DOI: https://doi.org/10.54393/pjhs.v7i5.3590

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 7, Issue 05 (May 2026)

Original Article

OPEN ACCESS

Association of TCF7L2 rs7903146 TT Genotype with Dyslipidemia in Type 2 Diabetes: A Case–Control Study in Pakistani Patients

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ARTICLE INFO

Keywords:
Dyslipidemia, TCF7L2, Gene Polymorphism, Lipid Profile, Type 2 Diabetes

How to Cite:
Azhar, S., Farrukh, G. M., Khalid, Z., Theba, F. K., Mughal, S. A., & Siddiqui, M. K. (2026). Association of TCF7L2 rs7903146 TT Genotype with Dyslipidemia in Type 2 Diabetes: A Case–Control Study in Pakistani Patients: Association of TCF7L2 rs7903146 TT Genotype with Dyslipidemia in Type 2 Diabetes. Pakistan Journal of Health Sciences, 7(5), 87-91. https://doi.org/10.54393/pjhs.v7i5.3590

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Received Date: 5th November, 2025
1st Revision Received: 24th December, 2025
2nd Revision Received: 6th February, 2026
3rd Revision Received: 3rd March, 2026
Acceptance Date: 4th March, 2026
Published Date: 31st May, 2026

ABSTRACT

Type 2 diabetes is often accompanied by dyslipidemia, which markedly increases cardiovascular risk. Genetic factors, particularly the TCF7L2 rs7903146 variant, have been implicated in alterations in glucose and lipid metabolism in T2DM. **Objectives:** To assess the association between dyslipidemia and the TCF7L2 rs7903146 polymorphism in patients with T2DM as compared to healthy controls. **Methods:** In Karachi, Pakistan, 100 T2DM patients and 100 age- and sex-matched healthy controls participated in case-control research. Blood samples obtained during fasting were examined for cholesterol and glucose levels. PCR-RFLP was used to genotype TCF7L2 rs7903146, and sequencing was used to confirm the results. Associations ($p<0.050$) were assessed using logistic regression and ANOVA. **Results:** TT genotype and T allele frequencies were greater in T2DM patients than in controls ($p<0.010$). Hence, genotype carriers had significantly higher triglycerides, total cholesterol, and LDL-C levels, and lower HDL-C levels. Multivariate logistic regression demonstrated that the TT genotype independently predicted dyslipidemia. **Conclusions:** The TCF7L2 rs7903146 TT genotype is strongly associated with dyslipidemia in T2DM patients and may assist in risk stratification and personalized management planning.

INTRODUCTION

The prevalence of type 2 diabetes mellitus is rising at the fastest pace, making it a serious and quickly spreading global public health concern [1]. Chronic hyperglycemia is the most common feature of this metabolic disease [2]. Since dyslipidemia is nearly always present in glucose homeostasis, cardiovascular morbidity and mortality are markedly increased in this population [3]. Lipid abnormalities are linked to diabetes directly [4]. Increased release of fatty acids in adipose tissue, combined with decreased lipoprotein lipase activity and increased hepatic triglyceride production result in a dyslipidemia phenotype of T2DM because of insulin resistance [5, 6]. The gene TCF7L2 is one of the strongest and most effective genetic risk factors for type 2 diabetes in most of the ethnic groups belonging to various populations [6]. It helps in the metabolism of lipids along with the regulation of glucose [7]. The rs7903146 single-nucleotide polymorphism (C→T) has been associated with impaired insulin secretion and

