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Original Article

Biochemistry Section

Association of Single Nucleotide Polymorphisms with Type 2 Diabetes Mellitus within the Punjabi Population: A Case-control Study

JASWANT KAUR[1], SAHIBA KUKREJA[2], MANDEEP KAUR[3], JASKIRAN KAUR[4]

ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2DM) is influenced by both genetic and environmental factors. The TCF7L2 gene, especially the rs12255372 polymorphism, is linked to a higher risk of T2DM in various groups. However, its effect on the genetically and environmentally unique Punjabi population is not well-studied.

Aim: To determine the impact of the TCF7L2 (rs12255372) polymorphism on T2DM in the Punjabi Population, India.

Materials and Methods: A case-control study was conducted at Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar, Punjab, India, from April 2022 to July 2024. The study included 200 participants, divided into two groups: Group I consisted of 100 T2DM patients (cases), while Group II comprised 100 healthy individuals (controls). A range of anthropometric, biochemical, and genetic parameters were assessed, including the genotyping of the rsrs12255372(G/T) SNP using real-time Polymerase Chain Reaction (PCR). Measurements were taken for Fasting Plasma Glucose (FPG), Glycated Haemoglobin (HbA1c), and lipid profiles. Odds Ratios (OR) were calculated and statistical analyses were performed using student's t-test, with a significance level set at $p<0.05$.

Results: In the present study, cases had significantly higher mean age (47.05±8.76 vs. 37.70±7.19 years, $p<0.001$) and had higher Body Mass Index (BMI) (27.7±5.8 vs. 21.8±1.6, $p<0.001$) than controls. Most participants in both groups were aged 41-50. Females were more prevalent in the case group (77 vs 62%). Cases also exhibited higher fasting blood glucose (248.8±82.36 vs 93.56±11.72) and HbA1c (9.7±2.1 vs 5.44±0.37%). The TCF7L2 rs12255372 "T" allele was more prevalent in cases. The GT genotype was more frequent in cases (38%) than controls (24%, OR=1.86, 95% CI 1.01-3.45), as was the TT genotype (4 vs 1%). Triglycerides (TG) were significantly higher in cases (176.0±38.8 vs. 153.76±36.61 mg/dL, $p<0.001$), with a significant association between high TGs and the rs12255372 GT/TT genotypes in cases ($p=0.001$).

Conclusion: The current study identified a significant correlation between the TCF7L2 gene (rs12255372 (G/T) polymorphism) and an increased risk of T2DM in the Punjabi population of India.

Keywords: Fasting blood glucose, Glycosylated haemoglobin, Insulin resistance, Lipid profile, Polymerase chain reaction

INTRODUCTION

The global prevalence of diabetes has escalated significantly, with diagnoses nearly quadrupling since 1980 [1]. T2DM constitutes approximately 90% of all diabetes cases, primarily influenced by genetic predispositions and lifestyle factors such as obesity and physical inactivity [2]. T2DM is characterised by insulin resistance and impaired blood glucose regulation, leading to severe health complications, including neuropathy, cardiovascular disease, and renal failure. This condition imposes a substantial economic burden, estimated at USD 3.1 trillion globally. In 2019, diabetes ranked as the ninth leading cause of death, impacting over 10% of adults aged 20 to 79 years [3].

According to the International Diabetes Federation (IDF), there is a significant projected increase in the global prevalence of diabetes. Projections indicate a substantial rise by 2045, with a particularly heavy burden expected in low and middle-income countries. Specifically, IDF projections show that by 2045, 783 million adults will be living with diabetes [4]. Numerous genes associated with the aetiology of T2DM have been identified, with TCF7L2 (Transcription Factor 7 Like 2) recognised as a significant candidate due to its critical role in regulating blood glucose levels and β-cell function. Strong initial associations between TCF7L2 and T2DM were first reported in the Icelandic population and subsequently corroborated in Danish and US cohorts. Notably, three SNPs within the TCF7L2 gene- rs7390146, rs12255372, and rs11196205 exhibited significant associations with T2DM and were further validated in a comprehensive meta-analysis, supporting their consideration in future genetic studies [5]. TCF7L2 facilitates the transcription of various proteins and is believed to play a role in the development of T2DM, mainly by affecting pancreatic β-cells [6]. TCF7L2 is a transcription factor with significant variability that plays a role in insulin secretion and enhances glucose production in the liver. It has been shown to protect pancreatic cells from apoptosis induced by interleukin-1 and interferon. TCF7L2 influences β-cell function by adjusting the β-cell's response to glucose or regulating the action or secretion of incretins [7].

