ORIGINAL ARTICLE

CONTENTS

Influence of different factors (duration of disease, gender, education, patients' history, job and age) in metformin response in type 2 diabetes mellitus patient

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ABSTRACT

Aim: This study aims to evaluate how various factors affect various aspects of glycemic control in individuals with type 2 diabetes who are undergoing metformin treatment.

Materials and Methods: A cross-sectional study involved 150 participants who met specific criteria, including being aged between 30 and 70, having a type 2 diabetes diagnosis, and using 1000 mg of metformin as the monotherapy for at least three months. Collected data encompassed various measures, such as levels of glycated hemoglobin (HbA1c), fasting blood glucose concentrations, fasting serum insulin levels, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and insulin sensitivity.

Results: Our research reveals that when it comes to factors such as several socio-demographic variables, there is no statistically significant difference (p-value ≥ 0.05) between patients who exhibit a positive response to metformin and those who do not. Nevertheless, distinctions were noted in patients' previous history and the duration of their illness, which did influence their treatment response.

Conclusions: Glycemic parameters in individuals with type 2 diabetes can be impacted by a range of factors, such as age, gender, and occupation also it's important to note that these outcomes influenced by additional variables like the adherence for medication, and the existence of diabetes-related complications.

KEY WORDS: genetic polymorphisms, metformin, multidrug and toxin extrusion pharmacogenomics, type 2 diabetes mellitus

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INTRODUCTION

Metformin is the preferred initial treatment for type 2 diabetes because of its strong glucose-lowering capabilities, proven safety, and affordability. Although metformin has multiple effects on glucose metabolism, it is widely agreed that its primary glucose-lowering action in type 2 diabetes patients is mainly through the suppression of hepatic gluconeogenesis [1]. Its primary mechanism of action involves enhancing insulin sensitivity by increasing the expression of insulin receptors and stimulating tyrosine kinase activity [2]. Numerous research studies and clinical trials have provided evidence supporting the effectiveness of metformin either as a monotherapy or in combination with other medications for managing type 2 diabetes (T2D) [3]. Metformin treatment reduces blood levels in type 2 diabetes by affecting multiple pathways, including the reduction of hepatic gluconeogenesis [4]. Approximately 50% of the orally administered metformin dose is absorbed into the bloodstream, after which it is distributed to various tissues [5]. Metformin is present in its unbound form and is eliminated unchanged through renal clearance. Notably, the effectiveness of metformin varies significantly, with over 30% of patients treated with metformin not responding effectively [6]. Recent independent studies have highlighted significant variability in individual responses to metformin therapy [7]. Additionally, metformin treatment has been linked to a higher incidence of gastrointestinal symptoms, ranging from 2% to 63% in different clinical trials, which is notably more common than with most other oral antidiabetic medications. In about 4% of cases, these gastrointestinal symptoms can be severe enough to lead to the discontinuation of metformin therapy prematurely [8].

AIM

This study aims to evaluate how various factors affect various aspects of glycemic control parameters in Iraqi individuals with type 2 diabetes who are with metformin treatment as a single therapy.

MATERIALS AND METHODS

STUDY DESIGN

A cross-sectional study was conducted between April 2022 and June 2023, involving a sample of 150 individuals diagnosed with type 2 diabetes mellitus depending on the American Diabetes Association criteria 2012. These criteria define type 2 diabetes using parameters such as HbA1c levels ≥6.5%, fasting plasma glucose (FPG) levels ≥126 mg/dl, 2-hour plasma glucose levels ≥200 mg/dl during an oral glucose tolerance test (OGTT), or random plasma glucose levels ≥200 mg/dl. The study participants were recruited randomly from the diabetes center at Al-Sadar Teaching Hospital in Najaf, Iraq, and the study received ethical clearance from the Medical Ethics Committee of the Faculty of Medicine at Kufa University.