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altered glucose homeostasis [7, 8]. According to a variety of studies, TCF7L2 variations may affect adipocyte differentiation, lipoprotein remodeling, and post-prandial triglyceride responses through the Wnt/β-catenin pathway. For example, in an Asian Indian cohort, T-allele carriers of rs7903146 exhibited significantly higher post-prandial glucose, higher HOMA-IR, and peak triglyceride response compared to non-carriers [6]. Hence, in South Asian people, type 2 diabetes was more common in earlier stages of life, and these people have more chances to develop dyslipidemia, which is again a greater risk factor for macrovascular disease [8]. In Pakistan and other neighboring nations, the early development and rapid progression of type 2 diabetes are frequently linked to the severe dyslipidemia phenotype and elevated cardiovascular risk [9]. Thus, from a clinical and public health perspective, it is extremely pertinent to look at genetic modifiers of lipid abnormalities, such as TCF7L2 polymorphisms, in the context of South Asian diabetes. Several investigations in populations with non-diabetes or mixed metabolic syndrome have discovered associations between TCF7L2 risk alleles and lipid variables, such as triglycerides or HDL-C, although the evidence is still limited and often conflicting [10]. Hence, individual polymorphism with dyslipidemia in Pakistani T2DM patients, controlling for the effects of age, sex, BMI, and duration of diabetes.

Pakistan does not have multi-ethnic genetic information on TCF7L2, and there are no mechanistic or intervention studies among the carriers of the TT genotype. The effects that are gender specific are not studied. Small single-centers restrict generalizability. Cross-sectional design prevents causality, results may be biased by unmeasured confounders, and functional validation of results is hampered by a lack of clinical translation. This study aims to assess the relationship of TCF7L2 rs7903146 individual polymorphism with dyslipidemia in Pakistani T2DM patients, controlling for the effects of age, sex, BMI, and duration of diabetes.

METHODS

The case-control study was done from January 2023 to December 2024 in the Department of Pharmacology and Molecular Biology Laboratory, Baqai Medical University and Hospital, Karachi, Pakistan. Informed Consent was taken from all the participants, and the institutional Review Board (BMU-EC/02-2020-04(OL)) approved the study protocol. The sample of this study consisted of 100 clinically diagnosed T2DM patients and 100 age- and sex-healthy matched controls without any history of diabetes or lipid disorders. The exclusion criteria included type 1 diabetes, liver or kidney disease, pregnancy, and other endocrine disorders. The 100 cases and 100 controls offered a power of more than 80 percent to discover genotype-associated variations in dyslipidemia at α = 0.05. Demographic data, family history, lifestyle, medication history, and diabetes duration were obtained using structured questionnaires. BMI was then calculated with the anthropometric measurements of height and weight used. Each participant was allowed to fast for 10-12 hours, and 5ml venous blood sample was gathered to undergo biochemical and molecular analyses. An automated clinical chemistry analyzer (Roche Cobas 311) was used to measure the fasting levels of glucose and lipids. Dyslipidemia was determined based on the criteria of the American Diabetes Association (ADA 2023): total cholesterol -200 mg/dL, triglycerides -150 mg/dL, LDL-C -100, and HDL-C <40 in men and women, respectively. The Qiagen QIAamp DNA Blood Mini Kit was used according to the instructions provided by the manufacturer to extract the genomic DNA from the EDTA blood samples. Genotyping The TCF7L2 (rs7903146 C> T) polymorphism was genotyped by polymerase chain reaction-restricted fragment length polymorphism (PCR-RFLP). The following primers were used in PCR in a Bio-Rad T100 Thermal Cycler: Forward: 5'-GGTGAAGTCTGTGAGAGTGC-3'. Reverse: 5'-AGTGCTGTTGAAGTTGAAGC-3'. PCR conditions: at 95°C for 30s for almost 35 cycles, 58°C for 30 s, 72°C for 30 s, and for 5 min at 72°C. PCR products were digested with RsaI restriction enzyme at 37C 2h and separated on 2% agarose gel stained with ethidium bromide. Genotypes (CC, CT, TT) were identified by the genotype patterns, and again, a 10 percent sample was re-genotyped, and the other 10 percent sequenced using Applied Biosystems 3500 Genetic Analyzer, with 100% concordance. Allele and genotype frequencies were determined by direct counting. Allele frequency was determined as the percentage of the number of times the allele appears within the total population of the study. Genotype frequency represents the percentage of those who have a given genotype. The chi-square (kh2) test was used to compare genotype frequencies in the control with the expected frequencies in the Hardy-Weinberg equilibrium (HWE) to determine the consistency of the population.