The transcription factor TCF7L2 plays a crucial role in the synthesis and secretion of insulin, both through GLP-1 and independent mechanisms [8]. A similar study by Cauchi S et al., (2006) identified the T-alleles of both rs7903146 and rs12255372 as significantly increasing the risk of Type 2 Diabetes. This finding has been replicated, including in a French population [9]. In contrast, study conducted by Devi BL. In the Chennai suburban population, the TCF7L2 gene polymorphism at rs12255372 (G/T) was not associated with T2DM [8].

The present study findings will not only provide new information on previously unknown regions associated with T2DM but demonstrate a putative population-specific association that could lead to additional biological insights into T2DM pathogenesis. Further, this study will also help in understanding the effect of ethnicity, if existent,

on the T2DM susceptible genes. Given that the population of this region was not genetically explored hitherto for any of the complex genetic disorders, T2DM in particular, it is necessary to assess the role of different candidate genes in the etiology of T2DM in Punjab.

However, research exploring the rs12255372 polymorphism's functional consequences with specific genetic context is likely lacking. So, this research was planned to determine the impact of the TCF7L2 (rs12255372) polymorphism on T2DM in the Punjabi Population, India.

MATERIALS AND METHODS

A case-control study was carried out at the Sri Guru Ram Das Institute of Medical Sciences and Research in Sri Amritsar, Punjab, India, from April 2022 to July 2024. The study protocol received approval from the Institutional Ethical Committee (SGRD/IEC/202235/04.03.2022, and written informed consent was taken from all participants.

Inclusion criteria: Subjects with T2DM were recruited from Punjab state in this study. T2DM diagnoses were made based on the criteria established by the American Diabetes Association in 2022 [10]. Gender-matched healthy individuals were included as controls.

Exclusion criteria: Individuals with cancer, severe renal disease, or autoimmune disorders and on medication were excluded from the study.

Sample size calculation: Sample size calculated based on certain assumptions and reference of similar studies. Assumptions for calculation of sample size are minimum 80% power and 5% significance level (significant at 95% confidence level). With the [11] reference/assumptions and a margin of error {Confidence Interval (CI)} of +10% and considering the normality of the data, the sample size will be calculated as 90 subjects per group and 180 for the study as there are two groups. Formula used for calculation of sample size is as follows:

Sample Size Formula=$(Z\text{-score})^2 \times (1-p)/(\text{margin of error})^2$

Where Z-score is 1.96, =p=0.378, q=0.622 and D (margin of error)=0.10

A total number of 200 participants were recruited in this study and divided into two groups. Group I involved 100 patients diagnosed with T2DM and group II 100 healthy controls.

Study Procedure

Sample collection and analysis: A total of 6 mL fasting venous blood was collected from each participant in the study using sterile disposable syringe. The samples were then centrifuged at 3500 rpm for 15 minutes to separate the serum, which was stored at -20°C until analysis. Before testing, the samples were allowed to reach room temperature and were mixed by inversion. Blood was collected in both plain and Ethylenediaminetetraacetic Acid (EDTA) vacutainers as follows: A 2 mL of blood was placed into a grey top vacutainer tube to obtain plasma for fasting blood glucose (cut-off range 70-100 mg/dL for control and ≥ 126 mg/dL for cases) [10] performed by the glucose oxidase method on a fully automated analyser (EM 360) with a kit from Erba. Another 2 mL blood sample was collected in a red top vacutainer for lipid profile analysis also conducted on the EM 360 using the kit method. The reference value was for total cholesterol 140-250 mg/dL [12], TGs 30-200 mg/dL [13], HDL cholesterol 30-65 mg/dL [14] and LDL cholesterol (10-125 mg/dL calculated by Friedwald [15]. Additionally, 2ml of whole blood was transferred to an EDTA (purple top vacutainer) tube for DNA isolation using a kit method (Merverick) according to the manufacturer's instructions, followed by genotyping via PCR (Alta 48). HbA1c levels (cut-off value for controls ≤5.6% and ≥6.5% for cases) [10] were measured by immunoturbidimetric method on the fully automated analyser (EM 360).

