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Effects of genetic variants of organic cation transporters on metformin response in newly diagnosed patients with type 2 diabetes

Huda M. AlKreathy, MD, PhD[a], Abdulhhakim A. Alzahrani, MSc[a,b], Ahmed Esmat, PhD[a], Zoheir A. Damanhouri, PhD[a,*]

Abstract

Type 2 diabetes mellitus (T2DM) is a chronic disease that affects millions of people worldwide. Metformin is the optimal initial therapy for patients with T2DM. Genetic factors play a vital role in metformin response, including variations in drug efficacy and potential side effects. To determine the effects of genetic variants of multidrug and toxin extrusion protein 2 (MATE2), ataxia telangiectasia mutated (ATM), and serine/threonine kinase 11 (STK11) genes on metformin response in a cohort of Saudi patients. This prospective observational study included 76 T2DM newly diagnosed Saudi patients treated with metformin monotherapy and 80 control individuals. Demographic data, lipid profiles, creatinine levels, and hemoglobin A1c (HbA1c) levels were collected before and after treatment. All participants were genotyped for 5 single-nucleotide polymorphisms (SNPs), including rs4621031, rs34399035, rs2301759, rs1800058, and rs11212617, using TaqMan R genotyping assays. This study included 156 subjects. The subjects' mean ± SD age was 50.4 ± 10.14 years. The difference in HbA1c levels in T2DM after treatment ranged from −1.20% to 8.8%, with a mean value of 0.927 ± 1.73%. In general, 73.7% of the patients with T2DM showed an adequate response to metformin (HbA1c < 7%). STK11 (rs2301759) significantly affects the response to metformin in T2DM patients. In the rs2301759 single-nucleotide polymorphisms, the prevalence of an adequate response to metformin was significantly higher among patients with C/C and T/C genotypes than among non-responders ($P = .021$). However, no statistically significant associations were observed for the other tested SNPs. Our study provides evidence of an association between STK11 (rs2301759) and response to metformin in Saudi patients with T2DM. The need for targeted studies on specific gene-drug associations is emphasized, and further studies with a larger population should be conducted.

Abbreviations: ATM = ataxia telangiectasia mutated, BMI = body mass index, HbA1c = hemoglobin A1c, HDL = high density lipoprotein, LDL = low density lipoprotein, MATE2 = multidrug and toxin extrusion protein 2, SNP = single-nucleotide polymorphisms, STK11 = serine/threonine kinase 11, T2DM = type2 diabetes mellitus.

Keywords: diabetes mellitus, metformin, pharmacogenetics, rs2301759, STK11 gene

1. Introduction

Diabetes mellitus is a chronic metabolic syndrome that affects the regulation of blood glucose level.[1] Type 2 diabetes mellitus (T2DM) is the most frequent type of diabetes, accounting for up to 90% of all diabetic conditions globally.[2] Metformin is considered the first-line treatment owing to its fewer side effects and high patient tolerance.[3] In general, metformin shows high efficacy and advantages over other T2DM oral medications for enhancing weight loss.[4,5] Additionally, metformin-induced weight loss has been reported to have the same advantages as exercise-induced weight loss and is dependent on patient compliance.

Metformin is excreted in urine, with a half-life of approximately 5 hours. The average renal clearance in the population was 510 ± 120 mL/min, with active tubular secretion being the main route of elimination. The drug is widely distributed in body tissues, such as the liver, intestine, and kidney, via transporters of organic cations. There is significant variation in metformin pharmacokinetics, as demonstrated by differences in trough steady-state plasma concentrations that widely range from 54 to 4133 ng/mL.[6] Metformin absorption by the intestine is principally mediated via the plasma membrane monoamine transporter and may involve organic cation transporter 3 (OCT3) and organic cation transporter 1 (OCT1) in enterocytes and hepatocytes, respectively. However, the specific effects of these transporters on the pharmacokinetics and pharmacological outcome of metformin remain unclear.[7] Metformin is a substrate for human multidrug and toxin extrusion 1 (MATE1) and multidrug and toxin extrusion protein 2 (MATE2-K). Interestingly,

AAA and ZAD contributed to this article equally.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Clinical Pharmacology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia, [b] Department of Clinical Pharmacy, Medical Affairs, Al-Baha Health Cluster, Al-Baha, Saudi Arabia.

