Subject Area:

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Transcription factor 7-like 2 rs7903146 polymorphism and therapeutic response to sulfonylureas in patients with type 2 diabetes

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Abstract

Background
Transcription factor 7-like 2 (TCF7L2) variations were related to a modified hypoglycemic reaction to sulfonylureas (SUs) in patients with type 2 diabetes mellitus (T2D).

Aim
The aim of the present work was to show the relationship between TCF7L2 rs7903146 polymorphism and the hypoglycemic reaction to SUs in T2D patients.

Patients and methods
We enlisted 54 already diagnosed T2D patients who were treated with SUs. Utilizing secondary SU treatment failure, defined as glycated hemoglobin more than 7%, they were divided into two groups: responders and nonresponders. We genotyped the TCF7L2 rs7903146 single-nucleotide polymorphism by utilizing TaqMan allelic discrimination assay-based real-time PCR.

Results
A relationship between the TCF7L2 rs7903146 genotypes TT, CC, CT and therapeutic response to SUs in T2D patients was assessed. In the nonresponders group, the most frequent genotype was the TT ($P=0.038$) and the most frequent allele was T ($P=0.034$). Binary logistic regression analysis showed predictors to failure of SUs treatment, providing that TCF7L2 rs7903146 was the significant factor. The TT genotype showed a statistically significant association with nonresponse to SUs, about 4.6 times more than the rest of the genotypes (CC or CT) [$P=0.029$; odds ratio (OR), 4.643; 95% confidence interval, 1.175–18.355]. The distribution of TCF7L2 rs7903146 alleles was found to be statistically significant, with the OR indicating that the nonresponder status was 2.291 times greater for T allele as opposed to C allele ($P=0.034$; OR, 2.29; 95% confidence interval, 1.059–4.959). The other factors as sex, age, and duration of the disease were not statistically significant ($P=0.334$, 0.267, and 0.242, respectively).

Conclusion
TCF7L2 rs7903146 variant was associated with therapeutic response to SUs and it was observed that the most frequent allele in the nonresponders group was the T allele, whereas the most frequent allele in the responders group was the C allele.

Keywords: Sulfonylureas, transcription factor 7-like 2 variants, type 2 diabetes

Introduction

Egypt is the nation with the ninth biggest population of diabetics in the world. According to International Diabetes Federation, there were 8.2 million diabetic patients in Egypt in 2017 [1]. It is expected that this number will bounce up to 13.1 million by

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2035 [2]. Among all diabetic cases, ~90% are type 2 diabetes mellitus (T2D) [3]. This is owing to many causes; lifestyle and genetics are the most essential ones [4,5]. Current treatments for T2D included sulfonylureas (SUs), which are standard among most of the oral antidiabetics, and are frequently utilized [6] (e.g. glyburide, glipizide, and glimepiride). They are insulin secretagogues that invigorate insulin discharge from pancreatic β-cells. They may likewise upgrade peripheral sensitivity to insulin secondary to an increase in insulin receptors or to changes in the events following insulin-receptor binding [7]. SUs first bind to the high-affinity SU receptor 1, which together with the potassium pore-forming inward-rectifier (Kir6.2) subunits make up the pancreatic β-cell ATP-sensitive potassium channel. This cooperation shuts the K^+ channel which hinders potassium efflux and depolarizes the plasma membrane, prompting an opening of voltage-gated calcium channels. Calcium influx, and a corresponding increase in intracellular calcium levels, causes release of insulin from the β-cells [8]. A large-scale United Kingdom Prospective Diabetes study demonstrated that T2D patients might achieve a state where the SU could not convey blood glucose to the objective range, known as 'SU failure' [9], which is characterized by an inability to keep up glycated hemoglobin (HbA1c) beneath 7% following SU treatment [10]. Approximately 10–20% of patients fail to come to the planned glycemic treatment objectives following the start of SU treatment (i.e. primary SU failure) [11]. For patients who had a good starting reaction to treatment, the rate of secondary SU failure was ~5–7% every year [12].

Transcription factor 7-like 2 (TCF7L2) gene, a key transcription factor, is a member of the T-cell factor family affecting the Wnt signaling pathways, which are signal transduction pathways made of proteins that pass signals into a cell through cell surface receptors, and are associated with glucose homeostasis, lipid metabolism, proliferation, and function of pancreatic β-cells, and the formation of glucagon-like peptide 1 [13]. Clinical studies proposed that TCF7L2 gene polymorphisms influenced the ability of pancreatic β-cells to discharge insulin instead of increasing insulin resistance [14,15], and the exact defect could possibly be related to impaired β-cell proinsulin-processing [16]. This was additionally enforced by recommending a role of TCF7L2 in β-cell differentiation [17].