STUDY POPULATION

The study population comprised 150 individuals with type 2 diabetes, including both males and females, who had been undergoing a monotherapy regimen of metformin tablets (1000 mg) once daily for at least three months duration [9]. These participants range between 30 to 70 years and exclusion criteria for the study encompassed patients with significant organ dysfunction, including heart, liver, and renal failure, individuals above 70 years of age, those with a BMI exceeding 30 kg/m^2, pregnant women, patients with chronic gastrointestinal disorders or malabsorption syndrome, and individuals concurrently using other oral hypoglycemic agents (OHAs) or insulin.

DATA COLLECTION

The process of collecting data involved the investigator using a standardized questionnaire to gather a range of demographic and clinical information from the patients. This information covered details such as their names, ages, body weight, height, duration of the disease, medical history, family history, dietary patterns, sleep routines, and occupations. To calculate the body mass index (BMI), measurements of the weight of the patient and height were taken. Height measurements were taken with patients standing upright, barefoot, arms resting at their sides, and feet together. Weight measurements were recorded with patients standing on a scale, wearing lightweight clothing, and without shoes or socks. The BMI was computed using the formula BMI = weight (in kilograms) / height (in square meters). Patients were then categorized as either normal (BMI<25 kg/m^2), overweight (BMI between 25 to 29 kg/m^2), or obese (BMI ≥30 kg/m^2) [10]. The glycemic control parameters measured include:

• FBG (fasting blood glucose): measured by "RanDox kit-UK", which is rely on the "PAP enzymatic" measurement of glucose.

• HbA1c: the percentage assessed by using immuno assay method by Stanbio/USA kit.

• Serum insulin: assayed according to the procedure recommended by (BTLAB®) company.

• Homeostasis-Model Assessment for Insulin Resistance (HOMA-IR): The approach presented by used the "Homeostasis-Model Assessment for Insulin Resistance (HOMA-IR)" index to measure insulin resistance [11], the of HOMA-IR was calculated in the following manner:

HOMA-IR = Fasting-insulin (μU/L) * Fasting-glucose (mmol/L)/22.5

• Insulin sensitivity: the quantitative insulin sensitivity check index (QUICKI) is derived using the inverse of the sum of the logarithms of the fasting insulin and fasting glucose [12]:

1 / (log(fasting insulin μU/mL) + log(fasting glucose mg/dL)

BLOOD SAMPLE COLLECTION

For the collection of blood samples, each patient fasted for 8-12 hours overnight, and venous blood was drawn while they were seated. 5 ml of blood was divided into an EDTA tube, with the remaining 2 ml slowly transferred into disposable serum tubes containing a separating gel. Within the EDTA tubes, the blood was allocated for HbA1c assessment using the Immunoassay method. The blood within the serum tubes was left to clot at room temperature for 10-15 minutes, after which it was centrifuged at 3000 × g for approximately 3 minutes. The resulting sera were stored at -80°C until analysis was carried out using the BT LAB® ELISA kit to measure serum insulin, following the recommended procedure provided by the company. Fasting blood glucose levels were determined using the RanDox® kit, which operates based on the PAP enzymatic glucose determination method.

STATISTICAL ANALYSIS

All data was managed by using SPSS version 22, ANOVA test and t-test used for multiple comparisons, and chi-square test for utilization of non-numerical variables. Values of ≤ 0.05 will be considered to be statistically significant.

RESULT

Table 1 shows the sociodemographic data of the participants of the study. 150 T2DM patients with an

Table 1. Socio-demographic data of the participants

Variables		HbA1c <6.5%	HbA1c >6.5%	χ^2	P value
Patients History	No	17	71	30.5713	3.224e-8
	Yes	22	39		
Age		52.00±1.648	53.90±1.82	1.131	0.260
BMI		27.93±0.58	28.01±0.63	0.076	0.940
Duration		6.13±0.94	7.94±0.55	1.681	0.095
Age category	<40	4	6	1.53978	0.4631
	40-50	13	30		
	>50	23	73		
Duration category	<5	22	37	6.5388	0.03803
	5-10	8	43		
	>10	10	29		
Education	Primary	26	82	1.66878	0.4341
	Intermediate	12	22		
	University	2	5		
Job	Yes	12	39	0.388916	0.5329
	No	28	71		
Drugs	No drugs	19	61	0.842973	0.3585
	Other drugs	21	48		
Gender	Male	10	44	2.99042	0.08376
	Female	30	65		
Another related disease	Yes	29	73	0.414034	0.5199
	No	11	36		
HbA1c		26.17%	73.82%	-	-