** Correspondence: Zoheir A. Damanhouri, Department of Clinical Pharmacology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia (e-mail: zdamanhouri@kau.edu.sa).*

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MATE1 (SLC47A1) is highly expressed in the skeletal muscle, liver, and kidney and may play a role in metformin elimination. However, the significance of MATE1 in hepatic secretion has been questioned, as human biliary elimination of metformin appears to be minimal.[7] Conversely, findings from a MATE1 knockout mouse study showed that metformin excretion through bile occurs.[8] Metformin uptake by renal epithelial cells is predominantly aided by OCT2 (SLC22A2), which is mainly expressed in the basolateral membrane of renal tubules.[9] Furthermore, renal excretion of metformin from tubular cells to the lumen occurs through MATE1 (SLC47A1) and MATE2-K (SLC47A2).[10]

Both MATE1 and MATE2-K are expressed in the apical membranes of proximal tubular cells and contribute to the normal renal excretion of metformin in healthy individuals.[8] Moreover, OCT1 may be expressed on the apical and subapical domain sides of both the renal proximal and distal tubules, suggesting a notable role in metformin reabsorption in the kidney tubules.[11] Furthermore, plasma membrane monoamine transporter (SLC29A4) is expressed in the apical membranes of renal epithelial cells, indicating its role in renal reabsorption of metformin.[9] However, no in vivo data support this hypothesis. Additionally, the efflux of metformin across placental apical membranes involves P-gp (ABCB1) and BCRP (ABCG2).[12]

The inhibition of metformin transporters (OCTs and MATEs) represents a potential source of clinically relevant drug–drug interactions because metformin is not metabolized by the liver. Thus, polymorphisms in these genes directly affect metformin pharmacokinetics and response variability. Notably, OCT1-mediated metformin transport was inhibited in vitro by repaglinide and rosiglitazone.[13] Moreover, co-administration of cimetidine reduced renal tubular secretion and increased the systemic concentration of metformin due to the inhibition of MATEs, but not OCT2.[14] More recently, the potential for this type of drug–drug interaction between metformin and specific tyrosine kinase inhibitors (e.g., imatinib, nilotinib, gefitinib, and erlotinib) might have clinical implications in all aspects of metformin (disposition, efficacy, and toxicity).[15] Many studies have focused on the accountability of genetic factors in predicting variations in the response to metformin. The association between genomic variations in metformin transporters and their pharmacokinetics and pharmacodynamics has been reported previously. However, large-scale studies are required to determine the clinical relevance of these variants. Currently, no proven genetic predictors have been used in clinical settings. Over the past few years, substantial progress has been made in interpreting the effects of transporter gene polymorphisms on the alteration of metformin pharmacokinetics. Extensive research has been performed on the organic cation transporter (SLC22A) family. OCT1 (SLC22A1) is fundamental for metformin uptake in the liver.[16] In a small study of 20 healthy volunteers, numerous genetic variants of OCT1, including G401S (rs34130495), R61C (rs12208357), G465R (rs34059508), and 420del (rs142448543, rs34305973, and rs35191146), had significant effects on metformin pharmacokinetics after oral administration.[17] Genetic variants (MATE1 and MATE2K), have not yet been clinically linked to alterations in the pharmacokinetics of metformin. However, the intake of pyrimethamine, an MATE inhibitor, resulted in significant increases in metformin C_{max} and AUC.[18] Moreover, in vivo studies have shown the importance of MATE1 in altering metformin pharmacokinetics via gene knockout.[19] In a cohort of 116 metformin users, the minor allele of MATE1/SLC47A1, rs2289669 G > A, was significantly associated with a better decrease in glycated hemoglobin (HbA1c) despite the absence of an association between the polymorphism and metformin pharmacokinetic parameters.[17] In addition, it has been shown that diabetic patients who were homozygous for g.-130 G > A (rs12943590) in MATE2-K displayed a significantly poorer response to metformin treatment. In addition to the above-mentioned transporters, the effects of OCT3 polymorphisms have also been explored.[19]

There are important inter-individual variations in responses to metformin pharmacotherapy. In 35% of patients, metformin failed to achieve the desired glycemic control, necessitating dose escalation or the use of a combined hypoglycemic treatment.[20] In children and adolescents with newly diagnosed T2DM, the failure rate is as high as 50%.[21] These results are particularly important in Saudi Arabia, where the prevalence of diabetes in children and adolescents is significantly high.[22] Some of this heterogeneity in drug responses can be explained, at least in part, by the underlying genetic differences.

The main aim of this study was to determine the effects of the genetic variants of MATE2, serine/threonine kinase 11 (STK11), and ataxia telangiectasia mutated (ATM) on the clinical response to metformin in the Saudi population. In addition, we aimed to correlate single-nucleotide polymorphisms (SNP) genotyping data with clinical phenotypes, such as fasting glucose, HbA1c levels, changes in HbA1c levels since the start of metformin monotherapy, and odds of achieving a target HbA1c of < 7, to determine differential SNPs.

