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# Relationship of Transcription Factor 7-Like-2 (TCF7L2) Gene Polymorphism rs12255372 and Glycemic Control in Type 2 Diabetes Mellitus

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## ABSTRACT

**Background:** Diabetes mellitus is a collection of metabolic illnesses defined by hyperglycemia caused by an insulin secretion deficiency and/or enhanced insulin cellular resistance. TCF7L2 (Transcription Factor 7-like 2) is a transcription factor that has been linked to blood glucose control. **Objective:** Our study aimed to assess the association of TCF7L2 rs12255372 gene polymorphism with T2DM and to evaluate the impact of TCF7L2 rs12255372 polymorphism on glycemic control in type 2 diabetic patients. **Patients and Methods:** The study was conducted on forty-seven (47) diabetic patients who were collected from the out-patient clinic and in-patient of Department of Internal Medicine and Endocrinology at Ain Shams University Hospitals; in addition, twenty-three (23) age- and sex- matched healthy subjects taken as healthy control group. Assay of TCF7L2 rs12255372 gene polymorphism was performed by real-time PCR analysis. **Results:** The study had showed that there was no significant association between TCF7L2 rs12255372 G>T gene polymorphism and T2DM. However, there was significant association between the concordance of this polymorphism and higher level of post treatment HbA1c and higher level of serum lipids among patients' group. **Conclusion:** TCF7L2 rs12255372 G>T gene polymorphism is associated with poor therapeutic response to oral antidiabetic agents and occurrence of dyslipidemia.

**Keywords:** Gene Polymorphism rs12255372, Poor glycaemic control, Real-time PCR, Transcription Factor 7-Like-2 (TCF7L2), Type 2 Diabetes Mellitus.

## INTRODUCTION

Diabetes mellitus (DM) is a collection of metabolic illnesses defined by hyperglycemia caused by an insulin secretion deficiency and/or enhanced insulin cellular resistance [(1)]. Long-term organ damage is caused by the metabolic abnormalities of diabetes and chronic hyperglycemia, which affect the eyes, kidneys, neurons, and vascular system. The great majority of diabetes patients fall into one of two main etiopathogenetic groups, with 90% having type 2 diabetes mellitus (T2DM) and only 10% having type 1 diabetes [(2)].

In T2D, the most prevalent type of diabetes, there is a combination of insulin resistance and an insufficient compensatory insulin secretory response. The underlying environmental variables are thought to produce T2DM only in the presence of genetic vulnerability [(3)]. TCF7L2 (Transcription Factor 7-like 2) is a transcription factor that has been linked to blood glucose control [(3)].

The TCF7L2 pleomorphic gene, which is found on chromosome 10q25.3, encodes the TCF7L2 protein. It's a part of the Wnt signaling pathway, which is important for beta-cell proliferation and insulin release. It affects the manufacture of glucagon-like peptide 1 (GLP-1) in intestinal cells, which are critical for blood glucose regulation, and it's been suggested that TCF7L2 gene variations may influence T2D vulnerability by modifying GLP-1 levels indirectly [(4)].

Our study aimed to assess the association of TCF7L2 rs12255372 gene polymorphism with T2DM and to evaluate the impact of TCF7L2 rs12255372 polymorphism on glycemic control in type 2 diabetic patients.

## PATIENTS AND METHODS

This study is a case-control study, conducted at Clinical Pathology and Internal Medicine Departments, Ain Shams University Hospitals, from December 2018 till December 2019. Subjects included in the study were two groups; **Group I: diabetic patients (n=47):** T2DM patients diagnosed according to **the American Diabetes Association [(5)]** criteria.

The response to treatment with sulfonylurea was defined by three criteria. Criterion "1" was a decrease of recent HbA1c level (e.g. after 3-months therapy) to be less than 7%. Criterion "2" was a decrease of $\geq 0.5\%$ in the recent HbA1c level ($\Delta HbA1c \geq 0.5\%$). Criterion "3" was a decrease of $\geq 1\%$ in the recent HbA1c level ($\Delta HbA1c \geq 1\%$) [(6, 7)].

