Original Article

Association of TCF7L2 Variants in Type 2 Diabetes Mellitus with Hypertriglyceridemia – A Case-Control Study

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Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic condition involving various genetic and environmental factors leading to impaired insulin secretion, resulting in hyperglycemia. The transcription factor 7-like 2 (TCF7L2) gene is an element of the Wnt signaling pathway that plays an important role in glucose and lipid metabolism. The aim of this study is to evaluate the association of TCF7L2 rs7903146 and rs12255372 polymorphisms in T2DM with hypertriglyceridemia. **Methods:** We investigated the effect of rs7903146 and rs12255372 on T2DM with high triglyceride (TG) levels in 60 patients and 20 controls. The anthropometric measurements and biochemical tests were assessed. Peripheral blood samples were collected, and genomic DNA was extracted. The genotyping of TCF7L2 polymorphisms was carried out using polymerase chain reaction (PCR)-based direct sequencing and allele-specific PCR methods. The T2DM patients and controls were compared by means of the t-test, Chi-square test, odds ratio (OR), and 95% confidence interval (CI) using *Epi Info v7*. **Results:** The HbA1c was found to be 9.7 ± 2.1 and 5.4 ± 0.5% in patients and controls, respectively. The average TG levels ($P < 0.005$) in patients were 205.2 ± 145.7 and 106.4 ± 27.4mg/dl in controls. Significant evidence of association was found in T2DM patients having high TG levels with rs7903146 CT/TT (OR: 4.89; $P = 0.0105$) and rs12255372 GT/TT (OR: 5.23; $P = 0.0101$) genotypes when compared to controls. **Conclusion:** The results of this study show that TCF7L2 rs7903146 CT/TT and rs12255372 GT/TT genotypes are significantly associated with the risk of hypertriglyceridemia in individuals with T2DM among the studied population.

Keywords: Polymorphism, rs7903146, rs12255372, TCF7L2, triglycerides

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder caused by the inability to produce or utilize insulin by the body, leading to hyperglycemia. Patients with T2DM have several complications, such as nephropathy, retinopathy, neuropathy, stroke, etc. Globally, the incidence of T2DM is increasing, and India has the second-largest number (74.2 million individuals as of 2021) of adults (20–79 years) with diabetes.[1] Diabetes-related healthcare outcomes, treatment options, care needs, and associated costs are complicated due to the presence of comorbidities in chronic conditions of T2DM. The common comorbidities of T2DM are cardiovascular complications,[2] end-stage renal disease,[3] and hypertension.[4] Hypertriglyceridemia is an abnormality with high triglyceride (TG) levels that can be caused due to varied factors and is associated with increased cardiovascular risk.[5]

Transcription factor 7-like 2 (TCF7L2) on chromosome 10q25.3,[6] is a high-mobility box-containing transcription factor that has a role in activating many genes downstream of the Wnt signaling pathway and in T2DM.[7,8] The TCF7L2 gene has a vital role in the progression of T2DM by influencing pancreatic islets, adipogenesis, and myogenesis. Also, TCF7L2 plays a significant role in controlling the biosynthesis, processing, and secretion of insulin.[9] Overexpression of TCF7L2 in human pancreatic islets was found to decrease glucose-stimulated insulin secretion. Hence, the higher risk of T2DM due to the variants in TCF7L2 comprises the entero-insular axis, increased expression of the gene in islet cells, and impaired secretion of insulin.[10]

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The TCF7L2 gene variants of intron 3, IVS3 C>T (rs7903146), and intron 4, IVS4 G>T (rs12255372) are reported to be strongly associated with T2DM and its complications.[11-14] In the North Indian population, it is also confirmed that rs7903146 and rs12255372 contribute to obesity and lipid concentrations.[15] Moreover, these TCF7L2 variants are found to be associated with altered TG responses independent of insulin. On the other hand, high TG levels lead to a higher incidence of cardiovascular risk, stroke, diabetic neuropathy, etc. Hence, to unravel the relationship, we aimed to evaluate the association of rs7903146 and rs12255372 polymorphisms in T2DM with hypertriglyceridemia among the study population.