Molecular analysis: The kit method facilitates the rapid preparation of high-quality genomic Deoxyribonucleic Acid (DNA), making it suitable for extraction from blood collected in EDTA tubes or whole blood treated with citrate. DNeasy spin columns and buffers are maintained dry at room temperature (15-25°C) to ensure stability. The kit includes a ready-to-use Proteinase K solution. A volume of 200µl of blood is processed through several steps as outlined in the kit instructions. The purified DNA is then stored at -20°C for future genotyping. The quality of the extracted DNA is evaluated using 1% agarose gel electrophoresis. Genotyping of the SNP rs 12255372 in the TCF7L2 gene is conducted via PCR. In the TCF7L2 gene for rs12255372, the PCR product of the T allele with 181 bp fragment was amplified using the extracted DNA as a template and its forward, and reverse primers as follows: Forward Primer-5' -CTGCCCAGGAATATCCAGGCAAGAGTT- 3' Reverse Primer-5' -GAGAGAGTGCACTAAAGACGTGGATTCT- 3'. Probes and master mix are utilised according to the kit's instructions. The genotyping process involves restriction digestion of the PCR-amplified product using TSP5091. The PCR amplification protocol includes an initial denaturation step at 95°C for five minutes, followed by 34 cycles consisting of denaturation at 95°C for 30 seconds, annealing at 56°C for 30 seconds, extension at 72°C for 30 seconds, and a final extension at 72°C for nine minutes. The amplified product-amplicons of 271 bp for the G allele and 181 bp for the T allele, at the rs 12255372 was identified by 2% agarose gel electrophoresis by comparison with a known 100 bp DNA ladder [8].

STATISTICAL ANALYSIS

The results obtained were statistically analysed Using Statistical Package for Social Sciences (SPSS) version 21. Demographic and anthropometric data was represented as mean and Standard Deviation (SD) for continuous data which was statistically analysed using student t-test and as a percentage for categorical data. Odd ratio was calculated to determine the association between polymorphism and the risk of T2DM. One-way ANOVA test was performed to compare various baseline characteristics and biochemical parameters with different genotypes of the TCF7L2 gene in group I. p<0.05- was considered significant.

RESULTS

In this case-control study, the genotype distribution of the TCF7L2 gene polymorphism was analysed in 100 individuals diagnosed with T2DM (cases as group I) and 100 healthy individuals (controls as group II). The relationship between each genotype and various clinical and biochemical parameters was assessed. The diabetic cases consisted of 33 males (33%) and 67 females (67%), while the control group-included 33 (33%) males and 67 (67%) females. An equal number of males and females were present in this study. Among patients with a disease duration of 1-3 years, the mean duration was 1.94±0.26 years.

As illustrated in [Table/Fig-1], the mean age of the cases was 47.05±8.76 years, compared to a mean age of 37.70±7.19 years for the controls. A statistically significant difference was observed between the mean ages of the two groups (p<0.001). In group I,

Age groups (years)	Group I (cases)			Group II (Controls)		
	Female (N=67)	Male (N=33)	Total (%) N=100	Female (N=67)	Male (N=33)	Total (%) N=100
30-40	32	14	46 (46%)	23	13	36 (36%)
41-50	14	10	24 (24%)	17	8	25 (25%)
51-60	13	7	20 (20%)	17	7	24 (24%)
61-70	8	2	10 (10%)	10	5	15 (15%)
Mean±SD (Age)	Group I 47.05±8.76			Group II 37.70±7.19		t-value=9.407 p<0.0001

[Table/Fig-1]: Distribution of study participants according to age in both groups. Mean±SD and p-value calculated; *p<0.05 considered as significant

the largest proportion of participants (46%) was in the middle-aged category (30-40 years), while in group II, 36% of participants were in the 30-40 year age range. Additionally, the age group of 60-70 years represented the smallest number of participants in both groups, comprising 7% of group I and 18% of group II. It was noted that there is a significant predominance of females in group I.