**Group II: Control Group (n=23):** age- and sex- matched healthy subjects. **Exclusion criteria**: type 1 diabetes mellitus, any other endocrinal disorders, chronic kidney or liver disease, alcoholism, and subjects taking medications as steroids, beta-blocking drugs, or women taking oral contraceptives.

All subjects enrolled in this study were subjected to complete history taking, careful clinical examination, laboratory tests including HbA1c, lipid profile; TC, HDL-C, LDL-C and TG and determination of TCF7L2 gene polymorphism by real-time quantitative polymerase chain reaction (RT-PCR).

### Analytical Method:

Serum lipid profile was assayed by enzymatic colorimetric method, glycated hemoglobin (HbA1c) was assayed by turbidimetric inhibition immunoassay and both were done using Roche/Hitachi Cobas® c501 System (Roche Diagnostics International Ltd., Switzerland). DNA was extracted from whole blood by using DNA purification mini kit; ThermoFisher® (ThermoFisher Scientific, USA) and TaqMan®



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genotyping master mix (Applied Biosystems, USA) was used.

The TCF7L2 rs12255372(G/T) SNP was detected by RT-PCR using the genotyping assay kit supplied by ThermoFisher® (ThermoFisher Scientific, USA) containing sequence-specific forward and reverse primers and two fluorescent (VIC/FAM) labeled TaqMan probes for distinguishing between the two alleles.

**Ethical consent:**

**An approval of the study was obtained from Ain Shams University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study.**

**This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

***Statistical analysis***

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Wilcoxon's rank sum test was used in Comparing between two independent mean groups. Meanwhile, Multiple-group comparisons were done using Kruskal-Wallis test. P value < 0.05 was considered significant.

**RESULTS**

The study conducted on 47 diabetic patients, included 34 (72.3%) females. Baseline HbA1c mean (±SD) was 7.5% (±1.6). Descriptive and comparative statistics of the demographic data and the various studied parameters between diabetic patients and healthy controls are shown in table (1).

**Table (1):** Descriptive and Comparative Statistics of the Demographic Data and the Various Studied Parameters between Diabetic Patients (Group I) and Healthy Controls (Group II)

| Parameter | Diabetic Patients (Group I) (n=47) | Healthy Controls (Group II) (n=23) | $Z^*/X^2$ | P- value | Significance |
|---|---|---|---|---|---|
| | n (%)/ Mean±SD | n (%)/ Mean±SD | | | |
| **Age (years)- Median (IQR)** | 60 (53 – 66) | 60 (44 – 63) | -0.833* | >0.05 | NS |
| **Sex**<br>Female gender<br>Male gender | <br>34 (72.3%)<br>13 (27.7%) | <br>14 (60.9%)<br>9 (39.1%) | 0.943 | >0.05 | NS |
| **BMI ($Kg/m^2$) Median (IQR)** | 27.3 (25.3 – 28.6) | 24.8 (26.3 – 27.7) | -0.419* | >0.05 | NS |
| **Baseline HbA1c (%)** | 7.5±1.61 | 5.4 ±1.11 | -6.739* | <0.01 | HS |
| **Total Cholesterol (mg/dL)** | 201 ±41.89 | 180 ± 37.21 | -0.883* | >0.05 | NS |
| **Triglycerides (mg/dL)** | 159 ±31.41 | 139 ± 28.91 | -1.220* | >0.05 | NS |
| **HDL-C (mg/dL)** | 45 ± 9.81 | 62 ± 13.31 | -2.154* | <0.05 | S |
| **LDL-C (mg/dL)** | 125 ± 24.61 | 92 ± 18.23 | -1.526* | >0.05 | NS |

BMI, body mass index; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NS: Non-significant difference; S: Significant difference; HS: Highly-significant difference. $X^2$: Chi-Square Test; Z: Wilcoxon`s Rank-Sum Test.