For analyzing the data, SPSS version 26.0 was used. An independent samples t-test (or nonparametric equivalents where applicable) was done to compare groups. To determine the homogeneity of variance of ANOVA, the Levene test was done. ANOVA was employed to determine the relationships between genotypes and lipid levels, and multivariate logistic regression was employed to correct the possible confounders. Hence, $p<0.005$ was considered a significant value.

RESULTS

The mean age of T2DM patients was 52.6, and that of controls was 51.9 (p=0.540). There was an equal number of

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males and females. T2DM patients had much higher BMI, systolic blood pressure, fasting glucose, and HbA1c levels as compared to the controls (Table 1).

Table 1: Clinical and Demographic Characteristics

Variables	T2DM (n=100)	Controls (n=100)	p-value
Age	52.6 ± 8.3	51.9 ± 7.9	0.540
Gender Ratio of Male: Female	1.2:1	1.1:1	0.720
BMI (kg/m^2)	28.4 ± 3.7	25.6 ± 3.2	0.001*
Systolic BP (mmHg)	134.2 ± 11.5	124.8 ± 9.3	0.003*
Fasting glucose (mg/dL)	158.6 ± 36.4	91.7 ± 12.8	<0.001*
HbA1c (%)	7.8 ± 1.1	5.4 ± 0.6	<0.001*

The diabetic group had significantly higher mean levels of LDL-C, triglycerides, and total cholesterol than the control group. On the other hand, individuals with diabetes had lower HDL-C levels (Table 2).

Table 2: Comparison of T2DM Patients and Controls Lipid Profiles

Parameters	T2DM Patients	Controls	p-value
Total Cholesterol (mg/dL)	213.5 ± 32.6	178.4 ± 28.3	<0.001*
Triglycerides (mg/dL)	192.8 ± 40.2	136.5 ± 31.9	<0.001*
HDL-C (mg/dL)	39.6 ± 6.5	48.1 ± 7.1	<0.001*
LDL-C (mg/dL)	131.7 ± 28.7	104.3 ± 24.1	<0.001*

HWE of the genotype distribution of the control of rs7903146 was also in Hardy Weinberg (2 = 0.46; p=0.500). Total genotype distribution was not the same between the two groups (cases and controls) (2 = 12.2; p=0.002). The TT genotype dominated in T2DM (28% vs 10%), and the T allele frequency of T2DM patients was higher (46% vs 27.5%; p=0.004) (Table 3).

Table 3: The arrangement of Genotype and Allele

Genotype/Allele	T2DM (n=100)	Controls (n=100)	χ^2	p-value
CC	36 (36%)	55 (55%)	12.2	0.002*
CT	36 (36%)	35 (35%)	–	–
TT	28 (28%)	10 (10%)	–	–
C allele	108 (54%)	145 (72.5%)	7.9	0.004*
T allele	92 (46%)	55 (27.5%)	–	–

Statistically significant at p<0.050

To understand whether the TCF7L2 polymorphism TCF7L2 rs7903146 would affect lipid levels in patients with diabetes, the latter were divided into various genotypes. Carriers of the TT genotype showed considerably higher LDL-C, triglyceride, and total cholesterol than carriers of the CC or CT genotype. The lowest levels of HDL-C were found in carriers of the TT genotype, and this could raise the possibility of a genetic component in lipid metabolism (Table 4).

Table 4: Lipid Levels by Genotype

Lipid Parameters	CC	CT	TT	p-value
Total Cholesterol	205.8 ± 29.1	216.2 ± 33.8	232.5 ± 31.4	0.018*
Triglycerides	181.6 ± 37.4	194.9 ± 39.2	211.8 ± 42.1	0.022*
HDL-C	41.2 ± 6.7	39.6 ± 5.9	36.9 ± 6.3	0.016*
LDL-C	122.6 ± 27.2	134.8 ± 28.5	145.7 ± 30.3	0.012*

In multivariate logistic regression analysis, age, sex, BMI, and diabetes duration were used to adjust the results, and TT genotype was found to be an important independent predictor of dyslipidemia (adjusted OR 2.93; 95% CI 1.36-6.29; p=0.005) and BMI was also found to be an important independent predictor (adjusted OR 1.15; 95% CI 1.05-127; p=0.002) (Table 5).

