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Impact of Single Nucleotide Polymorphism rs1799854 ABCC8 on Glibenclamide Glycemic Control in Patients with Type 2 Diabetes

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ABSTRACT

Background: The incidence of type 2 diabetes mellitus (T2DM) in Iraq is rising continuously. Glibenclamide (GLB), which is a sulfonylurea member, is an important treatment for T2DM. The sulfonylurea receptor-1 is encoded by the ABCC8 gene, and its rs1799854 genetic variation may alter the hypoglycemic activities of GLB.
Objectives: To determine the rs1799854 polymorphism in the ABCC8 gene and assess its potential role in modifying the therapeutic response to GLB among T2DM patients.
Materials and methods: An observational pharmacogenetic association study involved 120 T2DM patients on GLB medication who were screened for ABCC8 G>A (rs1799854) genotypes and glycemic health.
Results: The wild type (GG) was detected in 21.67% of T2DM cases. The mutant type (AA) and the heterozygous type (GA) were detected in 37.5% and 40.83% of the cases, respectively. The results did not exhibit a significant difference among GG, GA, and AA genotypes regarding glycemic status parameters (HOMA 2-IR (1.24 ± 0.93 for GG genotype, 1.3 ± 2.98 for GA genotype, and 1.52 ± 1.79 for AA genotype), HOMA 2-%β (27.05 ± 39.75 for GG genotype, 22.3 ± 44.6 for GA genotype, and 25.8 ± 31.85 for AA genotype), and HbA1c (9.7 ± 3.75 for GG genotype, 8.7 ± 2.65 for GA genotype, and 8.9 ± 2.35 for AA genotype) at P-value > 0.05.
Conclusion: The ABCC8 G>A (rs1799854) genotype was significantly prevalent among individuals with T2DM. There was no discernible association between the ABCC8 G>A (rs1799854) genomic variant and GLB's therapeutic effect.
Keywords: Type 2 diabetes mellitus; Glibenclamide; ABCC8 gene; Insulin.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disorder that causes the body to become resistant to insulin and the pancreatic β-cells to gradually lose their ability to generate the hormone, which disrupts glucose balance [1]. In the world, T2DM affects about 6.27% of the population, and in Iraq, its prevalence is notably raised, with overall occurrences between 8.5% to 13.9% and even greater figures in certain localized investigations [2]. T2DM is frequently investigated and monitored by using traditional glycemic control assessments, encompassing the glycated hemoglobin (HbA1c) test, showing the average blood glucose levels throughout the two to three months prior, and the HOMA2 (homeostatic model assessment 2 index), which evaluates HOMA2-IR (insulin resistance) and β-cell functionality (HOMA2%β) [3].

T2DM is managed through both medication and lifestyle adjustment. Among oral agents, sulfonylureas such as glibenclamide (GLB) remain common because they are inexpensive and have been shown to boost pancreatic β-cells' production of insulin [4]. However, some patients maintain high glucose levels despite treatment, suggesting reduced drug response or therapy failure [5].

GLB acts by interacting with the type 1 sulfonylurea receptor (SUR1), which is synthesized by a gene known as ATP-binding cassette sub-family C member 8 (ABCC8). This binding caused closure of the ATP-sensitive potassium

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(KATP) channels in the pancreatic β-cells. After that, depolarizing the membrane and enhancing of the flow of calcium ions will occur. This process links insulin secretion with glucose metabolism [6, 7]. ABCC8 variation may alter insulin release, the response to drugs, and metabolic control. This gene contains several single-nucleotide polymorphisms (SNPs), such as rs1799854, which has been studied extensively. The location of the rs1799854 polymorphism occurs in the promoter region of ABCC8 and may be related to the changes in transcriptional processes and affect sulfonylurea therapeutic response [8].

This study aimed to detect the rs1799854 polymorphism in the ABCC8 gene and determine its potential effect on GLB response in glycemic control among patients with T2DM.

MATERIALS AND METHODS

Patients

Eligible patients were aged 30-60 years and had T2DM for at least 3 years based on the American Diabetes Association criteria [9]. The target population at the Imam Hassan Centre for Endocrinology and Diabetes in Karbala included people with T2DM who were using GLB as a monotherapy.

Sample size was calculated using Fisher's formula [10], based on an estimated prevalence of T2DM, a 95% confidence level, and a 5% margin of error, yielding a required sample size of 174 participants. However, during the study period 120 patients were successfully enrolled.