In [Table/Fig-2], the mean plasma glucose levels in cases and controls are 248.8 mg/dl±82.30 and 93.56±11.72, respectively, which is highly significant (p<0.001). Similarly, the mean HbA1C values in cases and controls were 9.7±2.1 and 5.44±0.37, respectively, with significant differences (p<0.001). Additionally, the mean total cholesterol in cases and controls is 171.8±41.3 and 155.50±33.27, respectively, with a p-value of 0.001. The mean HDL-C, LDL-C, and TG in cases versus controls are 37.6±8.9 vs 48.05±8.39, 149.63±32.67 vs 100.01±25.75, and 208.3±144.6 vs 98.51±31.56, respectively, all showing significance (p=0.001).

Parameters	Group I (cases) Mean±SD	Group II (controls) Mean±SD	p<value
Fasting blood glucose (mg/dL)	248.8±82.30	93.56±11.72	<0.001*
HbA1c (%)	9.7±2.1	5.44 ±0.37	<0.001*
Total Cholesterol (mg/dL)	171.8±41.3	155.50±33.27	<0.001*
HDL-C (mg/dL)	37.6 ±8.9	48.05±8.39	<0.001*
LDL-C (mg/dL)	149.63±32.67	100.01±25.75	<0.001*
Triglycerides (TG) (mg/dL)	208.3±144.6	98.51±31.56	<0.001*

[Table/Fig-2]: Comparison of biochemical investigations in both groups.
Mean±SD and p-value calculated; *p<0.05 considered as significant

In [Table/Fig-3], the distribution of genotypes between cases and controls is presented. The GG genotype exhibits a prevalence of 61% in cases, in contrast to 75% in controls. The GT genotype is observed with a prevalence of 35% in cases compared to 24% in controls, yielding an OR of 1.86 with a 95% CI of (1.01-3.45). The TT genotype is found at a frequency of 4% in cases, while it is 1% in controls, resulting in an OR of 0.29 with a 95% CI of (0.03-2.71).

Gene: rs12255372	Groups N %		Odds Ratio (OR) 95% CI	p-value
	Cases (100)	Controls (100)		
GG	61 (61%)	75 (75%)	Ref.	0.001
GT	35 (35%)	24 (24%)	1.86 (1.01-3.45)	
TT	4 (4%)	1 (1%)	0.29 (0.03-2.71)	

[Table/Fig-3]: Genotype distribution of TCF7L2 gene at rs12255372 between cases and control.
%-Percentage frequency, odd ratio and p-value calculated; *p<0.05 considered as significant; Ref: Reference

In [Table/Fig-4], the distribution of allele frequencies between cases and controls is as follows: The frequency of the G allele in the control group is 84%, whereas in the case group, it is 76%. Conversely, the prevalence of the T allele is observed to be 24% in cases and 16% in controls.

Gene: rs12255372	Group N %				Odds Ratio (OR) 95% CI	Chi-Square test	p-value
	Cases (N=100)		Controls (N=100)				
G	76	(76%)	84	(84%)	1.66 (0.78-3.53)	1.748	0.005*
T	24	(24%)	16	(16%)			

[Table/Fig-4]: Allele distribution of TCF7L2 gene at rs12255372 between cases and control.
%-Percentage frequency, odd ratio, Chi-square test and p-value applied*; *p<0.05 considered as significant

DISCUSSION

This study examines the association between polymorphisms in the TCF7L2 gene and the incidence of Type 2 Diabetes in a Punjabi population. It includes a sample size of 200 individuals, divided equally into two groups: 100 diagnosed cases of Type 2 Diabetes and 100 healthy controls, to determine whether specific genetic variations in the TCF7L2 gene are more prevalent in individuals with Type 2 Diabetes compared to healthy controls. Such research is crucial for understanding the genetic factors that may contribute to the development of Type 2 Diabetes in this particular demographic.