2. Methods and materials

2.1. Study design

This was a prospective observational study in which the choice of treatment was decided by clinicians, with no involvement from the research team. The flowchart of the study is shown in (Fig. 1).

2.2. Study setting

Patients and controls were recruited from October 2021 to May 2023, either from the Department of Family Medicine Outpatient Clinics at King Abdulaziz University Hospital in Jeddah or from the Diabetic Center of King Fahad Hospital, Al Baha, Kingdom of Saudi Arabia.

2.3. Participants selection

This study recruited 76 patients and 80 healthy individuals. The inclusion and exclusion criteria are shown in Figure 1. Patients were administered monotherapy with metformin only, and blood samples were withdrawn before the beginning of treatment and after 6 months of treatment, whereas blood samples were withdrawn from the control only once.

All patients were newly diagnosed with T2DM based on WHO Health Organization criteria.[23] Based on the response to metformin monotherapy 6 months after treatment initiation, the patients were classified into 2 groups: the responder group, which showed a reduction in glycated hemoglobin (HbA1c) levels by more than 1% from the baseline. The non-responder group was defined as a reduction in HbA1C levels by <1% from baseline. These criteria were adopted from the American College of Physicians.[24,25] The control group included 80 healthy subjects with no history of diabetes or gestational diabetes mellitus.

The study protocol was subjected to rigorous review and received formal approval from the Unit of Biomedical Research Ethics Committees of the Faculty of Medicine at King Abdul-Aziz University. This significant endorsement was granted under the reference number (Reference No 246-20). All participants provided written informed consent prior to sample collection. The study adhered to the principles of the Declaration of Helsinki, and the clinical parameters of all participants were documented.: age, sex, lipid profile, HbA1C level at baseline and after 6 months treatment period and body mass index (BMI) for the patients only.