There was insignificant difference between both groups as regard genotypic and allele (Table 2)

**Table (2):** Descriptive and Comparative Statistics of the Genotypic and Allelic Frequency of TCF7L2 Gene G>T rs12255372 Polymorphism in Diabetic Patients (Group I) and Healthy Controls (Group II)

| Parameter | Diabetic patients (Group I), n=47 | Healthy Controls (Group II), n=23 | $X^2$ | P-value | Significance |
|---|---|---|---|---|---|
| | n (%) | n (%) | | | |
| **Genotypes** | | | | | |
| GG | 19.0 (40.4%) | 12.0 (52.2%) | | | |
| GT | 22.0 (46.8%) | 9.0 (39.1%) | 0.911 | >0.05 | NS |
| TT | 6.0 (12.8%) | 2.0 (8.7%) | | | |
| **Allele Distribution** | | | | | |
| G | 60.0 (63.8%) | 33.0 (71.7%) | 0.866 | >0.05 | NS |
| T | 34.0 (36.2%) | 13.0 (28.3%) | | | |

G, guanine; T, thiamine. NS: Non-significant difference; $X^2$: Chi-Square Test.

A highly statistically significant difference was detected between various genotypes as regard recent HbA1c level (after 3-months therapy) being higher with GT and TT genotypes mean as compared to GG genotype mean.

Similarly serum levels total cholesterol and triglycerides and LDL were significantly higher with GT and TT genotypes compared to GG genotype as shown in table 3.

**Table (3):** Comparative Statistics between the Different TCF7L2 Gene Genotypes among Diabetic Patients as Regards the Different Demographic and Laboratory Findings

| Parameter | GG (n=19) | GT (n=22) | TT (n=6) | $H^*/X^2$ | P-value | Sig. |
|---|---|---|---|---|---|---|
| | n (%)/ Mean±SD | n (%)/ Mean±SD | n (%)/ Mean±SD | | | |
| **Age (years) Median (IQR)** | 61.0 (57 – 68) | 57.0 (52 – 63) | 67.5 (50 – 70) | 3.695* | >0.05 | NS |
| **Sex** | | | | | | |
| Females | 15.0 (78.9%) | 14.0 (63.6%) | 5.0 (83.3%) | 1.610 | >0.05 | NS |
| Males | 4.0 (21.1%) | 8.0 (36.4%) | 1.0 (16.7%) | | | |
| **BMI ($Kg/m^2$) median (IQR)** | 27.7 (25.7 – 28.8) | 26.8 (25 – 27.7) | 28.1 (23.8 – 28.6) | 2.344* | >0.05 | NS |
| **Disease duration (years)** | 7.0 ± 1.57 | 6.5 ± 1.14 | 4.5 ±0.92 | 1.072* | >0.05 | NS |
| **Baseline HbA1c level (%)** | 8.2 ± 1.91 | 8.1 ±1.41 | 8.1 ±1.22 | 0.043* | >0.05 | NS |
| **Recent HbA1c level (%)** | 7.0 ±1.02 | 8.1 ±1.22 | 8.3 ± 2.11 | 20.723* | <0.01 | HS |
| **Total Cholesterol (mg/dl)** | 170.0 ± 39.31 | 206.5 ± 46.35 | 228.0 ± 48.64 | 38.264* | <0.01 | HS |
| **Triglycerides (mg/dl)** | 100.0 ± 18.91 | 160.0 ± 31.51 | 203.5 ±44.16 | 3.041* | <0.01 | HS |
| **HDL-C (mg/dl)** | 66.0 ±13.52 | 42.5 ± 8.51 | 30.5 ±6.32 | 34.987* | <0.01 | HS |
| **LDL-C (mg/dl)** | 84.0 ±17.52 | 132.0 ± 29.31 | 156.0 ±34.52 | 38.198* | <0.01 | HS |

BMI, body mass index; HDL-C, high density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low density lipoprotein cholesterol
NS: Non-significant difference; HS: Highly-significant difference; $X^2$: Chi-Square Test; H**:** Kruskal-Wallis Test.

The reduction of the recent HbA1c level to be less than 7%, the ΔHbA1c level, were highly significantly increased in GG genotypes as compared to GT and TT genotypes. Furthermore, the reduction of ΔHbA1c ≥0.5% and ≥1% following three months treatment with sulfonylurea were highly significantly increased in GG genotypes as compared to GT and TT genotypes as shown in table (4). Similarly, the same results were detected with G and T alleles as shown in table (5).

