2DM patients without dyslipidemia group, whilst the ANOVA test was implemented to compare numerical data across multiple groups. Statistical significance was assessed utilizing SPSS version 26.0 software (SPSS Inc., Chicago, IL). The Chi-squared test(x2) was utilized to assess differences in genotyping and allele frequencies between diabetic patients with dyslipidemia (case group) and diabetic patients without dyslipidemia (control group). Age and gender adjustments were performed to calculate odds ratios (ORs), 95% confidence intervals (CIs), and P-values. A significance level of < 0.05 was used to assess statistical significance.

3. RESULTS

3.1. Biochemical and Anthropometric Characteristics

There were significant differences in several biochemical values between the two recruited groups. Dyslipidemic diabetic patients exhibited significantly elevated FBG ($p < 0.001$), TG ($p < 0.001$), TC ($p < 0.001$), and LDL-C ($p < 0.001$) levels compared to the control group. Conversely, HDL-C was significantly lower in patients than in the control group ($p < 0.001$). Glycemic control, measured by HbA1c, TNF, and CRP, did not show significant differences between the two groups assessed.

3.2. Distribution of genotypic and allelic frequencies of TLR4 rs1927911 variant:

TLR4 gene amplification was performed using template DNA, specific primers, and a master mix. The PCR product was electrophoresed on 1.5% agarose (60 min at 75V) and immediately visualised under UV light. The amplification product of the TLR4 gene SNP rs1927911 A/G was found to be 309 bp (Allele A and Allele G), as shown in Figure 1.
The genotype distribution of the TLR4 rs1927911 polymorphism was comparable between diabetic patients with and without dyslipidemia. No statistically significant association was identified under the codominant, dominant, or recessive

genetic models after adjustment for age and sex (all P > 0.05). Likewise, allele frequencies did not differ significantly between the study groups (Table 2).

Table1: Anthropometric and biochemical characteristics of diabetic patients with and without dyslipidemia

	Controls (Mean ± SD)	Patients (Mean ± SD)	p-value	Cohen's d
Age	54.13 ± 9.77	55.07 ± 8.98	0.386	0.10
BMI	30.17 ± 4.73	30.70 ± 4.24	0.304	0.12
FBS	186.74 ± 62.01	230.30 ± 77.26	<0.001	0.62
HbA1c	8.55 ± 2.23	9.24 ± 1.90	0.133	0.17
TG	120.93 ± 17.25	244.09 ± 68.91	<0.001	2.45
TC	181.61 ± 26.48	228.67 ± 40.66	<0.001	1.37
LDL	94.24 ± 23.22	132.28 ± 39.96	<0.001	1.16
HDL	63.11 ± 9.47	48.01 ± 13.27	<0.001	-1.31
TNF	31.63 ± 12.68	32.08 ± 11.12	0.748	0.04
CRP	75.33 ± 31.22	85.70 ± 26.71	0.002	0.36

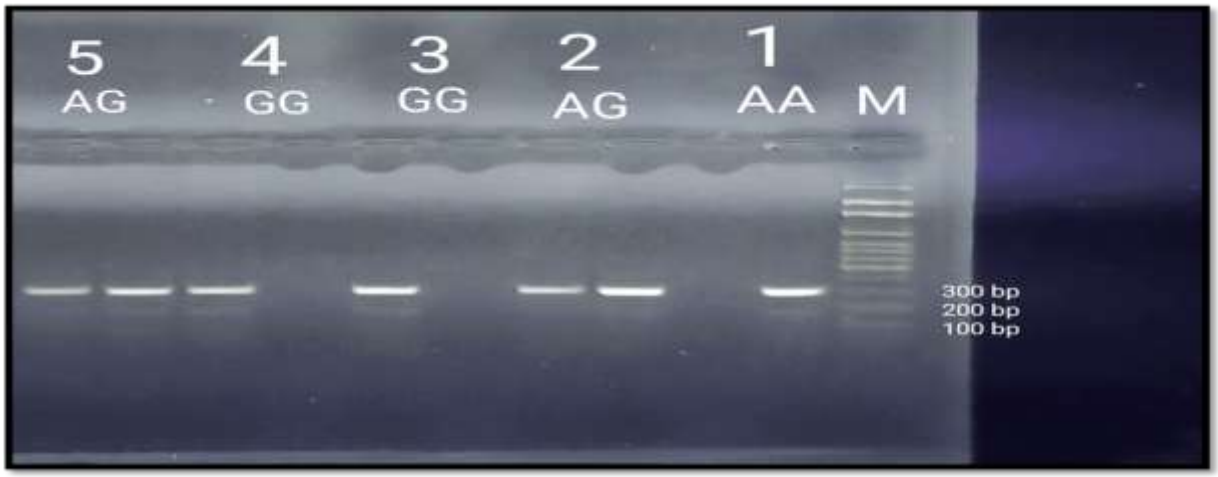

Figure 1: AS-PCR product of TLR4 rs1927911 on a 1.5% agarose gel electrophoresis. M: Ladder. Lane 1 indicates the genotype (AA) at 309 bp. Lanes 2 and 5 indicate the genotype (AG) at 309 bp. Lanes 3 and 4 indicate the genotype (GG) at 309 bp.