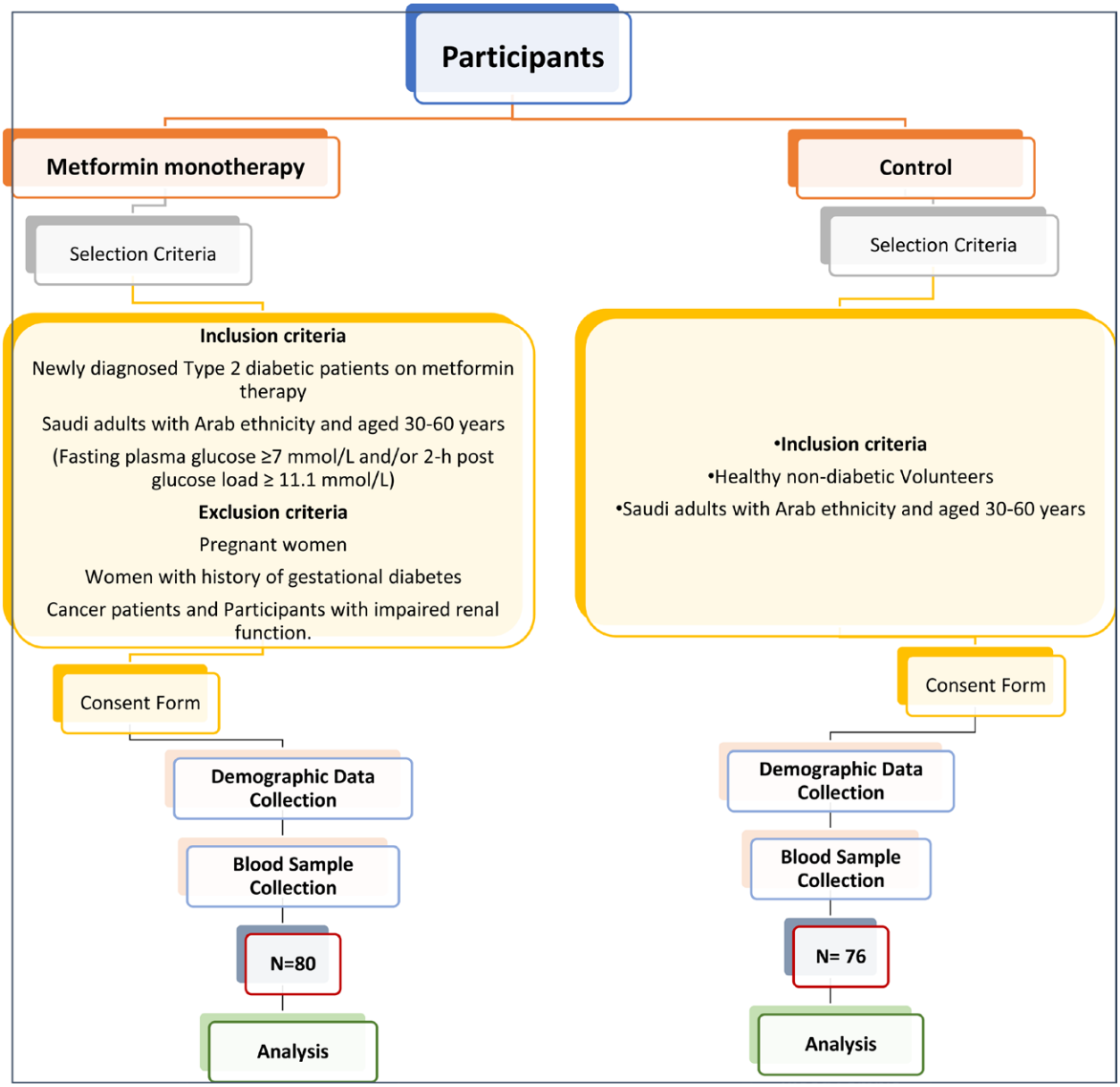

Figure 1. The study flowchart for the participants. The flowchart for the participants shows the selection criteria for metformin monotherapy and control as well as the subsequent procedures.

2.4. SNP genotyping

Whole venous blood was collected from all study participants in BD Vacutainer® spray-coated K2EDTA Tubes (PreAnalytiX GmbH, Switzerland) after overnight fasting for at least 12 hours. Genomic DNA was isolated from whole blood through the extraction process using a Magnesia® 16 Automated Nucleic Acid Extraction Instrument (Anatolia GeneWorks, Istanbul, Turkey). DNA samples were then evaluated for purity and quantified using a NanoDrop Spectrophotometer (Thermo Fisher Scientific Inc., Waltham).

All participants were genotyped for 5 SNPs, including rs4621031, rs34399035, rs2301759, rs1800058, and rs11212617, using TaqMan™ SNP Genotyping Assays (Thermo Fisher Scientific, Waltham).

2.5. Statistical analysis

All categorical variables were expressed as frequencies and percentages. When comparing 2 categorical variables, the chi-square test or Fisher's exact test was used, as appropriate. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) Version 20.0 (IBM Corp, Armonk). Logistic regression analysis was applied to further test the association of the allele with cases and controls. The 95% confidence intervals and odds ratio were also calculated. A P value cutoff of $< .05$ was used as a determinant of statistical significance.

3. Results

This study included 156 participants, patients (48.7%) and controls (51.3%). The included subjects had a mean ± SD age of 44.89 ± 11.40 years and mean BMI of 33 ± 5.17 kg/m^2. Regarding baseline characteristics, a significant difference was found between patients and controls in terms of age, sex, triglyceride, low-density lipoprotein (LDL), creatinine, and HbA1c % results. The mean ± SD age among patients was 50.45 ± 10.14 was significantly higher compared to controls, 39.6 ± 9.9 ($P < .001$). The mean triglyceride level among the

patients 2.39 ± 7.45 was significantly higher than that in the controls, 1.25 ± 0.66 ($P < .031$). In addition, the mean LDL among patients 3.32 ± 1.03 was significantly higher compared to controls 2.91 ± 0.89 ($P < .023$). The mean HbA1c level was significantly higher among patients (7.67 ± 2.31) than among controls (5.33 ± 0.36; $P < .001$). All data are presented in Table 1.

Three types of genes were examined (MATE2, STK11, and ATM), including 5 SNPs (rs4621031, rs34399035, rs2301759, rs1800058, and rs11212617; Fig. 2). T/T was the most frequently detected genotype for rs4621031 (46.1%), whereas C/C was the most frequently detected genotype (94.2%) for rs34399035. Regarding the rs2301759 SNP, the T/T genotype was the most frequently detected (53.8%). Only the C/C genotype was found for rs1800058, whereas A/C was the most frequent genotype found for rs11212617. There were no significant differences in gene variations between patients and controls. All the data are presented in Table 2.

Metformin showed a significant response to HbA1c% levels among the responders in the patients group. These patients had a significantly lower mean ± SD HbA1c % (7.13 ± 1.90) than those with an inadequate response, 9.74 ± 2.53 ($P < .001$). Other variables, including age, BMI, sex, cholesterol, triglyceride, LDL, high density lipoprotein, and creatinine, had no significant impact on the metformin response. The complete data are presented in Table 3.