Table 2. Glycemic variables levels (mean ± SE) in study groups

Variables	HbA1c <6.5%	HbA1c >6.5%	P value
FBC	138.7±9.755	248.62±8.843	0.000
HbA1c	6.036±0.070	9.77±0.203	0.000
Insulin	7.148±1.701	9.57±1.26	0.355
HOMA- IR	45.59±11.55	105.05±14.39	0.019
Insulin sensitivity	1.18±0.08	1.03±0.047	0.587

average age of 53.97±1.86 years and a mean BMI of 28.34±1.58 kg/m^2 (Table 2) were included in the study. Socio-demographic factors such as BMI, age, education, occupation, gender, presence of other medical conditions, past medical history, and dietary habits revealed differences between the two groups. However, these differences did not reach statistical significance (with p-values ≥ 0.05). On the other hand, there was a notable and statistically significant difference between the two groups in terms of disease duration and the patients' medical histories. The patients were classified into 2 subgroups according to their glycemic control; poorly controlled diabetics (HbA1c ≥ 6.5%) who were 73.82% compared to good glycemic control (HbA1c ≤ 6.5%) who were 26.17% (Table 1).

The difference in glycemic parameters between the good and poor responders is represented in table 2. The analysis reveals a substantial disparity in mean glycemic parameters between individuals who responded well and those who responded poorly to metformin treatment. Notably, there were highly significant differences in FBS, HbA1c, and HOMA-IR between these two groups, as indicated by p-values of 0.000, 0.000, and 0.019, respectively. While serum insulin level was observed to be higher in poor responders compared with good responders, but not statistically significant.

Table 3 represents data indicating variations in glycemic parameters (FBS, HbA1c, serum insulin, insulin sensitivity, and HOMA-IR) among good and poor responders about the duration of the disease.

Table 3. Means differences in study variables (mean ± SE) according to duration of disease

Variable	HbA1c <6.5%			P value	HbA1c >6.5%			P value
	<5 years	5 - 9 years	>10 years		<5 years	5 - 9 years	>10 years	
FBG (mg/dl)	122.36±7.21	141.12±16.9	172.70±31.75	0.099	249.32±9.53	246.13±24.95	249.58±18.47	0.843
HbA1C	5.99±0.094	5.98±0.16	6.18±0.14	0.488	9.65±9.21	10.53±0.52	9.34±0.34	0.401
IN	4.81±0.94a	5.56±7.36b	6.34±1.53ab	0.043	10.74±1.6	10.27±1.79	11.58±20.05	0.353
IR	27.98±6.05a	33.21±52.06b	39.86±9.14ab	0.046	118.95±18.76	106.05±17.01	144.67±245.89	0.162
IS	0.94±0.11a	1.41±0.15ab	0.02±0.14b	0.067	1.17±0.06	1.14±0.080	1.09±0.58	0.764

Table 4. Means differences in study variables (mean ± SE) according to gender

Variable	HbA1c <6.5%		P value	HbA1c >6.5%		P value
	Male	Female		Male	Female	
FBG (mg/dl)	124.27±8.61	144.17±13.46	0.378	252.75±15.21	255.76±10.39	0.695
HbA1C	6.16±0.08	5.99±0.09	0.312	9.86±23.40	9.69±0.92	0.088
IN	3.85±0.95	8.44±2.30	0.230	7.65±1.143	10.90±1.98	0.209
IR	24.29±8.34	52.10±15.92	0.294	80.04±10.60	122.25±23.06	0.150
IS	1.90±0.14	1.13±0.09	0.217	1.14±0.055	1.12±0.07	0.794