Table 2: Association of rs1927911 in the TLR4 gene with type 2 diabetic patients, adjusted for sex and age

	Genotype	Controls	Patients	OR (90% CI)	p-value
Codominant	A/A	19 (12.7%)	17 (11.3%)	1.00 (Ref)	—
	A/G	92 (61.0%)	82 (54.7%)	1.00 (0.54–1.82)	0.992
	G/G	39 (26.0%)	51 (34.0%)	1.46 (0.76–2.80)	0.338
Dominant	A/A	19 (12.7%)	17 (11.3%)	1.00 (Ref)	—
	A/G + G/G	131 (87.3%)	133 (88.7%)	1.13 (0.63–2.04)	0.722
Recessive	A/A + A/G	111 (74.0%)	99 (66.0%)	1.00 (Ref)	—
	G/G	39 (26.0%)	51 (34.0%)	1.47 (0.97–2.23)	0.131

3.3. Multivariable-Adjusted Association of TLR4 Polymorphisms with Metabolic Parameters

Results of multivariable-adjusted associations between rs1927911 and metabolic parameters are shown in Table 3. A significant association was found for the rs1927911 polymorphism with HbA1c levels, indicating lower values in individuals with variant genotypes (G/A + G/G) compared to the reference genotype (A/A) ($\beta = -2.15$, $p = 0.002$). This association remained significant despite the absence of a significant relationship between rs1927911 and diabetic dyslipidemia. No significant associations were observed for FSG, triglycerides, TC, LDL-C, or HDL-C, indicating that the observed effect of rs1927911 was specific to long-term glycemic control rather than lipid metabolism.

Table 3: Multivariable-Adjusted Association of TLR4 Polymorphisms with Metabolic Parameters in Type 2 Diabetic Patients Under a Dominant Genetic Model

rs1927911 (A/A vs G/A + G/G)			
Parameter	β	95% CI	P-value
FBS	-19.64	(-45.44 to 6.16)	0.135
HbA1c	-2.15	(-3.51 to -0.80)	0.002
TG	+10.85	(-16.96 to 38.66)	0.443
TC	+3.75	(-10.84 to 18.34)	0.614
LDL	-2.05	(-15.37 to 11.27)	0.762
HDL	+4.07	(-0.64 to 8.79)	0.090

3.4. Impact of the TLR4 Polymorphisms on the Inflammatory Load

The results of the multivariate-adjusted analysis of the relationship between TLR4 single SNPs and inflammation (TNF and CRP) in dyslipidemia-associated type 2 Diabetic patients are presented in Table 4. Neither TNF nor CRP levels were significantly associated with the rs1927911 variant genotypes (G/A and GG) compared with the reference genotype (AA).

Table 4: Adjusted Association of TLR4 Polymorphisms with Inflammatory Load (TNF and CRP) in Type 2 Diabetic Patients Under a Dominant Genetic Model

	TNF			**CRP**		
	β	95% CI	P-value	β	95% CI	P-value
A/A (Ref)	0.00	—	—	0.00	—	—
G/A + G/G	+2.42	(-0.92 - 5.76)	0.15	+7.48	(-0.76 - 15.72)	0.075

4. DISCUSSION

The principal finding was that carriers of the AG+GG genotypes showed an independent association with HbA1c compared with those with the AA genotype, after adjustment for age and sex. However, rs1927911 was not significantly associated with diabetic dyslipidemia under any genetic model. This observation suggests that rs1927911 may influence long-term glycemic regulation rather than lipid abnormalities in Iraqi patients with T2DM.

Chronic low-grade inflammation is now recognized as one of the fundamental mechanisms underlying the development and progression of T2DM. Persistent hyperglycemia, oxidative stress, and metabolic endotoxemia activate innate immune pathways (Lu et al., 2024). Activation of the TLR4 signalling cascade activates nuclear factor kappa B (NF-κB) and increases the production of pro-inflammatory mediators, resulting in insulin resistance (Makhijani et al, 2023). Consequently, genetic variation within the TLR4 gene may contribute to individual differences in glucose metabolism through modulation of inflammatory signaling rather than direct effects on lipid metabolism (Weinberg Sibony et al., 2024; Zeng et al., 2023).

The significant association of rs1927911 with HbA1c levels is biologically plausible because HbA1c reflects the average blood glucose concentration over the preceding two to three months and therefore represents long-term glycemic exposure. In contrast, fasting blood glucose is influenced by short-term physiological factors, including dietary intake, stress, medication adherence, and daily metabolic fluctuations. Consequently, HbA1c is considered a more stable indicator of detecting subtle genetic influences on glucose homeostasis than a single fasting glucose measurement (Lu et al., 2024).