The Kerbala University College of Pharmacy's Scientific and Ethical Committee approved this study, with the project assigned number 2024HU6 on August 4, 2024. Additionally, an approval was obtained from the Kerbala Health Department of the Iraqi Ministry of Health, with project number 3734 on August 28, 2024. After obtaining informed consent, inclusion required consistent treatment with GLB at a dose of five milligrams per day as the only antidiabetic medication for six months or more. Subjects with other forms of diabetes, liver or kidney impairment, or those using drugs influencing lipid metabolism or altering GLB pharmacokinetics or pharmacodynamics were excluded.

Study design

This observational pharmacogenetic association study was conducted from September 2024 to March 2025 and included 120 treated with GLB patients with T2DM. Demographic and glycemic data were individually gathered. At the same time, glycemic status [fasting blood sugar (FBS), insulin, HbA1c, HOMA2-IR, and HOMA2-%β] was assessed.

Evaluation of body mass index (BMI)

By dividing each patient's weight in kilograms by their height in meters squared, the BMI of each patient was calculated.

Collection of blood

Each subject provided a fasting (8-12 hours) blood sample (5 mL), divided as follows: 2 mL for HbA1c and genetic testing [Ethylenediaminetetraacetic acid (EDTA) tube], expeditiously, and 3 mL for biochemical serum analysis (gel tube).

Assessment of glycemic status

- Using the Lifotronic H8 automated HbA1c test (Shenzhen, China: Lifotronic Technology Co., Ltd.) according to high-performance liquid chromatography, HbA1c levels were ascertained.
- Values below 7% indicated adequate diabetes control, whereas levels of 7% or higher represented suboptimal glycemic regulation [11].
- FBG was measured by enzymatic assays performed on a Monarch 240 clinical chemistry analyzer (Instrumentation Laboratory, Bedford, Massachusetts, USA).
- Insulin: Quantified via electrochemiluminescence immunoassay using the Cobas e 411 immunoassay analyser (Mannheim, Germany: Roche Diagnostics GmbH).
- HOMA2 indices: Online HOMA2 calculator (www.homacalculator.dtu.ox.ac.uk/) was employed to compute HOMA2-%β and HOMA2-IR utilizing fasting glucose and insulin inputs, and was licensed on February 17, 2025, by Oxford University Innovation. Insulin resistance and β-beta-cell activity were contrasted using the following sources.: HOMA2-IR < 1 and HOMA2-%β 90–110%, with all metrics log-transformed for analysis [12].

Genotyping

The Geneaid Blood deoxyribonucleic acid (DNA) kit for isolation (New Taipei City, Taiwan: Geneaid Biotech Ltd.) was utilized to extract genomic DNA from whole blood. The final DNA concentration ranged from 50 to 70 ng/µL, and purity values ranged from 1.8 to 2.0 based on the A260/A280 ratio. Both parameters were measured utilizing a Thermo Fisher Scientific Inc. NanoDrop spectrophotometer (Waltham, Massachusetts, USA), and only samples within these ranges were used for further analysis Allele-specific polymerase chain reaction (AS-PCR) was used to detect the ABCC8 G>A (rs1799854) polymorphism [13]. Primers were designed in silico using the NCBI Primer-BLAST tool based on the published ABCC8 sequence, yielding a 320 bp amplicon. Primer sequences were as follows:

- Forward primer (G):
  5'-CACGATCATAGTCAGCTGGCCTG-3'
- Forward primer (A):
  5'-CACGATCATAGTCAGCTGGCCTA-3'
- Reverse primer:
  5'-TTCTTGGGACCACAAGGAGCCT-3'

PCR verification was based on primer design. A negative control without template DNA was included in each run to eliminate contamination and confirm assay reliability. Annealing temperature optimization was performed using repeated PCR runs with a temperature gradient while maintaining constant reaction conditions. The optimal annealing temperature was selected based on specific amplification of the expected product. PCR was performed as follows: 20 μL final reaction volume containing primer, template DNA, premix, dimethyl sulfoxide (DMSO), and water; cycling included initial denaturation, 35 cycles (denaturation, annealing at 61°C, extension), and a last extension. Samples were separated on a 1.5% Tris/Borate/EDTA (TBE) buffer agarose gel following PCR. After electrophoresis, they were visualized under a UV transilluminator (Syngene International Ltd., Cambridge, United Kingdom), with bands sized against a 100-1500 bp ladder and scored by two reviewers.