PATIENTS AND METHODS

Study design

Fifty four patients already diagnosed as T2D cases, according to the diagnostic criteria of the American Diabetes Association 2016 [18], aged between 40 and 65 years and getting SUs treatment were enrolled at the outpatient clinics of the National Institute of Diabetes and Endocrinology, Cairo, Egypt, between January 2017 and December 2017. Utilizing HbA1c levels as a phenotypic marker, there were 27 patients (23 females and four males) reacting to SUs (responders) with HbA1c less than 7.0%, and 27 patients (21 females and six males) not reacting to SUs (nonresponders) with HbA1c more than 7.0%. Exclusion criteria were type 1 diabetic patients, renal impairment, liver

dysfunctions, anemia, and hemoglobinopathies. Written consent was gotten from enrolled patients before taking samples and subsequent to clarifying investigations done for them. The protocol was affirmed by the General Organization of Teaching Hospitals and Institutes research ethics committee.

Sample collection and laboratory analysis

For sample collection, patients were instructed to have no caloric intake for 12–14 h. From every patient, venous blood was drawn into four sample tubes: 2 ml in a sterile EDTA vacutainer (stored at − 80°C) for real-time PCR assay; 4 ml in a serum separator tube for blood chemistry, assaying fasting blood glucose (FBG), lipid profile [total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL)], liver enzymes [alanine transaminase (ALT) and aspartate transaminase (AST)], and creatinine levels by utilizing ARCHI TECT 8000 science analyzer (Abbott, Lake Bluff, Illinois, Chicago, USA); and the last 2 ml in another EDTA vacutainer for HbA1c analysis utilizing D-10 HPLC ion exchange chromatography (Bio-Rad, USA).

Genetic analysis of single-nucleotide polymorphisms

Human genomic DNA extraction was done as follows: DNA was separated from 200 ml peripheral blood leukocytes (QIAamp DNA blood pack; QIAGEN, Hilden, Germany), as indicated by the manufacturer's protocol. The quantity and quality of DNA was estimated by Nano-Drop ND-1000 spectrophotometer (Thermo Scientific, Waltham, Massachusetts, USA) [19].

Genotyping of TCF7L2 rs7903146 single-nucleotide polymorphism (SNP) was done utilizing a TaqMan allelic discrimination assay with allele-specific designed fluorescent probes, acquired from Applied Biosystems (Foster City, California, USA). The assay was led by utilizing an ABI Prism 7500 Sequence Detection System (Applied Biosystems), with optimized thermal cycle (95°C for 10 min, followed by 40 cycles of 95°C for 15 s and 60°C for 1 min). The sequences of forward/reverse primers of rs7903146 SNP of TCF7L2 gene were as follows: 5′ACAATTAGAGAGCTAAGCACTTTTTAGGTA-3′ (forward) and 5′-GTGAAGTGCCCAAGCTTCTC-3′ (reverse). The genotyping success rate was superior to 95%, with a calculated error based on PCR duplicates of less than 1%.

Statistical analyses

Data were analyzed using the IBM program SPSS, version 13.0 SPSS Inc. 233 South Wacker Drive, 11th Floor Chicago, IL 60606-6412. The differences in genotype and allelic frequencies between groups were analyzed by χ^2 test. Clinical and laboratory characteristics were compared between groups by using unpaired Student's *t* test or χ^2. Variables with normal distribution are presented as mean±SD or percentage. The magnitude of associations of the TCF7L2 rs7903146 SNP with T2D were estimated using odds ratio (OR) with 95% confidence interval (CI). Binary logistic regression analyses were performed to assess the independent association of this SNP with T2D, adjusting for age, sex, duration of diabetes,

and TCF7L2 rs7903146. *P* values less than 0.05 were taken to indicate statistical significance.

RESULTS

The study enrolled 54 previously diagnosed T2D Egyptian patients who were under treatment with SUs. They were classified into two groups according to HbA1c results: SUs responders group (*n* = 27) with HbA1c less than 7.0% and SUs nonresponders group (*n* = 27) with HbA1c was more than 7.0%.

Clinical characteristics of all the participants in this study are given in Table 1. The nonresponders group had a higher HbA1c and FBG than the responders group, with statistically high significant difference (*P* = 0.001). The differences in age, BMI, cholesterol, LDL, HDL, triglycerides, AST, ALT, creatinine, and duration of diabetes between the two groups were not statistically significant (Table 1).

Regarding categorization according to genotype percentage among the responders and nonresponders groups, it was found that the CC genotype had a count of 12 patients, where four (33.3%) of them were nonresponders and eight (66.7%) were responders; and the CT genotype count was 27 patients, where 12 (44.4%) of them were nonresponders and 15 (55.6%) were responders; and the TT genotype count was 15 patients, where 11 (73.3%) of them were nonresponders and four (26.7%) were responders. The association between genotypes (CC, CT, TT) and response to SUs was found to be statistically significant (*P* = 0.038). It was observed that the most frequent genotype in the nonresponders group was the TT, whereas the most frequent genotype in the responders group was the CC (Table 2).

