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Original Research Article

ASSOCIATION OF TCF7L2 GENE rs7903146 POLYMORPHISM IN GESTATIONAL DIABETES MELLITUS

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Abstract

Background: Gestational Diabetes Mellitus (GDM) is a significant public health concern, affecting 7-10% of pregnancies worldwide. The prevalence is notably higher in Indian women, who face an 11-fold increased risk compared to their Western counterparts. This study aimed to determine the association of TCF7L2 gene rs7903146 polymorphism in Gestational diabetes mellitus. **Materials and Methods:** This case-control study included 66 pregnant women (33 with GDM and 33 controls) from K.A.P.V. Government Medical College and Mahatma Gandhi Memorial Government Hospital, Trichy for 6 months. The study involved clinical, biochemical, and genetic analysis, including anthropometric measurements and blood sample evaluation. Biochemical tests assessed glucose, urea, and creatinine, while genotypic analysis used DNA extraction, PCR amplification, and gel electrophoresis. Genotyping for the rs7903146 SNP was based on allele-specific PCR and visualised under UV light. **Result:** The mean age of GDM patients was 26.24±1.62, significantly higher than the controls (24.09±1.58, $p<0.0001$). Biochemical analysis revealed significantly elevated fasting and postprandial blood glucose levels in GDM patients (130.9±12.15 mg/dL and 188.4±23.08 mg/dL, respectively; $p<0.0001$). Genotype frequencies for CC, CT, and TT alleles were 32%, 41%, and 27%, respectively. The TT genotype was more prevalent in GDM patients (51%) than in controls ($p<0.00001$). Logistic regression indicated an odds ratio of 9.0667 (95% CI: 4.112-19.987, $p<0.0001$) for the T allele, suggesting a ninefold increased risk of developing GDM. **Conclusion:** The rs7903146 polymorphism in the TCF7L2 gene is significantly associated with an increased risk of GDM. Early genotyping for this SNP may aid in the timely screening and management of GDM, ultimately improving maternal and foetal health outcomes.

INTRODUCTION

Diabetes mellitus has become a serious global public health issue and will remain one of the greatest threats to human health for years to come. The incidence of diabetes mellitus is now estimated to be around 422 million worldwide, and its prevalence has reached epidemic proportions in both developed and developing countries.[1] Diabetes mellitus is defined as a cluster of common metabolic disorders characterised by hyperglycaemia that results from defective insulin secretion, defective response to insulin, or both. Based on the pathogenic process that leads to hyperglycaemia, diabetes mellitus can be classified into Type 1 Diabetes mellitus, Type 2 Diabetes mellitus, Other specific types of diabetes, and Gestational Diabetes mellitus.[2] In India, diabetes mellitus affects more than 7.1% of the adult population.[3]

These alarming numbers also include people with gestational diabetes mellitus, which is associated with increased incidence of multiple maternal and foetal complications like pre-eclampsia, polyhydramnios, preterm delivery, increased caesarean section, foetal macrosomia, dystocia, neonatal hypoglycaemia, prematurity, and respiratory distress syndrome, highlighting the urgent need for special attention to this population. Gestational diabetes mellitus accounts for about 7-10% of all pregnancies worldwide. In particular, Indian women have an 11-fold increased risk of developing gestational diabetes mellitus compared to Western women.[4]

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In Tamil Nadu, the prevalence of GDM is about 15%. Gestational diabetes mellitus is defined as carbohydrate intolerance of variable degrees of severity with onset or first recognition during pregnancy.[5] Generally, pregnancy is characterised by extensive hormonal rearrangements. It is considered a diabetogenic state due to the presence of insulin-antagonizing hormones like human placental lactogen, progesterone, and cortisol, which interfere with insulin's cell signalling pathways. These hormones are produced to secure an adequate glucose supply to the growing foetus.[6]

Gestational diabetes mellitus occurs when insulin secretion is insufficient to counter pregnancy-induced insulin resistance. Insulin resistance, a normal physiological change in the second trimester, unmasks genetically predisposed defects in pancreatic beta cell function or insulin sensitivity. This leads to reduced glucose tolerance in women with gestational diabetes mellitus. The risk of developing gestational diabetes mellitus is increased in women with obesity, sedentary lifestyles, and a positive family history of diabetes mellitus. The genetic predisposition of GDM is of polygenic inheritance, many of which are characterised as single nucleotide polymorphisms (SNPs).[7] SNPs represent changes in a nitrogenous base in the DNA sequence and differ from most classical mutations as they present higher frequencies (more than 1%) in the population. TCF7L2, or Transcription Factor 7 Like 2, is an HMG (High Mobility Group) box-containing transcription factor that belongs to the Wnt family signalling pathway and is involved in maintaining glucose homeostasis.[8]