Table 5. Means differences of study variables (mean ± SE) according to education

Variable	HbA1c <6.5%			P value	HbA1c >6.5%			P value
	Primary	Secondary	University		Primary	Secondary	University	
FBG	138.23±13.49	128.33±11.961	207.00±16.0	0.253	249.28±9.53	256.13±24.958	205.60±30.596	0.543
HbA1C	6.11±0.087	6.03±0.150	6.01±0.200	0.799	9.65±0.21	10.53±0.529	8.52±1.092	0.089
IN	8.76±2.49	4.16±0.849	8.03±4.09	0.469	10.74±1.63	6.24±1.206	3.94±1.071	0.238
IR	72.99±17.25	25.23±5.987	71.63±31.93	0.496	118.69±18.54	68.68±12.615	37.22±10.532	0.230
IS	1.09±0.107	0.94±0.13	1.27±0.24	0.503	1.05±0.060	1.13±0.053	1.95±0.126	0.720

Table 6. Mean differences in study variables (mean ± SE) according to patients' history

Variable	HbA1c <6.5%		P value	HbA1c >6.5%		P value
	No	Yes		No	Yes	
FBG	143.17±15.00	144.22±13.66	0.731	254.95±11.06	260.75±13.91	0.800
HbA1C	6.03±0.119	6.15±0.092	0.081	10.05±0.298	42.23±21.52	0.988
IN	4.67±0.91563	9.06±2.89	0.631	9.40±1.387	9.79±2.28	0.306
IR	31.78±6.806	53.90±20.176	0.711	104.03±15.739	106.17±25.88	0.369
IS	0.97±0.108	0.13±0.120	0.788	1.17±0.055	1.08±0.079	0.195

These differences do not reach statistical significance. Notably, both groups exhibit elevated mean values for glycemic control parameters as the duration of the disease progresses.

Table 4 presents the findings, indicating variations in glycemic parameters (FBS, HbA1c, serum insulin, insulin sensitivity, and HOMA-IR) between good and poor responders' patients. These differences do not reach statistical significance. Interestingly, when comparing genders, females exhibit higher mean values across glycemic control parameters in comparison to males except HbA1c is higher in males.

As documented in table 5, the data reveals differences in glycemic parameters (FBS, HbA1c, serum insulin, insulin sensitivity, and HOMA-IR) between good and poor responders. These differences do not achieve statistical significance. In general, individuals with higher education levels tend to exhibit lower values across most glycemic parameters compared to those with primary and secondary education.

Table 6 illustrates findings that indicate distinctions in glycemic parameters, FBS, HbA1c, serum insulin, insulin sensitivity, and HOMA-IR, between good and poor responders. However, it's important to note that

Table 7. Means differences in study variables (mean ± SE) according to job

Variable	HbA1c <6.5%		P value	HbA1c >6.5%		P value
	Yes	No		Yes	No	
FBG (mg/dl)	126.41±11.597	143.96±13.50	0.426	252.66±15.63	256.40±10.47	0.733
HbA1C	5.91±0.143	6.10±0.082	0.245	15.05±23.08	18.52±8.03	0.415
IN	4.47±1.01	8.33±2.39	0.302	6.31±0.912	11.37±1.872	0.056
IR	27.56±7.950	51.68±16.54	0.351	70.04±10.10	124.18±21.313	0.072
IS	1.96±0.139	1.11±0.102	0.404	1.09±0.05	1.06±0.06	0.513

Table 8. Means differences in study variables (mean ± SE) according to age categories

Variable	HbA1c <6.5%			P value	HbA1c >6.5%			P value
	<40 years	40-50 years	>50 years		<40 years	40-50 years	>50 years	
FBG	106.25±5.80	133.92±14.63	147.04±14.64	0.460	276.33±31.54	238.16±16.10	250.69±11.17	0.622
HbA1C	5.52±0.18a	5.99±0.10ac	5.15±0.093c	0.027	11.00±1.28	9.28±0.34	9.87±0.24	0.152
IN	5.52±2.95	10.66±4.80	5.09±0.93	0.398	15.08±6.15	9.49±2.19	9.08±1.61	0.567
IR	23.27±11.38	70.55±33.60	23.85±5.96	0.320	102.02±68.39	97.00±20.31	102.79±19.27	0.527
IS	1.14±0.24	1.11±0.174	1.01±0.099	0.954	1.40±0.176	1.10±0.10	1.12±0.05	0.377

these differences do not reach statistical significance. Interestingly, all glycemic parameters show higher values in patients with a previous family history of type 2 DM in both groups.