Regarding allelic distribution, the T allele showed a count of 34 (59.6%) and 23 (40.4%) in the nonresponders and responders groups, respectively, whereas the C allele count was 20 (39.2%) and 31 (60.8%) in the nonresponders and responders groups, respectively. T allele showed a statistically significant greater association with the nonresponder status than the C allele (*P* = 0.034) (Table 3).

Comparing non-TT (CC/CT) genotype combined group (*n* = 39) with TT genotype group (*n* = 15) showed higher HbA1c and FBG in the TT genotype group, which was statistically significant (*P* = 0.031 and 0.025, respectively). The difference in age, BMI, cholesterol, LDL, HDL, triglycerides, AST, ALT, creatinine, and duration of diabetes between these two groups was not statistically significant (Table 4).

Binary logistic regression analysis, showing predictors to failure of SUs treatment in patients with T2D, indicated that both the TT genotype and the T allele had statistically significant effects (*P* = 0.029 and 0.034 respectively). TT genotype was associated with nonresponse to SUs in T2D patients about 4.6 times more than the rest of the genotypes (CC/CT) (OR, 4.643; CI, 1.175–18.355). Concerning alleles, the odds indicated having nonresponder status 2.291 times greater for T allele as opposed to C allele (OR, 2.29; CI, 1.059–4.959),

Table 1: Clinical characteristics of all participants

Parameters	Nonresponders (*n*=27)	Responders (*n*=27)	*P*
Age (years)	50.89±8.03	52.07±10.91	0.651
Duration of diabetes (years)	9.00±7.73	7.59±4.85	0.426
BMI (kg/m²)	33.06±4.69	32.96±5.93	0.946
FBG (mg/dl)	206.41±81.73	132.93±49.57	0.001**
HbA1c (%)	8.81±1.36	5.80±1.19	0.001**
Cholesterol (mg/dl)	211.44±48.56	203.41±36.71	0.496
LDL (mg/dl)	135.37±39.54	128.04±30.31	0.448
HDL (mg/dl)	37.22±9.32	35.07±9.71	0.411
TG (mg/dl)	175.07±87.34	110.74±48.29	0.060
AST (U/l)	22.22±11.66	22.81±8.54	0.832
ALT (U/l)	25.85±13.76	22.37±11.40	0.316
Creatinine (mg/dl)	0.74±0.16	0.76±0.21	0.662

Data are presented as mean±SD. ALT, alanine transaminase; AST, aspartate transaminase; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides. **$P<0.001$, highly significant.

Table 2: CC, CT and TT distribution among nonresponders and responders groups

Genotype	Nonresponder	Responder	*n*=54
C/C	4 (33.3)	8 (66.7)	12 (22.2)
C/T	12 (44.4)	15 (55.6)	27 (50)
T/T	11 (73.3)	4 (26.7)	15 (27.8)
P		0.038*	

Data are presented as *n* (%). *$P < 0.5$ Significant.

Table 3: The distribution of T and C alleles among nonresponders and responders groups

Allele	Nonresponder	Responder	Total
T	34 (59.6)	23 (40.4)	57 (52.8)
C	20 (39.2)	31 (60.8)	51 (47.2)
P		0.034*	

Data are presented as *n* (%). *$P < 0.5$ Significant.

whereas the other factors such as sex, age, and duration of diabetes were not statistically significant (*P* = 0.334, 0.267, and 0.242, respectively) (Table 5).

DISCUSSION

A lot of advancement has been made in the form of building up a genetic clarification for etiological mechanisms by which T2D develops and the intraindividual and interindividual variability in response to oral antidiabetic standard treatments [20]. Some studies announced the solid relationship of T2D with TCF7L2 rs7903146 (*P* = 0.003) [21], and the higher distribution of T allele of TCF7L2 rs7903146 among Egyptian T2D patients (*P* < 0.001; OR, 5.96; 95% CI, 2.58–16.22) [22].

As TCF7L2 genotype has a key role in insulin secretion, which is additionally the primary role of SUs, there was a developing enthusiasm for exploring the effect of this gene

mutation on patient response to the SUs [23]. It was assessed that the patients with diabetes risk alleles at TCF7L2 rs7903146 had diminished β-cell function with an altered hypoglycemic reaction to SUs. They showed SUs treatment failure [24].