**Table (4):** Descriptive and Comparative Statistics between the Different TCF7L2 Gene Genotypes among Diabetic Patients as Regards Recent HbA1c Level and ΔHbA1c

| Parameter | GG (n=19) | GT (n=22) | TT (n=6) | $H^*/X^2$ | P-value | Sig. |
|---|---|---|---|---|---|---|
| | n (%)/ Mean±SD | n (%)/ Mean±SD | n (%)/ Mean±SD | | | |
| **Recent HbA1c level** | | | | | | |
| Less than 7% | 12.0 (63.2%) | 4.0 (18.2%) | 0.0 (0.0%) | 0.002 | <0.01 | HS |
| More than 7% | 7.0 (36.8%) | 18.0 (81.8%) | 6.0 (100.0%) | | | |
| **ΔHbA1c (%)** | 1.1 ±0.18 | 0.3 ±0.061 | 0.1 ±0.021 | 36.269* | <0.01 | HS |
| **ΔHbA1c (%)**: | | | | | | |
| ≥ 0.5 % decrease in HbA1c | 19.0 (100%) | 7.0 (31.8%) | 0.0 (0.0%) | 27.691 | <0.01 | HS |
| ≥ 1.0**%** decrease in HbA1c | 12.0 (63.2%) | 0.0 (0.0%) | 0.0 (0.0%) | 23.747 | <0.01 | |

ΔHbA1c: the difference between recent HbA1c (after 3-months therapy) and baseline HbA1c.
HS: Highly-significant difference; $\mathbf{X^2}$: Chi-Square Test.; $H^*$: Kruskal-Wallis Test.

**Table (5):** Descriptive and Comparative Statistics of the Various Studied Parameters between G and T alleles of TCF7L2 Gene among Diabetic Patients

| Parameter | G allele (n = 60) | T allele (n = 34) | $Z^*/X^2$ | P value | Significance |
|---|---|---|---|---|---|
| | n (%)/ Mean±SD | n (%)/ Mean±SD | | | |
| **Baseline HbA1c level (%)** | 8.2 ±1.82 | 8.3 ±1.91 | 0.816* | >0.05 | NS |
| **Recent HbA1c level (%)** | 7.3 ±1.41 | 8.3 ±1.72 | -3.173* | <0.01 | HS |
| **Recent HbA1c level** | | | | | |
| Less than 7% | 27.0 (45.8%) | 5.0 (14.3%) | 9.649 | <0.01 | HS |
| More than 7% | 32.0 (54.2%) | 30.0 (85.7%) | | | |
| **ΔHbA1c level (%)** | 0.9 ±0.21 | 0.1 ±0.017 | -4.111* | <0.01 | HS |
| **ΔHbA1c (%):** | | | | | |
| **≥ 0.5% decrease in HbA1c** | 24.0 (75.0%) | 3.0 (20.0%) | 12.638 | <0.01 | HS |
| **≥ 1.0% decrease in HbA1c** | 13.0 (40.6) | 0.0 (0.0%) | 8.424 | <0.01 | HS |
| **Total Cholesterol (mg/dL)** | 179 ±37.1 | 209 ±47.51 | 5.773* | <0.01 | HS |
| **Triglycerides (mg/dL)** | 130 ± 29.32 | 165 ± 36.21 | 5.430* | <0.01 | HS |
| **HDL-C (mg/dL)** | 61 ± 13.51 | 39 ±8.61 | 5.693* | <0.01 | HS |
| **LDL-C (mg/dL)** | 93 ± 19.32 | 136 ±28.12 | 5.830* | <0.01 | HS |

ΔHbA1c: the difference between recent HbA1c (after 3-months therapy) and baseline HbA1c.
HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol;
NS: Non-significant difference; HS: Highly-significant difference; -$X^2$: Chi-Square Test; Z: Wilcoxon`s Rank-Sum Test.