Based on the findings presented in table 7, the statistical analysis indicates that there is no notable difference in glycemic parameters, including FBS, HbA1c, serum insulin, insulin sensitivity, and HOMA-IR, when comparing good and poor responder patients. It is noteworthy that across both good and poor responder patient groups, all glycemic parameters exhibit lower values among individuals who are employed as opposed to those who are unemployed.

Table 8 reveals variations in glycemic parameters FBS, HbA1c, serum insulin, insulin sensitivity, and HOMA-IR between good and poor responder patients. These differences were statistically non-significant. Notably, among good responder patients, there is a significant distinction in HbA1c levels observed across various age subgroups. It's worth mentioning that for most of the glycemic parameters, the mean values are lower in patients aged over 50 years compared to their younger counterparts.

In this study, the correlation between the studied glycemic control parameters in two groups is clarified in table 9. There is a significant strong positive correlation between serum insulin and HOMA-IR, with R = 0.980 and P < 0.000. In addition, HOMA-IR has a significant positive correlation with insulin sensitivity (R= 0.729 and P < 0.000). This means that as insulin sensitivity decreases, insulin resistance increases since they are inversely related. There is a significant moderate positive correlation between HBA1C and FBG, with R = 0.393 and P < 0.000. This means that higher levels of HBA1C are associated with higher levels of FBG. There is a weak inverse correlation between age and HBA1C, with R = -0.072, P = 0.458. There is a significant positive correlation between the duration of diabetes and age, with R = 0.221, and P = 0.020.

DISCUSSION

It is crucial to customize glycemic management for individuals with type 2 diabetes, considering factors such as age, comorbidities, and the risk of hypoglycemia. Effective blood glucose control, with a target HbA1c level below 6.5%, has been shown to substantially reduce the risk of nephropathy and cardiovascular complications [11]. Metformin is actively transported and distributed in the body, and its effects can vary significantly among individuals [13, 14]. We found that the treatment outcome was not affected by the body measurements (such as BMI) of the patient or most of their social and demographic characteristics, as the difference was not statistically significant (p-value ≥ 0.05). However, we did notice that the medical history of a patient and how long they had the disease influenced their response to the treatment. Our finding agrees with a study from Iran that included 103 female diabetes patients who were divided into two groups based on their HbA1c levels. The study from Iran showed that there was no big difference in the social and body measurement data between the two groups using a single-variable analysis. However, using a multiple-variable analysis, the study found that waist size was an important factor for high HbA1c levels [15]. In a study conducted

Table 9. The correlation coefficients among study variables in study groups

		FBG	HBA1C	IN	HOMA-IR	INS	Age	Duration
FBG	R		0.372	0.054	0.136	-0.100	0.383	0.171
	P		0.018	0.740	0.401	0.450	0.015	0.292
HBA1C	R	0.393		0.066	0.149	-0.085	0.390	0.160
	P	0.000		0.689	0.366	0.607	0.014	0.330
IN	R	-0.016	-0.153		0.980**	0.693	-0.188	0.107
	P	0.867	0.112		0.000	0.000	0.253	0.518
HOMA-IR	R	0.159	-0.081	0.959		0.636	-0.175	0.110
	P	0.098	0.401	0.000		0.000	0.288	0.503
INS	R	-0.008	-0.066-	0.775	0.729		-0.129	0.186
	P	0.938	0.495	0.000	0.000		0.435	0.256
Age	R	-0.050	-0.072	-0.014	-0.023	-0.007		0.452
	P	0.602	0.458	0.883	0.808	0.943		0.004
Duration	R	0.007	-0.098	0.087	0.123	-0.085	0.221	
	P	0.945	0.309	0.364	0.202	0.375	0.020	