Statistical Analysis

International Business Machines Corporation's Statistical Package for the Social Sciences V26 (Armonk, New York,

USA) was used for the analysis. To confirm normality, a Shapiro-Wilk test was employed. For normal distributed data, the mean ± standard deviation (SD) was reported, and for non-normally distributed data, the median ± interquartile range (IQR). Categorical values were given as counts and percentages. For non-normal variables, including ABCC8 G>A (rs1799854) genotypes, Kruskal-Wallis post hoc - Dunn's test was used, and the Mann-Whitney U test was utilized to assess the association between responders and non-responders. Allelic frequencies were evaluated using the Hardy–Weinberg equilibrium, among other tests. Linear regression–β coefficient test was employed to assess the association of ABCC8 G>A (rs1799854) genetic variation with glycemic status in Iraqi patients with T2DM. Significance was indicated by a P-value < 0.05.

RESULTS

Demographic data of diabetic patients

The mean age and BMI were 50.16 ± 10.71 and 27.95 ± 4.54, respectively. The male patients comprised 51.7% of the total Iraqi patients with T2DM, and about 36.7% of them had a family history of diabetes, as exhibited in Table 1.

The effect of GLB on glycemic status

The efficacy of GLB was evaluated based on HbA1c levels, unexpectedly revealing that approximately 21 (17.5%) patients with T2DM on GLB therapy for 3 years demonstrated a significant response, with HbA1c of 6.3 ± 0.55 and FBS of 119 ± 65.5. In contrast, 99 patients exhibited inadequate response, GLB for four years, with a HbA1c of 9.3 ± 2.1 and FBS of 217 ± 107, at a P-value <0.05. No notable differences were observed between patients with T2DM who responded to GLB and those who did not, regarding the length of GLB usage, insulin levels, and HOMA2-IR, with a P-value ≥ 0.05. The percentage of HOMA2-%β in diabetic patients who responded to GLB was noticeably greater than that of diabetic patients who did not respond to GLB at a P-value of less than 0.05 (Table 2).

Genotyping

Prevalence and allele distribution of ABCC8 G>A (rs1799854) gene

The distinct bands of 320 bp in molecular size indicated the outcomes of ABCC8 G>A (rs1799854) genotyping. The size of this gene amplicon was ascertained by comparison with a DNA ladder ranging from 100 to 1500 bp, with genotypes categorized into three types: the predominant wild type (GG) for allele G, the homozygous mutant type (AA) for allele A, and the heterozygous type (GA), as illustrated in Figure 1. The wild type (GG) was identified in 21.67% of individuals with T2DM. The mutant type (AA) and the heterozygous type (GA) were identified in approximately 37.5% and 40.83% of instances, respectively, as illustrated in Figure 2. The distribution of alleles and genotypes for ABCC8 G>A (rs1799854) is presented in Table 3.

Table 1. Demographic data of 120 patients with type 2 diabetes mellitus.

Variables	Mean ± SD or no (%)
Age	50.16 ± 10.71
Sex	
Male	62 (51.7%)
Female	58 (48.3%)
Boby mass index	27.95 ± 4.54
Family history of diabetes	
No	76 (63.3%)
Yes	44 (36.7%)

Table 2. The effect of glibenclamide on the glycemic status of 120 patients with type 2diabetes mellitus*.

Variable	Diabetic patients on GLB therapy		P-value
	Responded No=21	Non-responded No=99	
Duration use of GLB (year)	3 ± 7.25	4 ± 7	0.541
HbA1c (%)	6.3 ± 0.55	9.3 ± 2.1	< 0.000001
FBS (mg/dl)	119 ± 65.5	217 ± 107	0.000001
Insulin(μU/dl)	11.2 ± 11.18	7.52 ± 6.03	0.129
HOMA2-IR	1.56 ± 1.87	1.35 ± 2.28	0.959
HOMA2-%β	62.3 ± 59.35	21.3 ± 28.7	< 0.000001

* Mann-Whitney U, two-sided P-value <0.05, data in median ± IQR format, GLB: Glibenclamide, HbA1c: Glycated hemoglobin, FBS: Fasting blood sugar, HOMA 2-IR: Homeostatic model assessment 2-insulin resistance, HOMA 2-%β: Homeostatic model assessment 2- beta-cell functionality.

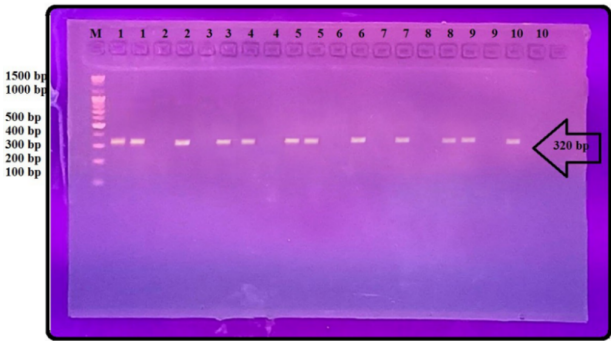

Figure 1. Genotyping of rs1799854 G>A polymorphism.