The impact of gene variation on the metformin response was examined (Table 4 and Fig. 3). Only STK11 (rs2301759) significantly affected metformin response among patients. T/T was the most frequent genotype (85%) in the inadequate-response group ($P = .021$). Other SNPs (rs4621031, rs34399035, rs1800058, and rs11212617) had no significant impact on metformin response. Logistic regression analysis showed that there was no significant impact on the metformin response (Table 5). Bivariate logistic regression analysis of genetic variations in metformin response among T2DM patients revealed no significant differences.

Table 1

Demographic characteristics and laboratory results of participants.

Factors		Subjects		Total	*P* value
		Patients	Controls		
Age	Mean ± SD	50.45 ± 10.14	39.60 ± 9.90	44.89 ± 11.4	**<.001****
	Median (IQR)	51.50 (43–57)	37.00 (33–44)	43.50 (36–53)	
Gender	Female	34 (44.70%)	53 (66.20%)	87 (55.80%)	**.007***
	Male	42 (55.30%)	27 (33.80%)	69 (44.20%)	
Cholesterol	Mean ± SD	4.80 ± 1.04	4.62 ± 1.08		.324***
Triglyceride	Mean ± SD	2.39 ± 7.46	1.25 ± 0.66		**.031****
	Median (IQR)	1.38 (0.88–1.89)	1.12 (0.67–1.74)		
LDL	Mean ± SD	3.32 ± 1.03	2.91 ± 0.89		**.023****
	Median (IQR)	3.33 (2.51–4.15)	2.84 (2.25–2.84)		
HDL	Mean ± SD	1.28 ± 0.40	1.32 ± 0.52		.818**
	Median (IQR)	1.21 (0.98–1.47)	1.25 (0.97–1.25)		
Creatinine	Mean ± SD	76.52 ± 36.70	64.25 ± 16.91		**.202****
	Median (IQR)	74 (60–48)	61 (53–76.5)		
HbA1c %	Mean ± SD	7.67 ± 2.31	5.33 ± 0.36		**<.001****
	Median (IQR)	6.95 (5.92–8.1)	5.30 (0.50)		

P values patients vs controls. Statistical significance was deemed at $P < .05$.

HbA1c = hemoglobin A1c, HDL = high density lipoprotein, IQR = interquartile range, LDL = low density lipoprotein.

* Chi-square test.

** Mann–Whitney test.

*** Independent *t* test.

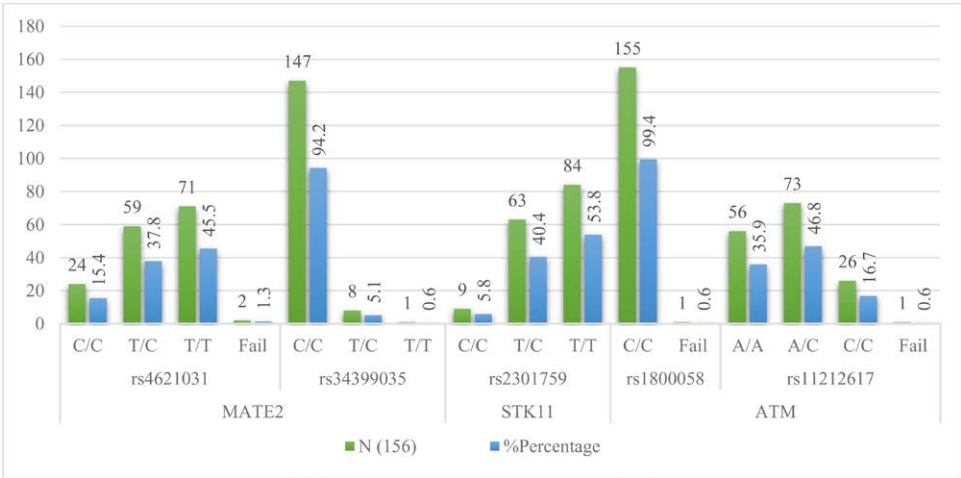

Figure 2. Genetic variations among the study participants. ATM = telangiectasia mutated, MATE2 = multidrug and toxin extrusion protein 2, STK11 = serine/threonine kinase 11.

4. Discussion

This study focused on the complex relationship between variations in 3 important genes, ATM, STK11, and MATE2, and the response to metformin treatment in patients with T2DM. This area has become highly important due to the increased use of metformin as a major treatment for diabetes in addition to the identification of genetic components that may lead to variations in clinical response. In this regard, ATM, STK11, and MATE2 have been identified as the major genes involved in metformin pharmacodynamics and pharmacokinetics.[26] These could

Table 2

Genetic variations among patients and control.