by Ghazanfari Z et al. [16] was revealed that a longer duration of diabetes was closely linked to suboptimal glycemic control. Our research findings, as shown in table 3, corroborate this observation. We noticed that among both good and poor responder patients, glycemic control parameters tended to worsen as the duration of the disease increased but were statistically non-significant. This finding is in line with numerous other studies that have consistently shown a significant relationship between the duration of diabetes and the deterioration of glycemic control [14]. This phenomenon can be explained by the gradual decrease in insulin production over time, which is associated with dysfunction in beta cells. This might clarify why dietary changes or oral diabetes medications become less successful as the duration of the disease increases [17]. A 2016 study showed that there is a discrepancy in the effect of gender on HbA1c levels. The study reported that males had higher HbA1c levels than females (0.165%, $p<0.0001$). However, this difference was not important clinically except for people aged 30 to 59 years old [18]. Our results agree with this trend, showing that males had a higher mean HbA1c level than females in both groups, as shown in table 4. On the other hand, a study with children who had type 1 diabetes mellitus found a significant rise in HbA1c levels in females compared to males at diagnosis. This difference may be related to the start and timing of puberty [19]. As shown in table 5, our research found that people with higher education had lower average levels of different blood sugar indicators than those with lower education in both groups. This finding agrees with another study that proposes that at least 12 years of education is an essential factor for patients, as it helps them understand their disease better, communicate effectively with healthcare providers, and manage their condition successfully [20]. We investigated the possible link between a patient's diabetes mellitus family history and their blood glycemic control indicators in our recent study. Our results showed that patients who had a family history of diabetes mellitus had slightly higher blood sugar control indicators than those who did not. However, these differences were not statistically significant, as shown in table 6. This finding agrees with another study that also found that people with a diabetes family history had higher levels of blood sugar control indicators, especially HbA1c and fasting plasma glucose levels [21]. On the other hand, some other studies, such as the one by Ghazanfari et al. in 2010, did not find any significant relationship between family history and blood glucose control indicators [22]. We examined the effect of employment status on blood sugar control indicators in our study, as presented in table 7. We observed that the glycemic control indicators were better in employed patients than in unemployed ones. A systematic review and meta-analysis of the literature from electronic databases was done on the therapeutic effect of exercise on blood sugar levels in people with type 2 diabetes mellitus. The review showed that exercise plays a significant role in improving blood sugar control and life quality, BMI, and waist size. Exercise could be a safe and effective addition to drug treatments in these patients [23]. We found that both groups had worse blood sugar control in younger people than in older people, as shown in table 8. This finding agrees with a study by *Sanal et al.* in 2011, which reported that patients who were 60 years old or older had better blood sugar control. The possible explanation for this difference in blood sugar

control between younger and older people could be that younger patients may not take their treatment plan as seriously as older patients [24].

CONCLUSIONS

The glycemic parameters of type 2 diabetic patients are influenced by various factors, such as age, sex, job, patient education, family history, and duration of disease. Some studies have found that younger patients, male patients, unemployed patients, and patients with a family history of diabetes have worse glycemic control than their counterparts. However, these findings are not consistent across all studies and may depend on other variables, such as the type and intensity of treatment, the level of adherence, and the presence of complications. Patient education is an important factor that can improve glycemic control by enhancing the understanding of the disease and self-management skills. Therefore, it is essential to consider the individual characteristics and needs of each patient and provide tailored interventions to optimize their glycemic outcomes.

LIMITATION OF STUDY

One of the main limitations of this study is that cannot establish a causal relationship between the variables of our study. For example, we find that age, sex, job, patient education, family history, and duration of disease are associated with glycemic parameters in type 2 diabetic patients with metformin, you cannot conclude that these factors cause or affect the glycemic outcomes. There may be other factors that influence both the exposure and the outcome, such as lifestyle, or genetic factors. These factors are called confounding variables and they can bias the results of a study.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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