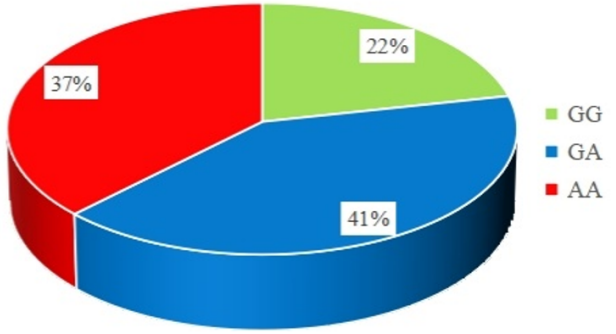

Figure 2. The prevalence of the rs1799854 G>A polymorphism among 120 patients with type 2 diabetes mellitus.

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Table 3. The allele distribution of ATP-binding cassette sub-family C member 8 G>A (rs1799854) genes in 120 patients with type 2 diabetes mellitus.

Genotype (N:120)	Frequency (%)	Allele	Frequency	Chi-square value	P-value
GG (wild type)	26 (21.67%)	G	0.42	3.165	0.205
GA (heterozygous type)	49 (40.83%)	A	0.58		
AA (homozygous type)	45 (37.5%)				

Table 4. The effect of ATP-binding cassette sub-family C member 8 G>A genetic variation on the glycemic status of 120 patients with type 2 diabetes mellitus.*

Parameters	Alleles of ABCC8 G>A Genotypes			P-value
	GG	GA	AA	
HbA1c (%)	9.7 ± 3.75	8.7 ± 2.65	8.9 ± 2.35	0.441
FBS (mg/dl)	116.5 ± 168.75	212 ± 113.5	200 ± 70.5	0.615
Insulin (μU/dl)	7.34 ± 5.21	7.2 ± 14.47	9.56 ± 11.06	0.194
HOMA2-IR	1.24 ± 0.93	1.3 ± 2.98	1.52 ± 1.79	0.507
HOMA2-%β	27.05 ± 39.75	22.3 ± 44.6	25.8 ± 31.85	0.896

* Kruskal-Wallis's, two-sided P-value <0.05, data in median ± IQR format, HbA1c: Glycated hemoglobin, FBS: Fasting blood sugar, HOMA2-IR: Homeostatic model assessment 2-insulin resistance, HOMA2-%β: Homeostatic model assessment 2- beta-cell functionality.

Table 5. The linear regression of ATP-binding cassette sub-family C member 8 G>A genetic variation and glycemic status of 120 patients with type 2 diabetes mellitus.†

Variable	B	SE. B	B	T	P-value	95% CI for B	
						Lower bound	Upper bound
Constant	2.218	0.487		4.559	.000	1.254	3.182
HbA1c (%)	-0.062	0.049	-0.158	-1.284	.202	-0.158	0.034
FBS (mg/dl)	-0.002	0.002	-0.208	-1.063	.290	-0.005	0.001
Insulin (μU/dl)	0.025	0.009	0.392	2.872	.005*	0.008	0.043
HOMA2-IR	-0.007	0.013	-0.068	-0.543	.588	-0.033	0.019
HOMA2-%β	-0.012	0.005	-0.455	-2.684	.008*	-0.022	-0.003

† Linear regression-β coefficient, two-sided P-value < 0.05, B: Unstandardized coefficient beta, SE. B: Standard error for the unstandardized beta, β: Standardized coefficient beta, t: t test statistic, CI: Confidence interval, and *: Significant association.

Effects of ABCC8 G>A genetic variation on the glycemic status

The results did not exhibit a significant difference among patients with T2DM who received GLB and carried GG, GA, and AA genotypes regarding glycemic status parameters (HbA1c, FBS, Insulin, HOMA2-IR, HOMA2-%β) at P-value> 0.05 (Table 4). There was no significant (P-value > 0.05) association between the ABCC8 G>A genetic variation and the glycemic status (regarding HbA1c, FBS, and HOMA2-IR) of patients with T2DM (Table 5).

DISCUSSION

T2DM is a significant health risk in Iraq, and most diabetic patients remain uncontrolled despite using many hypoglycemic agents [14, 15], including GLB, which is characterized by its significant glucose-lowering efficacy and cost-effectiveness [16]. Certain studies indicate a correlation between the ABCC8 G>A (rs1799854) genetic polymorphism and heightened T2DM risk or modified medication response, whilst others report no significant association, suggesting that the impact of this variant on sulfonylurea efficacy is likely contingent upon diverse genetic and demographic factors [17].