			Subjects				
Gene	SNP ID	Genotype	Patients n = 76	Control n = 80	Total (n = 156)	*P* value	Holm–Bonferroni correction
MATE2	rs4621031	C/C	14 (18.9%)	10 (12.5%)	24 (15.6%)	.451	
	P xx	T/C	29 (39.2%)	30 (37.5%)	59 (38.3%)		0.05
		T/T	31 (41.9%)	40 (50%)	71 (46.1%)		
		C	57 (38.5%)	50 (31%)	107 (34.7%)		
		T	91 (61.5%)	110 (69%)	201 (65.3%)		
	rs34399035	C/C	70 (90.9%)	77 (97.25%)	147 (94.2%)	.160**	
		T/C	6 (7.8%)	2 (2.5%)	8 (5.2 %)		0.0125
		T/T	0 (0%)	1 (1.25%)	1 (0.6%)		
		C	146 (96%)	156 (97.5 %)	302 (96.8%)		
		T	6 (4%)	4 (2.5%)	10 (3.2%)		
STK11	rs2301759	C/C	5 (6.6%)	4 (5%)	9 (5.8%)	.335**	
		T/C	26 (34.2%)	37 (46.2%)	63 (40.4%)		0.0167
		T/T	45 (59.2%)	39 (48.8%)	84 (53.8%)		
		C	36 (23.7%)	45 (28.1%)	81 (26 %)		
		T	116 (76.3%)	115 (71.9 %)	231 (74%)		
ATM	rs1800058	C/C	75 (100%)	79 (100%)	154 (100%)	–	
	P x	T/C	0 (0%)	0 (0%)	0 (0%)		
	C x	T/T	0 (0%)	0 (0%)	0 (0%)		
		C	150 (100%)	158 (100%)	308 (100%)		
		T	0 (100%)	0 (0%)	0 (0%)		
		A/A	29 (38.7%)	27 (33.8%)	56 (36%)	.419*	
	rs11212617	A/C	31 (41.3%)	42 (52.5%)	73 (47%)		0.025
	P x	C/C	15 (20%)	11 (13.7%)	26 (17%)		
		A	89 (59.3%)	96 (60%)	185 (59.7%)		
		C	61 (40.7%)	64 (40%)	125 (40.3%)		

ATM = telangiectasia mutated, MATE2 = multidrug and toxin extrusion protein 2, STK11 = serine/threonine kinase 11.

* Chi-square test.

** Fisher exact test. Statistical significance was deemed at $P < .05$.

Table 3

Demographic and clinical characteristics regarding metformin response among patients.

		Metformin response		
Factors		Responder No = 56	Non-responder No = 20	*P* value
Age	Mean ± SD	50.29 ± 10.95	51.67 ± 7.69	.813**
	Median (IQR)	52 (40.5–57.5)	50.5 (44.5–55)	
BMI	Mean (SD)	33.66 ± 5.18)	31.15 ± 4.82	.062***
Gender	Female	28 (50%) 82%	6 (30%) 18%?	.123*
	Male	28 (50%) 67%	14 (60%) 33%	
Cholesterol	Mean (SD)	4.82 ± 1.09	4.73 ± 0.89	.750***
Triglyceride	Mean (SD)	2.67 ± 8.78	1.678 ± 1.09	.797**
	Median (IQR)	1.49 (0.88–1.84)	1.32 (0.84–2.02)	
LDL	Mean (SD)	3.389 ± 1.05	3.04 ± 0.89	.145**
	Median (IQR)	3.37 (2.57–4.28)	2.97 (2–2.96)	
HDL	Mean (SD)	1.28 ± 0.423	1.28 ± 0.33	.888**
	Median (IQR)	1.21 (0.97–1.21)	1.20 (1.01–1.19)	
Creatinine	Mean (SD)	78.44 ± 42	70.67 ± 17.3	.574**
	Median (IQR)	73 (62.35–87.5)	74.5 (58.75–79.25)	
HbA1c %	Mean (SD)	7.13 ± 1.90	9.74 ± 2.53	**<.001****
	Median (IQR)	6.6 (5.82–7.3)	8.25 (7.52–12.05)	

Statistical significance was deemed at $P < .05$.

BMI = body mass index, HbA1c = hemoglobin A1c, HDL = high density lipoprotein, IQR = interquartile range, LDL = low density lipoprotein

* Chi-square test.

** Mann–Whitney test.

*** Independent *t* test.

Table 4

Genetic variations regarding metformin response to metformin among T2DM patients.