The rs7903146 SNP is characterised by the substitution of cytosine (C) by thymine (T) at position 299 of the TCF7L2 gene, which is located at ch.10q25.3. Studies have shown that the presence of the T allele increases the risk of gestational diabetes mellitus.[9] Understanding the genetic aetiology of GDM will help identify pharmacological targets for intervention. Hence, early screening and appropriate management to minimise or prevent maternal and foetal complications is of paramount importance.

Aim

This study aimed to determine the association of TCF7L2 gene rs7903146 polymorphism in Gestational diabetes mellitus.

MATERIALS AND METHODS

This Cases-Controls study included 66 patients (cases=33, controls=33) in the Department of Biochemistry at K.A.P.V. Government Medical College and the Department of Obstetrics and Gynaecology at Mahatma Gandhi Memorial Government Hospital, Trichy, for 6 months. Approval was obtained from the Institutional Ethics Committee, and informed consent was secured from all patients involved in the study.

Inclusion Criteria

Primigravid women aged 21 to 30 years were diagnosed with gestational diabetes mellitus (GDM) through a 75g glucose challenge test and those with blood glucose levels exceeding 140 mg/dL after a 2-hour oral glucose tolerance test were included as cases.

Exclusion Criteria

Patients with a known diagnosis of diabetes mellitus prior to pregnancy were excluded.

Methods

The study utilised various medical and laboratory equipment, including a proforma for data collection, anthropometric measurement tools (weighing machine, inch tape), clinical examination instruments (sphygmomanometer, fetoscope), biochemical analysis materials (glucose reagent, semi-automated analyser, DNA extraction kit, PCR-related reagents), and electrophoresis equipment (gel electrophoresis apparatus, thermocycler, GelDoc). The study included 33 women with Gestational Diabetes Mellitus (GDM) in their third trimester as Cases and 33 pregnant women with normal glucose tolerance as Controls.

The study involved detailed data collection, including personal, obstetric, and family history of diabetes, along with anthropometric measurements such as weight and height. A comprehensive clinical examination was performed, assessing vital signs like blood pressure, pulse, and respiratory rate, along with cardiovascular and abdominal evaluations. Blood sample collection and biochemical analysis were key components, where a Glucose Challenge Test (GCT) was conducted by administering 75g of glucose, followed by blood glucose measurement after two hours. Additionally, fasting and postprandial venous blood samples were analysed for glucose, urea, and creatinine levels using standard biochemical methods.

For genotypic analysis, DNA extraction was performed using the QIAGEN DNA extraction kit, followed by allele-specific PCR to detect the rs7903146C and rs7903146T alleles. DNA samples underwent PCR amplification, agarose gel electrophoresis, and visualisation under UV light to determine genotype. The key laboratory methods included glucose estimation using the Glucose Oxidase-Peroxidase Method (measured at 505 nm), urea estimation by the Urease-Glutamate Dehydrogenase Method (measured at 340 nm), and creatinine estimation via the Modified Jaffe's Method (measured at 505 nm). PCR amplification was performed with 32 cycles, involving denaturation, annealing at 58°C, and extension at 72°C, followed by gel electrophoresis.

The genotypic interpretation was based on the presence or absence of a 205 bp band in PCR products, classifying samples as homozygous CC, homozygous TT, or heterozygous CT.

Statistical Analysis

Statistical analyses were performed using the SPSS. Continuous variables, including biochemical

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parameters, were compared between GDM and normoglycemic pregnant women using the student's t-test. Categorical variables, such as genotype distributions between Cases and Controls, were analysed using the Chi-square (χ^2) test. Logistic regression analysis was conducted to estimate OR with 95% CI. Statistical significance was set at $p<0.05$, with $p<0.001$ considered highly significant.

RESULTS

The study included patients with GDM and a control group. The mean age of patients with GDM was 26.24±1.62 years, while the control group had a mean age of 24.09± 1.58 years. A significant correlation was observed, indicating that the risk of developing GDM increases with age ($p<0.0001$).