The current study was performed in a trial to assess the relationship between TCF7L2 gene rs7903146 polymorphism and therapeutic response to SUs in Egyptian patients with T2D. As no clinical phenotype conveniently predicts response to SUs, patients were divided into two groups, considering that, responders are the patients with HbA1c less than 7.0% and nonresponders are those with HbA1c more than 7.0%.

The count of TT genotype in our study indicated a noteworthy significant increase in the nonresponders group than the responders group ($P = 0.038$). In concurrence with our outcomes, TT homozygotes were twice as likely to fail SU treatment as CC homozygotes [25].

This study also showed a statistically significant increase in the T allele count in the nonresponders when compared with the responders group ($P = 0.034$; OR, 2.29; 95% CI, 1.059–4.959). Similarly, several papers stated that the rs7903146 T allele was significantly more frequent in the group of patients who failed to respond to SUs [26–28].

We found higher mean levels of HbA1c and FBG (i.e. SU treatment failure) in TT genotype group compared with non-TT (CC/CT) genotype combined group, which were statistically significant ($P < 0.031$ and < 0.025, respectively). Regarding other biochemical and anthropometric parameters, no statistically significant difference between the means of the two groups was found. In consistent with this finding, the rs7903146 TT homozygote diabetic patients had a higher HbA1c than the CC homozygote ones, whereas other parameters such as age, BMI, biochemical parameters, and duration of treatment did not have any statistically significant difference [24]. Moreover, significant reductions in HbA1c and FBG levels were found following SU treatment between T2D patients with CC/CT genotypes than those with TT genotype [12].

Regarding predictor factors influencing the response to SU treatment, binary logistic analysis of the current study population was performed including several factors, with the TCF7L2 genotype factor involving two possibilities, namely, TT and non-TT (CC/CT). Results demonstrated that both the TCF7L2 genotype and the T allele showed statistically significant influence on predicting nonresponder state ($P = 0.029$ and 0.034, respectively). Similar to these outcomes, GoDARTS (Genetics of Diabetes Audit and Research Tayside) study [24] found that carriers of the T allele had increased odds of failure with SU treatment (OR, 1.27; $P = 0.017$). Another study strengthened this finding by detailing that the TCF7L2 genotype was observed to be the only predictor of SU treatment failure [25]. In contrast to these findings, it was expressed that SU treatment failure in patients with T2D was affected by dose, adherence, and sex, in addition to variation in TCF7L2 [12].

Table 4: Comparison between clinical characteristics in genotype groups (C/C and C/T versus T/T)

Parameters	C/C and C/T (n=39)	T/T (n=15)	P
Age (years)	50.97±8.95	52.80±11.04	0.532
Duration of diabetes (years)	8.18±6.85	8.60±5.38	0.832
BMI (kg/m2)	32.97±5.31	33.12±5.44	0.927
FBG (mg/dl)	155.36±63.03	206.87±96.64	0.025*
HbA1c (%)	7.14±1.78	8.35±1.77	0.031*
Cholesterol (mg/dl)	210.92±40.25	198.33±49.25	0.338
LDL (mg/dl)	135.51±36.19	121.80±31.01	0.201
HDL (mg/dl)	36.60±9.91	34.70±8.43	0.502
TG (mg/dl)	141.46±64.32	146.67±74.49	0.849
AST (U/l)	22.33±10.06	23.00±10.64	0.831
ALT (U/l)	25.13±12.36	21.47±13.41	0.345
Creatinine (mg/dl)	0.76±0.20	0.73±0.13	0.538

Data are presented as mean±SD. ALT, alanine transaminase; AST, aspartate transaminase; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein. *$P < 0.5$, Significant.

Table 5: Predictors on failure of sulfonylureas treatment in patients with type 2 diabetes mellitus

Parameters	Odds ratio (95% CI)	P
Sex	2.076 (0.472-9.120)	0.334
Age (year)	1.040 (0.970-1.116)	0.267
Duration of diabetes (<5 years vs. >5 ears)	0.940 (0.848-1.042)	0.242
TCF7L2 genotype (CC/CT) vs. (TT)	4.643 (1.175-18.355)	0.029*
C vs. T alleles	2.29 (1.059-4.959)	0.034*

CI, confidence interval; TCF7L2, transcription factor 7-like 2. *$P < 0.5$, Significant.

Conclusion

The present information regarding Egyptian T2D patients agrees with the already revealed findings concerning other populations, suggesting that the TT genotype and T allele polymorphism of TCF7L2 rs7903146 confer failure in treatment with SUs. However, replications of these studies are expected to enhance the quality of the current findings. As the low cost makes SUs still an extremely moderate and affordable choice in T2D treatment, more grounded pharmacogenomic confirmation may enable genetic testing for these polymorphisms to foresee clinical outcomes and create personalized SU pharmaceutical for T2D management in the future.

Conflicts of interest
There are no conflicts of interest.

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