Despite being used for three years, this study found that 17.5% of the selected patients attained the desired glycemic control, depending on HbA1c levels and HOMA 2 indicators. Serious concerns were raised from these findings about the decrease in GLB response in this population. This small percentage shows that many patients had little therapeutic benefit from GLB. A multicenter European study supports this observation. In that study, involving 662 patients with T2DM across 71 centers in eight countries, GLB effectiveness declined with time. After 52 weeks, only 46.5% of patients achieved the American Diabetes Association HbA1c goal of below 7% [18].

In the current study, the ABCC8 G>A (rs1799854) gene polymorphism was observed in individuals with T2DM, with heterozygous GA and homozygous AA genotypes being predominant. The minor allele frequency of the A allele is approximately 58%, which is not significantly elevated compared to the reference major allele (G) in the selected patients. This polymorphism is linked to T2DM in some populations, al-

though the findings are inconsistent. Prevalence statistics indicate that the G allele and GG genotype were present in greater proportions in patients with T2DM compared to controls in certain studies [19]. However, other research reported no significant difference in the northern part of Brazil [20]. There is a statistically significant connection between T2DM and ABCC8 G>A (rs1799854), with the risk allele (A) showed the largest prevalence (49.5%) [19]. The A allele of this variant appears to have a significant frequency in the Asian and American populations, at 55.1% and 53.6%, respectively [21]. Though these effects are stochastic and interact with environmental factors, genetic polymorphisms have a significant impact on susceptibility, disease development, and management responses in T2DM. Numerous T2DM risk loci have been related to decreased insulin secretion and action by genetic research, especially Genome-Wide Association Studies, which have revealed novel potential targets for pharmaceutical development [22].

The presence of this polymorphism did not significantly affect insulin output, glycemic measurements, or surrogate markers of β-cell function among GLB-treated patients, according to genetic stratification based on the ABCC8 rs1799854 gene. This result is consistent with studies involving 61 T2DM individuals who received GLB or gliclazide as prescribed. Furthermore, patients with the rs757110 variant (P-value = 0.39 for FBS and P-value = 0.76 for HbA1c) and those with rs1799854 (P-value = 0.24 for FBS and P-value = 0.36 for HbA1c) did not show significant variation in the changes of FBS and HbA1c after SFUs treatment in the Iranian study [17]. Polymorphisms in the ABCC8 gene, namely variants rs1799854 and rs1801261, have been reported in three papers. The ABCC8 gene is crucial for the synthesis of SUR1, a component of the K-ATP channel in pancreatic β cells, which regulates insulin release and influences blood glucose levels. As blood glucose levels rise, these channels will close, prompting insulin production from β cells. The ABCC8 gene influences the functionality of this channel and impacts the maintenance of blood glucose homeostasis [4, 23].

We acknowledge that observational design limits our ability to establish causal relationships between genotype and treatment response. The small sample size was primarily attributed to the short study duration, financial constraints, and the refusal of some patients to participate. We were unable to collect additional variables, which may limit our analysis, and larger studies are required. Other genes, such as the gene encoding the metabolizing enzyme cytochrome P2C9, may affect GLB pharmacokinetics; therefore, further studies involving these genes are needed.

CONCLUSION

The ABCC8 G>A (rs1799854) genotype was significantly more prevalent among patients who have T2DM. The genetic variation ABCC8 G>A (rs1799854) did not significantly affect the therapeutic response to GLB, including glycemic parameters (HbA1c, FSB, and HOMA2-IR).

ETHICAL DECLARATIONS

Acknowledgments

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Ethics Approval and Consent to Participate

Both the Ministry of Health of Iraq's Kerbala health department (number 3734, dated August 4, 2024) and the scientific and ethical committee at Kerbala University, College of Pharmacy (number 2024HU6, dated August 28, 2024) authorized this study. All participants gave their informed consent.

Consent for Publication

Not applicable (No personal information was published).

Availability of Data and Material

Upon reasonable request, the corresponding author will make the data created and analyzed during this work available.

Competing Interests

The authors declare that there is no conflict of interest.

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Use of Artificial Intelligence

Artificial intelligence has been used in limited ways to correct spelling, grammar, and punctuation, as well as to edit specific texts.

Authors' Contributions

M.A. participated in the study's design and execution, analysis of the results, and manuscript composition. R.M. contributed to the review and editing of the study and supervised the research. A.H. and M.Q. contributed to data collection and evaluated the manuscript attentively. The completed manuscript has received approval from all authors.

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