Methods

Study subjects

Peripheral blood samples were collected from 60 T2DM patients and 20 non-diabetic controls. The T2DM patients were stratified into 2 groups, namely, Group A having normal TG levels (n = 30) and Group B having high TG levels (n = 30). Patients with lipid-lowering medications, chronic alcoholism, chronic liver disease, and chronic kidney disease were excluded from the study. The study was conducted at Alpha Health Foundation and Alpha Hospital and Research Centre with written informed consent from the participants for their participation and the use of patient data for research. The proposed study was approved by the institutional ethics committee (Ref. No.: EC/01/2017; Dated: 07/02/2018) and was carried out in accordance with the Declaration of Helsinki.[16]

Clinical assessment and genotyping

Clinical assessments such as anthropometric measurements and biochemical tests were performed according to standard protocols, which include body mass index (BMI), blood glucose, total cholesterol, and TG. Genomic DNA was extracted from the peripheral blood samples using the QIAamp DNA Blood Mini Kit (QIAGEN India Pvt. Ltd., India). Quantitative and qualitative (260/280 nm absorbance ratio) assessments of the extracted DNA samples were carried out using a nanodrop (Thermo Scientific, USA). The genotyping of TCF7L2 rs7903146 and rs12255372 polymorphisms was carried out using the PCR amplification method.[17] The PCR products were visualized using a UV gel documentation system after electrophoresis. Further, the gel was extracted, purified, and used for direct DNA sequencing to distinguish wild-type, homozygous, and heterozygous carriers for the TCF7L2 polymorphisms.

Statistical analysis

Statistical analysis was carried out using *Epi Info v7*. The T2DM patients and non-diabetic controls were compared by means of the t-test, Chi-square test, odds ratio (OR), and 95% confidence interval (CI). Deviations from Hardy Weinberg equilibrium (HWE) were assessed in patients and controls. A P value of <0.05 was considered to be statistically significant.

Results

Characteristics of the study subjects

The demographic characteristics of T2DM patients and non-diabetic controls are given in Table 1. The genotype frequencies of TCF7L2 rs7903146 and rs12255372 polymorphisms adhered to HWE ($P > 0.05$) among patients and controls. The mean ages of patients and controls were 48.9 ± 11.7 and 41.3 ± 10.3 years, respectively. The HbA1c was found to be 9.7 ± 2.1 and 5.4 ± 0.5% in patients and controls, respectively. There was no significant difference in BMI between group A and group B patients. The average TG levels ($P < 0.005$) in patients were 205.2 ± 145.7 and 106.4 ± 27.4 mg/dl in controls. Further, group A patients have TG levels of 101.8 ± 26.8 and group B patients have 308.6 ± 142.6 mg/dl.

Triglyceride levels and genotype distribution

The TG levels with respect to TCF7L2 genotypes in T2DM patients and controls are given in Table 2. Significantly high TG levels were observed in patients when compared to controls in the studied genotypes. Group B patients with CT/TT genotypes showed significantly high TG levels (320.3 ± 147.3 mg/dl) compared to controls (<0.005). Whereas, the GG genotype of rs12255372 showed significantly high TG levels in Group B (378.2 ± 177.1 mg/dl) compared to controls (<0.005). The genotype distribution of rs7903146 and rs12255372 polymorphisms in T2DM patients and controls is given in Table 3. Significantly higher frequencies of T2DM patients having high TG levels with rs7903146 CT/TT (OR: 4.89; $P = 0.0105$) and rs12255372 GT/TT (OR: 5.23; $P = 0.0101$) genotypes were observed when compared to controls. On

Table 1: Demographic characteristics of type 2 diabetes patients and non-diabetic controls