Regarding biochemical parameters, the mean blood urea levels in the GDM group were 29.33±4.37 mg/dL, compared to 30.24±5.17 mg/dL in Controls. There was no significant difference in blood urea levels between the two groups ($p=0.442$). However, the mean serum creatinine levels were significantly higher in the GDM group at 0.84± 0.16 mg/dL compared to 0.72±0.12 mg/dL in the Controls ($p=0.001$).

Blood pressure measurements indicated that the mean systolic blood pressure was significantly elevated in the GDM group (112.3±10.4 mmHg) compared to the control group (103±5.85 mmHg), with a significant (p-0.0001). Similarly, the mean diastolic blood pressure in the GDM group was 74.24±8.3 mmHg, while in the Controls, it was 67.27±6.7 mmHg, also showing a significant increase ($p=0.0001$).

The OGTT results revealed mean values of 164.3 mg/dL for Cases and 116.1 mg/dL for Controls, demonstrating a significant difference ($p<0.0001$).

Fasting blood glucose levels were markedly higher in the GDM group (130.9±12.15 mg/dL) compared to the control group (77.36±4.17 mg/dL), with an extremely significant ($p<0.0001$). Similarly, postprandial blood glucose levels were significantly elevated in patients with GDM (188.4±23.08 mg/dL) compared to Controls (108.7±6.52 mg/dL), also yielding a ($p<0.0001$) [Table 1].

Table 1: Comparison of clinical parameters.

		Mean±SD	P-value
Age (In years)	Cases	26.24±1.62	<0.0001
	Controls	24.09±1.58	
Urea (mg/dl)	Cases	29.33±4.37	0.442
	Controls	30.24±5.17	
Creatinine (mg/dl)	Cases	0.84±0.16	0.001
	Controls	0.72±0.12	
Systolic BP (mm/Hg)	Cases	112.3±10.4	0.0001
	Controls	103±5.85	
Diastolic BP (mm/Hg)	Cases	74.24±8.3	0.0004
	Controls	67.27±6.7	
OGTT	Cases	164.3±14.1	<0.0001
	Controls	116.1±10.6	
Fasting (mg/dl)	Cases	130.6±12.15	<0.0001
	Controls	77.36±4.17	
Postprandial (mg/dl)	Cases	188.4±23.08	<0.0001
	Controls	108.7±6.52	

In the study population, the genotype frequencies of the CC, CT, and TT alleles were observed to be 21 (32%), 27 (41%), and 18 (27%), indicating that the results are not significant (p-0.147). [Table 2].

Table 2: Hardy Weinberg equilibrium for TCF7L2 rs7903146 polymorphism

Genotypes	Observed	Expected	P-value
CC	21	18.03	0.147
CT	27	32.93	
TT	18	15.03	

The genotype distribution among patients with GDM and pregnant women with normal glucose tolerance was as follows: the CC genotype was observed in 2 (7%) of cases and 19 (57%) of controls. In comparison, the CT genotype was in 14 (42%) of cases and 13 (39%) of controls. Notably, the TT genotype was found in 17 (51%) of cases and only 1 (4%) of controls showing highly significant ($p<0.00001$).

In terms of allele distribution, the C allele was in 18 (27%) of cases compared to 51 (77%) in controls. In comparison, the T allele was in 48 (73%) of cases versus 15 (23%) in controls, showing highly significant ($p<0.00001$) [Table 3].

Table 3: Distribution of TCF7L2 gene at rs7903146

		Cases	Controls	P-value
Genotype	CC	2 (7%)	19 (57%)	<0.00001
	CT	14 (42%)	13 (39%)	
	TT	17 (51%)	1 (4%)	
Allele	C	18 (27%)	51 (77%)	<0.00001

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	T	48 (73%)	15 (23%)	

The mean GCT values in individuals with the C allele were 128.4±21.6 mg/dL, while those with the T allele had mean GCT values of 152.6±23.42 mg/dL. The presence of the T allele significantly increases the risk of developing GDM (p <0.0001) [Table 4].

Table 4: Comparison of GCT values

		Mean±SD	P-value
GCT	C	128.4±21.6	<0.0001
	T	152.6±23.42	

Logistic regression analysis was conducted, showing an OR of 9.0667 for GDM. This indicates that subjects carrying the T allele have a ninefold increased risk of developing GDM compared to those with the C allele. This association was deemed significant (p<0.0001). Therefore, identifying the presence of the T allele may serve as a predictive marker for the risk of developing GDM [Table 5].