The analysis of SNPs in the present study, which examined the relationship between genetic variations and various epidemiological and clinical parameters of diabetes- specifically BMI and fasting blood glucose levels, HbA1c indicates a significant association between the SNP rs12255372 of the TCF7L2 gene and blood glucose levels in the Punjabi population. This finding suggests that the TCF7L2 gene may play a crucial role in glucose metabolism, similar to findings observed by Chandak GR in the Indian population [16]. In the present study, cholesterol and TG levels were found to be significantly elevated in patients with T2DM compared to non-diabetic controls. Conversely, High-Density Lipoprotein (HDL) levels were significantly reduced in T2DM patients, particularly in those with elevated TG levels. These findings are consistent with the results reported by Biadgo B et al., [17]. It was observed in [Table/Fig-3] that the risk alleles of rs12255372 were linked to increased BMI and TGs in both individuals with T2DM and controls. The study indicates an increased risk of T2DM associated with the genotype GT/TT (rs12255372), particularly in patients exhibiting elevated TG levels. Similar studies revealed a correlation between the rs12255372 variant in T2DM and present significant evidence of the T allele's increased TG levels in Mexican and Finnish populations [18].

The present study identified a notable correlation between the T allele of the rs12255372 (G/T) SNP and T2DM within the study population. The prevalence of the T allele in the present cohort was comparable to that observed in the Finnish population [19], but significantly lower than that found in the Icelandic population [20]. The current study identified a significant link between the TCF7L2 gene (rs12255372 (G/T) polymorphism) and an increased risk of T2DM in the Punjabi population. Lyssenko V et al., discovered that the SNPs rs12255372 and rs7903146 in the TCF7L2 gene are strongly linked to the risk of developing T2DM [21]. The risk alleles of these SNPs are associated with impaired function of pancreatic β-cells across all individuals. In this regard, Srinivasan S et al., reported that carriers of the T allele for TCF7L2 rs12255372 demonstrated a significant increase in TCF7L2 mRNA expression within human pancreatic islets [22]. This elevation was linked to impaired insulin secretion and increased hepatic glucose production. Additionally, it indirectly influenced GLP-1 levels, as the gene for GLP-1 is transcriptionally regulated by this transcription factor. However, some studies found no association between a TCF7L2 rs12255372 variant and T2DM.

The study found that the T allele of the TCF7L2 rs12255372 G/T gene polymorphism can reduce both insulin secretion and insulin

Authors name	Place/year of the study	Population, sample size	Findings	Conclusion
Present study	Punjab	Punjabi population, a total 100 participants, 50 cases, and 50 Controls	The TCF7L2 rs12255372 "T" allele was more prevalent in cases. The GT genotype was more frequent in cases (38%) than controls (24%, OR=1.86, 95% CI 1.01-3.45), as was the TT genotype (4% vs. 1%). Triglycerides (TG) were significantly higher in cases (176.0±38.8 vs. 153.76±36.61 mg/dl, p<0.001), with a significant association between high triglycerides (TG) and the rs12255372 GT/TT genotypes in cases (p=0.001).	The current study identified a significant correlation between the TCF7L2 gene (rs12255372 (G/T) polymorphism) and an increased risk of Type 2 Diabetes Mellitus (T2DM) in the Punjabi population.