When comparing wild type group to either heterozygous mutant (GT) or homozygous mutant (TT) groups, recent HbA1c level was found to be highly significantly increased in GT and TT genotypes when compared to GG genotype. In contrast, ΔHbA1c and ΔHbA1c ≥0.5% and ≥1% following three months treatment with sulfonylurea were highly significantly increased in GG genotypes as compared to GT and TT genotypes as shown in table (6).

**Table (6):** Descriptive and Comparative Statistics between The GG versus GT Genotypes and GG versus TT Genotypes of TCF7L2 Gene among Diabetic Patients as Regards Baseline HbA1c Level, Recent HbA1c Level and ΔHbA1c

| Parameter | Baseline HbA1c level | Recent HbA1c level | ΔHbA1c | ≥ 0.5% decrease in HbA1c | ≥1.0% decrease in HbA1c |
|---|---|---|---|---|---|
| | Mean±SD | Mean±SD | Mean±SD | n (%) | n (%) |
| **GG** | 8.2 ± 1.71 | 7.0 ± 1.32 | 1.1 ±0.15 | 19.0 (100.0%) | 12.0 (63.2%) |
| **GT** | 8.1 ±1.51 | 8.1 ± 1.37 | 0. 3 ±0.06 | 7.0 (31.82%) | 0.0 (0.0%) |
| **P-value** | >0.05 | <0.01 | <0.01 | <0.01 | <0.01 |
| **$Z^*/X^2$** | 3.861* | 0.157* | 5.382* | 20.428 | 19.644 |
| **Significance** | NS | HS | HS | HS | HS |
| **GG** | 8.2 ±1.90 | 7.0 ±1.61 | 1.1 ±0.17 | 19.0 (73.21%) | 12.0 (100.0%) |
| **TT** | 8.1 ±1.61 | 8.3 ±1.42 | 0.1 ±0.02 | 0.0 (0.0%) | 0.0 (0.0%) |
| **P-value** | >0.05 | <0.01 | <0.01 | <0.01 | <0.01 |
| **$Z^*/X^2$** | 3.670* | 0.000* | 3.639* | 25.000 | 7.287 |
| **Significance** | NS | HS | HS | HS | HS |

ΔHbA1c: the difference between recent HbA1c (after 3-months therapy) and baseline HbA1c. NS: Non-significant difference; HS: Highly-significant difference; $X^2$: Chi-Square Test; Z: Wilcoxon`s Rank-Sum Test.

## DISCUSSION

The discovery by **Grant *et al.* [8]** that the genetic factors could play an important role in the development of T2DM in an Icelandic case-control study has launched a new direction in diabetes research. After that, many studies have investigated the relation between the susceptible genes like transcription factor 7-like 2 (TCF7L2) gene and other genes in the development of T2DM. **Potapov *et al.* [9] and Faranak *et al.* [10]** found that there is a significant relation between TCF7L2 rs12255372 gene polymorphism and the risk of developing T2DM in Russian and Iranian population. Furthermore, these results were confirmed in other ethnic groups through multiple genome-wide association studies (GWAS).

The underlying mechanism of action of TCF7L2 polymorphism in the etiology of T2D is still uncertain. All the identified SNPs of TCF7L2 are located so far in the intronic regions. So that it is necessary to clarify how the intronic variants affect TCF7L2 gene expression. In this context, **Srinivasan *et al.* [11]** found that TCF7L2 rs12255372 T allele

carriers exhibited a significant elevation of TCF7L2 mRNA expression in human pancreatic islets, which was associated with impaired insulin secretion, and enhanced rates of hepatic glucose production. Also, it has an indirect effect by altering GLP-1 levels, whose gene is transcriptionally regulated by this TCF.

The present study aimed to investigate the potential association of TCF7L2 rs12255372 G>T gene polymorphism in patients with T2DM and to evaluate the impact of TCF7L2 rs12255372 polymorphism on glycemic control in diabetic patients. This study was conducted on forty-seven (47) diabetic patients in addition to twenty-three (23) age- and sex-matched healthy subjects taken as a healthy control group.

Data of the present study revealed that the frequencies of (GG) wild genotype and the (G) allele were higher in healthy controls when compared to diabetic patients. On the other hand, the frequencies of heterozygous genotypes (GT) and homozygous genotypes (TT), as well as the (T) allele, were higher among diabetic patients as compared to healthy controls. However, a non-significant difference was revealed between both studied groups as regards genotypic distribution and allelic frequency.