Table 5: Logistic Regression of T allele for predicting GDM

		OR for GDM	95% CI for OR	P-value
Allele	T	9.0667	4.112 to 19.987	<0.0001
	C	1	-	

DISCUSSION

GDM has become a growing public health concern, with a notably higher risk in South Asian women compared to Western women. This study examined the genotype of pregnant women with GDM and those with normal glucose tolerance, focusing on the rs7903146 single nucleotide polymorphism.

Maternal age is a key risk factor for GDM, with our study showing a mean age of 26.24 years in women with GDM, significantly higher than the control group's mean of 24.1 years (p<0.0001). This aligns with previous studies, such as Vinoth et al., which found a strong association between maternal age over 25 and GDM, and research by Mghanga et al. and Bowker et al., which highlight the link between older age and increased GDM risk. Moreover, rising GDM rates are connected to changing maternal characteristics, including age and obesity.[10-12]

Our study also found a significant association between GDM and preeclampsia, with women with GDM showing elevated blood pressure readings: systolic (112.3 mmHg) and diastolic (103 mmHg), compared to 74.2 mmHg and 67.2 mmHg in women with normal glucose tolerance (p<0.0001). This is consistent with findings by Barden et al., who reported that women with GDM have a 10-50% increased risk of preeclampsia, compared to 5-7% in those without GDM.[13]

In our study, the significant increase in serum creatinine levels observed in patients with GDM compared to the control group (p=0.001) highlights the potential impact of glucose intolerance on renal function. Elevated serum creatinine is a recognised marker of renal impairment, indicating that hyperglycaemia may lead to nephron damage over time. Shah et al. and Wei et al. showed that prolonged hyperglycaemia in diabetic patients correlates with increased serum urea and creatinine levels, suggesting a deterioration in renal function.[14,15] Furthermore, Shah et al. and Kontomanolis et al. reported that the presence of renal function abnormalities in women with GDM necessitates routine screening, as early detection can facilitate timely interventions to mitigate the risk of further renal complications.[14,16]

Our study indicates a significant association between the rs7903146 C/T SNP and GDM, with a notably higher prevalence of the homozygous TT allele (51%) in women with GDM compared to just 4% in those with normal glucose tolerance (p<0.00001). This aligned with Cruciat, Lin et al., and Barabash et al., who recognise the T allele of rs7903146 as a risk factor for GDM, suggesting that individuals carrying this allele may experience impaired insulin secretion and increased insulin resistance.[17-19]

The T allele has been linked to a higher risk of developing T2DM, which is often a precursor to GDM, indicating a potential genetic predisposition.[18,20,21] Furthermore, Cruciat and Barabash et al. have shown that the presence of the T allele is associated with inadequate insulin secretion, necessitating insulin treatment in GDM patients.[17,19]

We found A significant reduction in glucose tolerance associated with the presence of the T allele, as evidenced by the mean GCT values of 152.6 mg/dl in women with the T allele compared to 128.4 mg/dl in those without (p<0.00001), underscores the genetic influence on glucose metabolism during pregnancy. This finding is reliable with Freathy et al., who have identified specific genetic polymorphisms, such as those in the TCF7L2 and GCK genes, which predispose individuals to impaired glucose tolerance and GDM.22 The strong association between the T allele and elevated GCT values suggests that genetic factors play a critical role in the pathophysiology of GDM, potentially through mechanisms involving insulin resistance and beta-cell dysfunction.[23] These results show the importance of genetic screening in pregnant women to better predict and manage the risk of GDM.

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The genotypic frequencies of CC, CT, and TT alleles are 32%, 41% & 27%, respectively. This obeys Herdy Weinberg's law, and the genotypic distribution was in equilibrium (p=0.147). The logistic regression analysis conducted in our study revealed that the presence of the T allele significantly increases the risk of developing GDM. This aligned with Huerta et al., showing an odds ratio of 2.07 at a 95% CI.[24] These results strengthen the importance of incorporating genetic screening into routine prenatal care to better manage and mitigate the risks associated with GDM.

CONCLUSION

The presence of the T allele associated with the rs7903146 single nucleotide polymorphism in the TCF7L2 gene significantly increases the risk of developing GDM. Genotyping women for this polymorphism can facilitate early screening for GDM, which is crucial for improving obstetric outcomes. Early detection and intervention can lead to better management of GDM, ultimately enhancing maternal and foetal health. Additionally, a deeper understanding of the genetic basis of GDM can inform the development of more effective disease intervention strategies.

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