Uma Jyothi K et al., 2013 [5]	Hyderabad, 2013	Population of Hyderabad, 758 patients and 621 controls	Three TCF7L2 SNPs (rs7903146, rs11196205, rs12255372) were significantly associated with increased T2DM risk, with homozygous genotypes conferring higher risk than heterozygous, particularly for rs12255372. rs12255372's risk genotype also correlated with elevated fasting and 2-hour plasma glucose, and increased HOMA-R in non-diabetic individuals. No association was found between TCF7L2 genotypes and age at diagnosis, BMI, or WHR.	This study confirms a strong association between TCF7L2 gene variants and type 2 diabetes in Indian subjects, consistent with findings in other populations. The results suggest TCF7L2 plays a key role in T2DM pathogenesis by affecting both insulin secretion and resistance, highlighting its importance as a susceptibility gene across ethnicities.
Mahmood IA, et al., 2020 [24]	Iraq, 2020	Iraqi population, 76 patients with T2DM and 54 healthy controls	SNPs rs12255372G/T, TT genotype, and T allele of a specific SNP were significantly more frequent in diabetic patients. The TT genotype was associated with four-fold increased odds of diabetes. (OR=4.04, 95%CI=1.04-15.71, p=0.044). Additionally, patients with the TT genotype exhibited significantly higher HOMA-IR values, indicating increased insulin resistance, compared to those with GG or GT genotypes.	This study strongly indicates that the T allele of the TCF7L2 rs12255372 variant is a risk factor for type 2 diabetes (T2DM), likely by increasing insulin resistance (IR).
Cauchi S et al., 2006 [9]	France, 2006	European population, 2,367 French type 2 diabetic subjects and 2,499 control subjects	Both the T-allele of rs7903146 and the T-allele of rs12255372 significantly increase type 2 diabetes risk with an allelic OR of 1.69 (95% CI 1.55-1.83) ($P = 6.0 \times 10^{-35}$) and 1.60 (1.47-1.74) ($P = 7.6 \times 10^{-28}$), respectively	TCF7L2 is a major determinant of type 2 diabetes risk in European populations and suggests that this transcription factor plays a key role in glucose homeostasis.
Lavanya Devi B et al., 2019 [8]	Chennai, 2019	Chennai suburban population, 80 subjects were enrolled, 44 T2DM cases and 44 healthy controls.	The T allele of rs7903146 was significantly more frequent in diabetic subjects (30.7%) compared to controls (2.0%), though the p-value was borderline significant (p=0.093). For rs12255372, the T allele frequency was higher in diabetics (23.9%) than in controls (15.9%), but this difference was not statistically significant (p=0.093).	Study support that as in many ethnic groups, the TCF7L2 gene polymorphism at rs7903146 (C/T) could be an important genetic risk factor for T2DM among the urban Chennai population

[Table/Fig-5]: Comparison of the findings in present study with contrast studies [5,8,9,24].

sensitivity to glucose. Another study indicated that individuals carrying the T allele exhibited higher glucose levels during the 2-hour post-meal period and throughout fasting [23]. Additionally, these individuals demonstrated lower insulin production compared to those with the G allele. Collectively, these factors increase their susceptibility to T2DM [24]. Comparison of the findings in present study with contrast studies is discussed in [Table/Fig-5] [5,8,9,24]. Further research involving a larger sample size is necessary in North Indian populations to confirm the clinical implications of the TCF7L2 gene polymorphism.

Limitation(s)

To understand the role of TCF7L2 in T2DM, future studies with larger sample sizes are needed. Furthermore, the genetic variants that have been studied are present in the introns rather than in the coding regions. However, this may still lead to functional consequences in terms of protein stability and/or expression of alternatively spliced variants.

CONCLUSION(S)

Given all the observations of the present study, significantly higher levels of fasting plasma glucose, HbA1c, and lipid profile were found in T2DM patients as compared to healthy controls. The T allele and GT genotype of rs12255372 polymorphism of the TCF7L2 gene is associated with a two to threefold increased risk of T2DM. The study indicates that individuals with the TT genotype of the polymorphism should undergo regular diabetes screening and may represent a valuable focus for future research on diabetes management and prevention in this population. To strengthen the validity of the findings of the present study, future studies should aim to replicate these results with larger sample sizes. Furthermore, investigations into the clinical utility of rs12255372 SNP genotyping are necessary, specifically exploring its potential as a predictive biomarker for drug response and determining the most effective treatment approaches in diabetes management.

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PARTICULARS OF CONTRIBUTORS:
1. Ph.D. Scholar, Department of Biochemistry, Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar, Punjab, India.
2. Professor and Head, Department of Biochemistry, Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar, Punjab, India.
3. Assistant Professor, Department of Biochemistry, Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar, Punjab, India.
4. Professor, Department of Biochemistry, Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar, Punjab, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Jaskiran Kaur,
Professor, Department of Biochemistry, Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar-143001, Punjab, India.
E-mail: jaswantkaur_2006@yahoo.co.in

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