Parameters	Controls	Total Patients	*P**	Group A	*P*#*	Group B	*P*$*
n	20	60		30		30	
Age (years)	41.3±10.3	48.9±11.7	**0.0043**	53±9.3	**<0.005**	44.8±12.6	0.1413
BMI (Kg/m^2)	22.8±1.5	27.6±5.9	**<0.005**	27.4±4.6	**<0.005**	27.8±7	**<0.005**
HbA1c (%)	5.4±0.5	9.7±2.1	**<0.005**	9.7±2.2	**<0.005**	9.8±2	**<0.005**
Triglycerides (mg/dl)	106.4±27.4	205.2±145.7	**<0.005**	101.8±26.8	0.2827	308.6±142.6	**<0.005**
Total cholesterol (mg/dl)	152.9±33.5	171.9±41.4	**0.0228**	156.7±39.6	0.3555	187±38.1	**<0.005**
High density lipoproteins (mg/dl)	50.5±5.5	38.6±8.9	**<0.005**	40.8±9.5	**<0.005**	36.3±7.8	**<0.005**

Significant P values indicated in bold; * - Total patients Vs control; # - Group A Vs control; $ - Group B Vs control

Table 2: Triglyceride levels in type 2 diabetic patients and non-diabetic controls with TCF7L2 genotypes

Genotypes	Control (20)	Total Patients (60)	*P**	Group A (30)	*P*#	Group B (30)	*P*$
rs7903146 **CC**	100±20.3	147.9±93.8	**0.0138**	107.8±30.5	0.213	261.5±121.7	**0.0112**
rs7903146 **CT/TT**	108.4±33.9	240.8±161.2	**<0.005**	94±19.6	0.0677	320.3±147.3	**<0.005**
rs12255372 **GG**	102.6±24.3	215.2±173.3	**<0.005**	109.3±27.2	0.2234	378.2±177.1	**<0.005**
rs12255372 **GT/TT**	121.3±37.9	192.9±104.5	**0.0118**	86.9±19.7	0.0831	255.3±79.8	**<0.005**

Significant *P* values indicated in bold; * - Total patients Vs control; # - Group A Vs control; $ - Group B Vs control

Table 3: Genotype distribution of rs7903146 and rs12255372 in type 2 diabetic patients and non-diabetic controls

	Controls (20)	Total Patients (60)			Group A (30)			Group B (30)		
	n (%)	*n* (%)	OR (95% CI)	P_c*	*n* (%)	OR (95% CI)	P_c#	*n* (%)	OR (95% CI)	$P_c$$
rs7903146 **CC**	11 (55)	23 (38.3)	0.51 (0.18-1.42)	0.2962	17 (56.7)	1.07 (0.34-3.34)	1	6 (20)	0.2 (0.06-0.72)	**0.0241**
rs7903146 **CT/TT**	9 (45)	37 (61.7)	1.97 (0.71-5.47)	0.2962	13 (43.3)	0.93 (0.3-2.92)	1	24 (80)	4.89 (1.39-17.16)	**0.0241**
rs12255372 **GG**	16 (80)	33 (55)	0.31 (0.09-1.02)	0.085	20 (66.7)	0.5 (0.13-1.9)	0.4794	13 (43.3)	0.19 (0.05-0.71)	**0.0225**
rs12255372 **GT/TT**	4 (20)	27 (45)	3.27 (0.98-10.95)	0.085	10 (33.3)	2 (0.53-7.58)	0.4794	17 (56.7)	5.23 (1.41-19.43)	**0.0225**

P_c – Yates corrected *P* value; Significant P_c values indicated in bold; * - Total patients Vs control; # - Group A Vs control; $ - Group B Vs control

the other hand, rs7903146 CC (OR: 0.2; $P = 0.0105$) and rs12255372 GG (OR: 0.19; $P = 0.0101$) genotypes were observed to be significantly increased in controls.