Table 5: Logistic Regression of Risk of Dyslipidemia

Variables	Adjusted OR	95% CI	p-value
CT vs CC	1.48	0.71–3.07	0.290
TT vs CC	2.93	1.36–6.29	0.005*
Age	1.02	0.98–1.06	0.210
BMI	1.15	1.05–1.27	0.002*
Duration of Diabetes	1.04	0.97–1.11	0.320

DISCUSSION

In Karachi, Pakistan, this case-control study indicated that this polymorphism contributes to both the dysregulation of lipid metabolism and the risk of diabetes; the TCF7L2 rs7903146 (C→T) variant was found to be significantly associated with abnormal lipid profiles [11]. Hence, the growing body of evidence shows that TCF7L2 is necessary to preserve lipid and glucose homeostasis [12]. In this study, diabetic patients with the TT genotype had lower HDL-cholesterol values and higher levels of total cholesterol, LDL-cholesterol, and triglycerides than those with the CC genotype [13, 14]. A crucial modulator of the Wnt signaling system that regulates the production of insulin, proliferation of pancreatic β-cells, and lipid metabolism of the hepatic system, transcription factor 7-like 2 is encoded by the gene [15]. Therefore, changes in this gene that affect the transcription of metabolic targets may result in resistance to insulin and subsequent dyslipidemia. The variant TCF7L2 rs7903146 is one of the most potent genetic predictors of type 2 diabetes in several populations worldwide [16]. The polymorphism TCF7L2 has a complex effect on lipid levels. Alterations in Wnt signaling have been proposed to promote fatty acid synthesis and inhibit hepatic lipid oxidation, which raises blood levels of triglycerides and LDL cholesterol [17]. Alterations in TCF7L2 can also lead to changes in insulin signaling, which can lower HDL cholesterol and lipoprotein lipase activity [18]. A study conducted in KSA revealed that for type 2 diabetes susceptibility polymorphism is a good indicator as it has less effect on lipid levels after adjusting

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for factors like body mass index and insulin resistance [19]. Further, the results of the study revealed that the T allele of females is strongly linked with dyslipidemia as compared to males [20]. The site of adipose tissue or the hormonal control of lipid metabolism may be the cause of this gender disparity [21]. Dyslipidemia may therefore be more common in female diabetic patients with the TCF7L2 risk mutation due to a combination of genetic predisposition and gender-specific metabolic responses. Therefore, it is crucial that genetic testing be used to treat type 2 diabetes from a public health perspective. Therefore, in addition to functional evaluations and demographic coverage, more multicentric research should be carried out.

A consistent sample and a thorough laboratory analysis were two drawbacks of the study. Although the sample size is sufficient to identify associations, it could not accurately reflect the heterogeneous Pakistani population. Future studies should examine the potential of TCF7L2-targeted therapies to reduce diabetic dyslipidemia and extend to larger, multiethnic groups.

CONCLUSIONS

TCF7L2 rs7903146 TT genotype is closely linked to dyslipidemia in Pakistani (T2DM) patients. Carriers of the TT genotype had 28% of T2DM patients and 10% of controls, and the T allele frequency was much more prevalent in the patients (46% vs 27.5; p=0.004). People who were carriers of the TT genotype carried much more triglycerides, total cholesterol, and LDL-C with low levels of HDL-C than people who carried the CC or CT genotype. Multivariate logistic regression established that the TT genotype was an independent predictor of dyslipidemia (adjusted OR 2.93; 95% CI 1.36-6.29; p=0.005) even after age, sex, BMI, and diabetes duration were controlled. These findings suggest that the TCF7L2 rs7903146 variant is also linked with impaired lipid metabolism in T2DM and could be used to determine patients at increased risk of cardiovascular complications, which has substantiated the application of personal metabolic risk evaluation and genetic screening in the management of diabetes.

Authors' Contribution

Conceptualization: SA
Methodology: SA, SMF, ZK, SAM
Formal analysis: SMF, FKT
Writing and Drafting: SA, MKS
Review and Editing: SA, SMF, ZK, FKT, SAM, MKS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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