Although the exact functional consequence of rs1927911 remains incompletely understood, this polymorphism is located within the regulatory region of the TLR4 gene and may influence transcriptional activity or gene expression (Uvarova et al., 2024). Variations affecting TLR4 expression could modify the intensity of inflammatory responses induced by endogenous danger-associated molecular patterns generated during chronic hyperglycemia (Ali & Salloom, 2026). Such alterations may gradually influence insulin sensitivity and glucose regulation, ultimately affecting HbA1c levels without necessarily producing measurable changes in fasting glucose or circulating lipid concentrations (Algenabi et al., 2021). Recent reviews continue to emphasize that dysregulated TLR4 signaling contributes to insulin resistance and chronic inflammation in diabetes, supporting the biological plausibility of our findings (Kumar et al., 2024).

The observed association with HbA1c but not with diabetic dyslipidemia suggests that rs1927911 may primarily affect pathways involved in glucose regulation rather than lipid metabolism. This distinction is important because the metabolic abnormalities observed in T2DM are influenced by multiple genetic and environmental factors (Li et al., 2020). Long-term glycemic control reflects the combined effects of insulin secretion, insulin sensitivity, and chronic inflammatory activation (Soták et al, 2025). Dyslipidemia is strongly affected by obesity, dietary habits, physical activity, and pharmacological treatment. Therefore, promoter-region variants within TLR4 may exert measurable effects on glycemic regulation even in the absence of significant alterations in serum lipid profiles (Berbudi et al., 2025).

The present study did not identify a significant association between the TLR4 rs1927911 polymorphism and diabetic dyslipidemia under any of the evaluated genetic models. Likewise, multivariable analysis demonstrated no independent relationship between rs1927911 and serum TG, TC, LDL-C, or HDL-C. These findings suggest that the influence of rs1927911 may be more specific to long-term glucose regulation than to lipid metabolism (Weinberg Sibony et al, 2024).

The absence of an association with dyslipidemia should be interpreted cautiously. Lipid abnormalities in patients with T2DM are multifactorial disorders resulting from the interaction of genetic susceptibility with obesity, dietary habits, physical inactivity, duration of diabetes, and pharmacological treatment (Zubirán et al., 2024). Consequently, the contribution of a single promoter polymorphism may be relatively small and may become obscured by stronger

environmental and metabolic determinants (Hussain et al, 2019). Similar observations have been reported in previous genetic association studies, in which individual TLR4 variants showed inconsistent associations with lipid parameters across different ethnic populations. These discrepancies probably reflect differences in genetic background, linkage disequilibrium patterns, environmental exposures, and study design rather than true biological contradictions (Fan et al., 2020).

An additional finding of the present study was the absence of significant associations between rs1927911 and circulating TNF or CRP after adjustment for age and sex. Although TLR4 is a central regulator of innate immune activation, circulating inflammatory biomarkers are downstream mediators influenced by numerous clinical and environmental variables (Mantovani & Garlanda, 2023). BMI, visceral adiposity, glycemic control, medications, smoking status, intercurrent infections, and disease duration may affect serum cytokine concentrations (Rohm et al, 2022). Therefore, the biological effect of a promoter polymorphism may not necessarily be reflected by measurable differences in circulating inflammatory markers in a cross-sectional clinical study (Nikolaidis et al., 2025).

Previous studies investigating TLR4 rs1927911 have produced heterogeneous findings. Earlier work in Asian populations reported an association of rs1927911 with susceptibility to vascular disease. However, no significant relationship with FSG or lipid concentrations was found across genotype groups (Fan & Liang, 2020). These observations are partially consistent with the present results, in which no association with lipid parameters was detected despite evidence of an independent relationship with HbA1c(Song et al., 2015). More recently, an Iraqi study evaluating the TLR4 rs1927911 variant in patients with T2DM reported differences in genotype distribution and serum TLR4 concentrations between patients with T2DM and healthy controls (Ali & Salloom, 2026). However, that investigation primarily focused on disease susceptibility, whereas the present study specifically evaluated glycemic status in patients with diabetes and employed multivariable regression analysis. Therefore, the two studies address different clinical questions and should be regarded as complementary rather than contradictory.

In conclusion, the TLR4 rs1927911 polymorphism was not associated with diabetic dyslipidemia or inflammatory markers (TNF and CRP), but was significantly associated with HbA1c, suggesting a role in glycemic regulation rather than inflammation.

The current study has several limitations that should be acknowledged. The study was conducted in a single center and included a moderate sample size. The findings may not be generalizable to all Iraqi or Middle Eastern patients. The study did not measure TLR4 gene expression, receptor protein levels, or downstream signaling activity. Therefore, the functional mechanism by which rs1927911 may influence HbA1c cannot be directly confirmed. The lifestyle factors, such as dietary patterns, physical activity, and medication adherence, were not fully incorporated into the regression models, although these factors can strongly influence HbA1c and lipid parameters.

Ethical approval

The present study was approved by the Ethical Committee of the Faculty of Medicine at the University of Kufa (MEC-8). All participants submitted written consent prior to their inclusion.

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