Our results were in accordance with the studies performed in Iran by **Pourahmadi *et al.*** [12], as well as in USA by **Moran *et al.*** [13] whose results showed a non-significant association between TCF7L2 rs12255372 gene polymorphism with T2DM. Similar study conducted among the Turkish population by **Demirsoy *et al.*** [14] and the Balinese population by **Saraswati *et al.*** [15] showed the same results. These results were further supported by a study performed among the Egyptian population by **Mandour *et al.*** [16], where the T allele was not found to be associated with T2DM, representing 51.7% of healthy controls and 39.2% of the diabetic patients, while the G allele represents 48.3% of healthy controls and 60.8% of the diabetic patients.

However, other studies replicated among various ethnicities showed that the presence of the T allele was linked with an increased risk of T2D. In the Chinese population, **Wu *et al.*** [17] found a statistical significance of the presence of the T allele with T2D. **Alnaggar *et al.*** [18] studied TCF7L2 polymorphism among the Egyptian population and revealed that there was a statistically significant association between TCF7L2 gene rs12255372 G>T polymorphism and the development of T2D. **Hassan *et al.*** [19] in the Iraq population and **Zhou *et al.*** [20] in the Korean population came to the exact conclusion of the significant association of the TCF7L2 rs12255372 G>T polymorphism and T2D susceptibility. A meta-analysis conducted by **Li *et al.*** [21] on subjects from different ethnic groups, showed a positive correlation of the TCF7L2 rs12255372 G>T with T2D and this was further confirmed by another meta-analysis study by **Xia and Ma** [22] where they observed a significant reduction in heterogeneities in both Asians and Caucasians, which suggests that the genetic association between TCF7L2 gene and T2D may be ethnic-specific.

The present work studied also the relationship between TCF7L2 gene rs12255372 G>T polymorphism genotypes and the different demographic, clinical, and laboratory findings among diabetic patients. The TCF7L2 gene genotypes didn`t show any statistically significant variation in relation to age, sex, BMI and disease duration. These results were in agreement with the results reported by **Nanfa *et al.*** [23] who conducted a study on the Cameroonian population that revealed a non-statistically significant difference between different genotypes of TCF7L2 gene rs12255372 G>T polymorphism among diabetic patients as regards the same studied variables.

**Palizban *et al.*** [24] stated that TCF7L2 protein plays a critical role in the Wnt signaling pathway through regulation of adipocytes differentiation and adipogenesis, therefore impaired Wnt signaling pathway is associated with a minor increase in TCF7L2 expression in adipose tissue resulting in unfavorable dyslipidemia, which is confirmed in our study showing a highly significant increase in serum total cholesterol, triglycerides, and LDL-C in homozygous genotypes (TT) compared to heterozygous genotypes (GT) and wild genotypes (GG) and in T allele than G allele. While there was a significant increase in HDL-C in wild genotypes (GG) than heterozygous genotypes (GT) and homozygous genotypes (TT) and in G allele than T allele. This was explained by **Zhou *et al.*** [25] whose results confirmed that impaired Wnt signaling pathway is associated with the generation of ectopic fat, insulin resistance with a subsequent elevation of plasma level of lipids.

Same results were recorded by **Chiang *et al.*** [26], who stated that TCF7L2 protein is expressed in the adipocytes and its expression can be down regulated by insulin. In insulin-resistant human subjects, there is an increase in TCF7L2 protein level in subcutaneous adipose tissue leading to unfavorable dyslipidemia.

Similarly **Blanco *et al.*** [27] conducted a study among Mexican population revealing that the TCF7L2 rs12255372 TT genotype was associated with higher levels of LDL-C, as compared with the GG genotype.

On the other hand, **Meshra *et al.*** [28] **and Kaur *et al.*** [29] conducted a study among North Indians demonstrated that there is no link between TCF7L2 rs12255372 G>T polymorphism and dyslipidemia. These different results could be attributed to the ethnic differences affecting the way by which TCF7L2 polymorphism affects lipid metabolism and/or due to the lower age of their study subjects and lastly the smaller number of their study subjects when compared to other studies.