Gene	SNP ID	Genotype	Metformin response		*P* value	Holm–Bonferroni correction	Odds ratio
			Responder N = 56	Non-responder N = 20			
MATE2	rs4621031	C/C	13 (24.1%)	1 (5.0%)	.140*		
		T/C	21 (38.9%)	8 (40.0%)		0.025	
		T/T	20 (37.0%)	11 (55.0%)			
		C	47 (44%)	10 (25%)			2.31 (1.03–5.20)†
		T	61 (56%)	30 (75%)			
	rs34399035	C/C	53 (94.6%)	17 (85%)	.183**		
		T/C	3 (5.4%)	3 (15%)		0.05	
		T/T	0 (0%)	0 (0%)			
		C	109 (97.3%)	37 (92.5%)			2.95 (0.57–15.23)‡
		T	3 (2.7%)	3 (7.5%)			
STK11	rs2301759	C/C	5 (8.9%)	0 (0%)	**.021****		
		T/C	23 (41.1%)	3 (15%)		0.0125	
		T/T	28 (50%)	17 (85%)			
		C	33 (29.5%)	3 (7.5%)			5.15 (1.48–17.89)§
		T	79 (70.5%)	37 (92.5%)			
ATM	rs1800058	C/C	55 (73.3%)	20 (26.7%)	–		
		T/C	0 (0%)	0 (0%)			
		T/T	0 (0%)	0 (0%)			
		C	55 (100%)	20 (100%)			–
		T	0 (0%)	0 (0%)			
	rs11212617	A/A	21 (37.5%)	6 (33.3%)	.115*		
		A/C	21 (37.5%)	11 (61.1%)		0.0167	
		C/C	14 (25%)	1 (5.6%)			
		A	63 (56.2%)	33 (71.7%)			1.97 (0.94–4.15)‖
		C	49 (43.8%)	13 (28.3%)			

Statistical significance was deemed at $P < .05$.

ATM = telangiectasia mutated, MATE2 = multidrug and toxin extrusion protein 2, STK11 = serine/threonine kinase 11.

† The proportion of responders among the C Genotype was 2.31 times more than responders among the T Genotype.

‡ The proportion of responders among the C Genotype was 2.95 times more than responders among the T Genotype.

§ The proportion of responders among the C Genotype was 5.15 times less than responders among the T Genotype.

‖ The proportion of responders among the C Genotype was 1.97 times less than responders among the A Genotype.

* Chi-square test.

** Fisher Exact test.

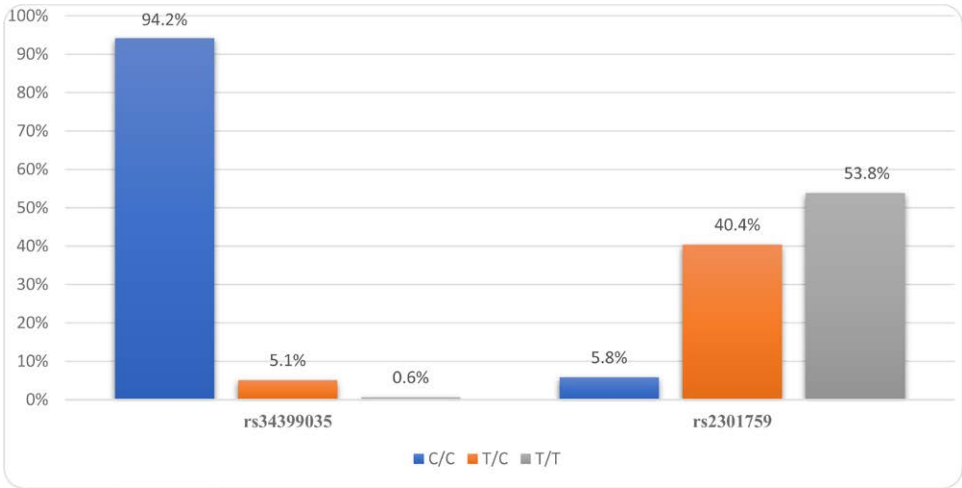

Figure 3. Genotype and allele frequencies for rs34399035 and rs2301759 in the metformin response participants. It is noted that patients who were carriers of the CC alleles in rs34399035 responded well to metformin, whereas carriers of the CC alleles in rs2301759 responded poorly to metformin.

comprise components such as baseline glycemic control, period of diabetes, BMI, sex, and age.

The gender dimension of the study showed a somewhat higher percentage of females (55.8%), which acknowledges the potential sex-specific differences in diabetes and treatment responses. These demographic details are essential for generalizing the conclusions of this study to a range of patient demographics. Other studies have also shown a larger percentage of diabetic females and stressed the need for gender-specific treatment strategies for managing diabetes-related problems.[27] Their study indicated that treatment options are greatly affected by sex-specific variations. Therefore, demographic considerations are crucial for properly personalizing therapies and generalizing findings.