Discussion

Diabetic dyslipidemia, especially high TG levels, is a major risk factor for cardiovascular diseases.[18] TCF7L2 is a highly variable transcription factor that is involved in insulin secretion and an increased rate of production of hepatic glucose. It has been reported to guard pancreatic cells against interleukin-1 as well as interferon-mediated cell apoptosis.[19,20] TCF7L2 affects β-cell function either by modulating β-cell response to glucose or by modulating incretin action or secretion.[21] In the current study, cholesterol and TG were significantly higher in T2DM patients as compared to non-diabetic controls. However, HDL is significantly lower in T2DM, especially among patients with high TG levels. This is in agreement with Biadgo *et al*.[22] reporting a significant increase in the levels of cholesterol and TG in diabetic patients compared to controls. In the same context, Mukherjee *et al*.[23] have reported low levels of HDL among patients with T2DM compared to controls. Thus, these reports show that insulin resistance could play an important role toward dyslipidemia in T2DM patients. The causes of hypertriglyceridemia in diabetic patients could be insufficient function or secretion of insulin that causes higher hepatic secretion of VLDL together with the late elimination of TG-rich lipoproteins, mostly due to greater substrate levels for TG synthesis.[24]

TCF7L2 rs7903146 polymorphism is found to be associated with an altered postprandial TG response that is independent of insulin.[25] The rs7903146 and rs12255372 polymorphisms located within the intronic regions are thought to modify alternative splicing mechanisms, resulting in changes in mRNA variants that may excrete distinct physiological roles in the activation of Wnt signaling.[26] There are several studies in T2DM based on TCF7L2 rs7903146 and rs12255372 polymorphisms.[12-15] Our study is in line with these studies, which are based on the evaluation of TCF7L2 rs7903146 and rs12255372 polymorphisms in association with T2DM. The aim of our study is to focus on the TCF7L2 polymorphisms with TG levels, whereas these studies[12-15] evaluated the distribution of TCF7L2 polymorphisms and compared them with other clinical parameters in different ethnicities.

Results of our study show an increased risk of genotypes CT/TT (rs7903146) and GT/TT (rs12255372) towards T2DM, especially among patients with high TG levels. This data are supported by several studies representing the rs7903146 polymorphism, where the T allele is significantly associated towards T2DM with complications compared to T2DM without complications. Also, TT and CT genotypes were significantly increased in the T2DM without complications and T2DM with complications groups.[27] The same is also evidenced by Nanfa *et al*.[28] and Demirsoy *et al*.,[29] who have reported that the T allele at rs7903146 is related to the risk of T2DM. The presence of the rs7903146 T allele disrupted the lipid metabolism, inducing low levels of HDL-C and apolipoprotein (Apo)-A1 in healthy young men[30] and high levels of TG in familial combined hyperlipidemia patients.[31] rs7903146 and rs12255372 show significant evidence for the association of the T allele with high TG levels in the Mexican and Finnish population.[31] Taken together, these findings strongly support our results.

Data from our study show a significant association of TCF7L2 rs7903146 CT/TT and rs12255372 GT/TT genotypes and hypertriglyceridemia in T2DM patients in the study population. TCF7L2 polymorphisms affect the effectiveness of anti-hyperglycemic drugs, including the variability in the effects of incretin-based therapy and sulphonylurea derivatives.[32] Pearson *et al*.[33] have reported that the variants in TCF7L2 gene influence the initial treatment success with sulfonylurea therapy in patients with T2DM. In addition, improvement in glycemic control has been established in

patients with T2DM among carriers of the T allele rs7903146 of the TCF7L2 gene during metformin therapy in combination with a low-calorie standard diet.[34] Pharmacogenetic studies have the greatest potential for selecting the optimal drug therapy based on preliminary genetic testing, which might improve the effectiveness of treatment and reduce several life-threatening complications. Further investigations with a larger sample size and functional analysis of polymorphisms could elucidate the complex relationship between these polymorphisms and T2DM associated with TG levels. To the best of our knowledge, our study is the first to demonstrate that the T allele-carrying genotypes of rs7903146 and rs12255372 polymorphisms is significantly associated with hypertriglyceridemia in T2DM among the studied population.

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Conflicts of interest

There are no conflicts of interest.

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