In the treatment of type 2 diabetes, glycemic control is the primary objective. Despite the availability of several anti-diabetic medicines and guidelines, over half of diabetes patients do not achieve their treatment goals and incur problems. As a result, identifying

indicators of anti-diabetic medication response is critical for therapy tailoring [30].

Recent studies focusing on the association between TCF7L2 polymorphism and glycemic control in diabetic patients confirmed that rs7903146 C/T is related to the efficacy of gliclazide therapy. Thus far, few studies have reported data for the relationship between TCF7L2 rs12255372 G>T and glycemic control. Therefore, a corner stone in our study was to identify the relationship between TCF7L2 rs12255372 polymorphism and the therapeutic effect of sulfonylurea in our studied population [30].

Our study revealed that TCF7L2 rs12255372 GG patients exhibited a significant improvement in recent HbA1c level to be less than 7% following three months treatment with sulfonylurea and subsequently a better ΔHbA1c than those of GT and TT patients. However, we failed to detect a change in the baseline HbA1c level in comparing between the different gene genotypes. In accordance with our findings **Dhawan and Padh**[31] **and Chiara *et al.*** [32] highlighted the clinical value of TCF7L2 gene rs12255372 G>T polymorphism in the therapeutic response to hypoglycemic agents revealing that TT genotype exhibited a greater increase in recent HbA1c level following three months treatment with sulfonylurea than GG genotype.

Moreover, we recorded a highly significant difference among the different TCF7L2 genotypes in relation to ΔHbA1c after three months treatment with sulfonylurea. A highly significant reduction in HbA1c ≥ 0.5 was observed in GG patients as compared to GT and TT patients. Additionally, a highly significant reduction in HbA1c ≥ 1% was observed in GG patients, while no reduction in HbA1c ≥ 1% was observed in both GT and TT patients.

Furthermore, we found that T allele carriers consistently exhibited a higher recent HbA1c level of more than 7%, a lower reduction in HbA1c level ≥ 0.5% and no reduction in HbA1c level ≥ 1%. While G allele carriers exhibited a lower recent HbA1c level of less than 7 %, a higher reduction in HbA1c level ≥0.5% and a higher reduction in HbA1c level ≥ 1%, revealing a highly significant association between the concordance of risk T allele and impaired response to oral hypoglycemic therapy.

Based on all these findings, we hypothesized that rs12255372 polymorphism of TCF7L2 gene might be associated with the individual variations in response to oral hypoglycemic therapy. Specifically, the rs12255372 G allele could improve the response to sulfonylurea with respect to stimulation of insulin secretion and lowering glucose levels; however, the underlying mechanism remains to be elucidated. This was supported by **Pearson *et al.***[6] who hypothesized that rs12255372 T allele expression has been found to be associated with impaired insulin secretion and gastrointestinal incretins, leading to decreased insulin sensitivity and augments incretin resistance which affects the response to oral hypoglycemic agents.

A recent study conducted by **Holstein *et al.*** [33] confirmed that the risk T allele carriers of T2D have an altered hypoglycemic response to oral hypoglycemic treatment resulting in earlier secondary failure where the T allele represents about 36% of patients who failed to respond to sulfonylurea and about 26% in the control group.

However, in contrast to our study, **Martínez *et al.*** [34] revealed that there is no significant association between TCF7L2 rs12255372 G>T gene polymorphism and response to oral hypoglycemic therapy.

The discrepancy in the results seen in the different association studies may be due to different pharmacodynamics characteristics of oral antidiabetic agents. It would be expected that a specific, biologically supported interaction between gene and drug would be conserved across different ethnicities. Also, this could be due to the differences in several genetic, environmental factors, ethnic stratification, and variations in study design and sample size [32].

## CONCLUSION

TCF7L2 rs12255372 G>T gene polymorphism is associated with poor therapeutic response to oral antidiabetic agents and occurrence of dyslipidemia.

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**Author contribution:** Authors contributed equally in the study.

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