Table 5

Bivariate logistic regression analysis of genetic variations regarding metformin response among T2DM patients.

Gene	Categories	Odds ratio (95% of confidence interval)	*P* value	Holm–Bonferroni correction
MATE2	rs4621031 (T/T = ref)			
	C/C	5.14 (0.5–49)	.155	0.01
	T/C	1.02 (0.3–3.6)	.982	0.05
	rs34399035 (T/C = ref)			
	C/C	2.01 (0.3–13.4)	.470	0.025
STK11	rs2301759 (T/T = ref)			
	T/C	3.98 (0.98–16.1)	.053	0.0083
ATM	rs11212617 (C/C = ref)			
	A/A	0.42 (0.04–4.3)	.466	0.0167
	A/C	0.25 (0.02–2.6)	.245	0.0125

Statistical significance was deemed at $P < .05$.

ATM = telangiectasia mutated, MATE2 = multidrug and toxin extrusion protein 2, STK11 = serine/threonine kinase 11.

An average BMI of 33 kg/m^2 among T2DM patients indicates that the study population was primarily overweight. This observation was consistent with the documented relationship between diabetes and obesity.[28] Given that obesity is known to affect insulin sensitivity and general metabolic health, the emphasis of this study on BMI is noteworthy. This practical significance is demonstrated by the participants' overweight profiles, which reflect the rising incidence of obesity and overweight among those with diabetes.[28] The results also showed that 73.7% of patients responded well to metformin. This is in agreement with other studies that have reported a high response rate to metformin.[4,20] This large proportion demonstrates how well metformin controls blood sugar levels in the study population, thus emphasizing its position as a cornerstone in the management of diabetes. In fact, a small percentage of patients do not experience metformin's efficacy which could be due to genetic changes.[29]

In this regard, the investigation of genetic variants in this study provided important new information on the intricate connection between specific SNPs and metformin responses in patients with T2DM, such as STK11 and its SNP rs2301759, which showed a strong correlation with metformin response. Moreover, the possible involvement of STK11 gene in the regulation of metformin efficacy is suggested by the higher percentage of C/C and T/C genotypes in responders to metformin than in non-responders. Consequently, the C allele could have a positive response to metformin and could be more beneficial for glycemic control of the STK11 gene. This finding is in line with other studies that investigated metformin pharmacogenomics and discovered among various genes strong genetic connections between the SNP rs2301759 and metformin response.[30] Therefore, this SNP (rs2301759) could influence metformin response in various ethnicities.

Unfortunately, other SNPs investigated in the present study (rs4621031, rs34399035, rs1800058, and rs11212617) did not show any significant effect on the metformin response. This emphasizes the intricate genetic environment that influences the drug response. Genetic differences in response to drugs are frequently multifactorial. Hence, the lack of significance of these specific SNPs could be explained by many variables, such as the influence of other genes or environmental factors.[31] Despite the insignificance of some of these SNPs in metformin response in this study, some observations are worth mentioning. For SNP rs4621031, the C allele showed a positive response to metformin, as demonstrated by the responders' carriers of the CC genotype (24.1%) compared to non-responders (5.0%). Other studies have also found an association between rs4621031 and metformin response in white Europeans.[30]

Similar findings were observed for SNP rs11212617, in which the C allele also showed a positive response to metformin, as shown by the responder carriers of the CC genotype (25.0%) compared to non-responders (5.6%). SNP rs11212617 was also found to be associated with a significant metformin response in a previous study of South Indian population.[32] Although the current results showed no association between SNP rs34399035 and metformin response, another study indicated a minor decrease in HbA1c over 24 months of metformin treatment in a South Danish cohort.[33]

In conclusion, the present study could contribute considerably to the development of customized medicine for the treatment of T2DM in Saudi patients. This emphasizes the importance of considering the clinical features, demographics, and genetic variants when determining metformin responses. The results offer a strong basis for further research, and it is essential to overcome the noted limitations, such as increasing sample sizes and genetic panels, to further our understanding of the genetic foundations of medication responses in a variety of populations. With the potential to enhance the results for a wide spectrum of variants and genes related to metformin response, this study represents a step toward more customized and focused approaches for diabetes therapy.

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Author contributions

Data curation: Abdulhhakim A. Alzahrani.
Investigation: Huda M. AlKreathy.
Methodology: Huda M. AlKreathy, Ahmed Esmat, Zoheir A. Damanhouri.
Project administration: Huda M. AlKreathy.
Validation: Zoheir A. Damanhouri.
Writing – original draft: Abdulhhakim A. Alzahrani.
Writing – review & editing: Ahmed Esmat, Zoheir A. Damanhouri.

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