ORIGINAL ARTICLE

CONTENTS

Diet control and BMI impact on Metformin response in type 2 Diabetes mellitus patients

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ABSTRACT

Aim: To assess the impact of BMI and diet control on variation in response to metformin monotherapy in Iraqi people with type 2 DM.

Materials and Methods: a cross-sectional study included 150 patients who met specific criteria, such as being between 30 and 70 years old, diagnosed with type 2 diabetes, and on a daily dose of 1000 mg metformin as a monotherapy for at least three months. Data collected included body mass index (BMI) and glycemic control parameters such as: glycated hemoglobin (HbA1c) levels, fasting blood glucose levels, fasting serum insulin levels, HOMA-IR, and insulin sensitivity. The patients according to their metformin response classified into two groups based on HbA1c as following: poor (HbA1c≥6.5% and good (HbA1c≤6.5%) responder's patients.

Results: The statistical analysis suggests that there is no meaningful distinction in glycemic control parameters when comparing good and poor responders within specific BMI subgroups and among individuals practicing diet control. However, in a broader context, it is evident that glycemic control parameters tend to be lower in patients with lower BMI and those who are following a controlled diet.

Conclusions: The correlation between diet control and BMI with glycemic control in diabetic patients, underscoring the significance of lifestyle adjustments in the management of diabetes.

KEY WORDS: BMI, metformin response, type 2 diabetes mellitus, diet control

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM), a prevalent metabolic disorder, results from the interplay of two main factors: impaired insulin secretion by pancreatic β-cells and the reduced responsiveness of insulin-sensitive tissues to insulin [1]. Insulin synthesis, release, and recognition are tightly regulated molecular processes that are essential for maintaining glucose balance. Any disruptions in these mechanisms can lead to metabolic disturbances, potentially contributing to the development of certain medical conditions [2]. Metformin is extensively employed as the initial medication for managing type 2 diabetes (T2D). Acting primarily on the liver, metformin effectively reduces hepatic glucose production [3]. Metformin helps maintain glucose balance by inhibiting gluconeogenesis, encouraging glycolysis, and suppressing glycogenolysis, which is closely linked to increased hepatic glucose production (HGP). Furthermore, metformin improves insulin sensitivity and lowers abnormal lipid levels in individuals with type 2 diabetes (T2D) [4-5]. Diet control is a cornerstone of managing T2DM. Patients are often advised to adopt a diet that helps regulate blood sugar levels. Maintaining a balanced intake of carbohydrates, proteins, and healthy fats, along with portion control and carbohydrate counting, can lead to better blood sugar control. This, in turn, can reduce the need for medications or insulin therapy [6]. The recommended nutritional therapy for diabetic patients includes a balanced nutritional calculation from carbohydrates, fruits, vegetables, whole grains, nuts, and low-fat milk [7]. Measuring diet control in diabetic patients is crucial for managing their condition and preventing complications. Several ways are used to assess and monitor diet control in diabetic individuals such as blood glucose monitoring and HbA1c test [8]. BMI is a measure of body weight relative to height and is commonly used to assess whether an individual is underweight, normal weight, overweight, or obese. Excess

body weight, especially obesity, is a major risk factor for the development of T2DM. High BMI is associated with insulin resistance, where the body's cells do not respond effectively to insulin, leading to elevated blood sugar levels. Weight loss and maintaining a healthy BMI can improve insulin sensitivity and help manage T2DM [9]. Both diet control and achieving a healthy BMI can improve insulin sensitivity in patients with T2DM. When the body's cells become more responsive to insulin, it becomes easier to regulate blood sugar levels. Weight loss, in particular, has been shown to have a positive impact on insulin sensitivity [10]. In clinical settings, it is frequently observed that patients diagnosed with type 2 diabetes (T2DM) and given the same antidiabetic treatments often exhibit significant variability in their capacity to manage blood sugar levels, their HbA1c levels, the efficacy of the prescribed medications, their ability to tolerate these drugs, and the occurrence of adverse side effects [11].

AIM

To assess the impact of BMI and diet control on variation in response to metformin monotherapy in Iraqi people with type 2 DM.

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 based on the 2012 American Diabetes Association criteria. 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, encompassing both males and females, who had been undergoing a monotherapy regimen of metformin tablets (1000 mg once daily) for a minimum of three months [12]. These participants fell within the age range of 30 to 70 years. 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/m2, pregnant women, patients with chronic gastrointestinal disorders or malabsorption syndrome, and individuals concurrently using other oral hypoglycemic agents (OHAs) or insulin. The participants in the study were divided into two groups based on their adherence to diet control criteria recommended by the American Diabetic Association in 2018. These criteria include: low carbohydrate/high protein intake. Patients choose complex carbohydrates like whole grains and distributed carbohydrate intake evenly throughout the day to prevent spikes in blood sugar levels, avoided refined carbohydrates, sugary food, and beverages. Patients taken lean protein which include: fish, legumes, and low-fat dairy. Patients incorporated high-fiber foods like vegetables, fruits, whole, beans, and nuts into their diet. As well as increased intake of healthy fats like those found in nuts, seeds, and olive oil and limited saturated and trans fats found in fried foods, fatty cuts of meat, and processed snacks. According to the glycemic control the patients were classified into two groups based on HbA1c into well (HbA1c levels≤6.5%) ≤ and poor responders (HbA1c levels ≥6.5%).

DATA COLLECTION

The data collection process involved the investigator administering a standardized questionnaire to gather demographic and clinical information from patients. This information encompassed their names, ages, body weight, and height, duration of illness, medical history, family medical history, dietary habits, sleep patterns, and occupations. To calculate the Body Mass Index (BMI), measurements for weight and height were taken. Height measurements were acquired with subjects standing upright, barefoot, with arms at their sides, and feet close together. Weight measurements were recorded with patients standing on a scale, wearing lightweight clothing, and without shoes or socks. BMI was calculated using the formula BMI = weight (in kilograms) / height (in meters squared), and it was used to categorize patients as either normal (BMI < 25 kg/m^2), overweight (BMI between 25 and 29.9 kg/m^2), or obese (BMI ≥ 30 kg/m^2) [12]. 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 immune 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 [13].

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 [13]:
- 1 / (log(fasting insulin μU/mL) + log(fasting glucose mg/dL)

BLOOD SAMPLE COLLECTION

Morning blood samples were collected from each patient after an overnight fast of 8-12 hours. While patients were seated, about 5mL of venous blood was drawn using disposable syringes. This blood collection involved distributing 3mL of blood into tubes containing EDTA and cautiously transferring the remaining 2mL into serum tubes equipped with separating gel. The blood is stored in EDTA tubes for assessing HbA1c via Immunoassay technique. Blood within the serum tubes was allowed to coagulate at room temperature for around 10-15 minutes, followed by centrifugation at approximately 3000 × g for approximately 3 minutes. The resulting serum was then stored at a temperature of -80°C until analysis. Serum insulin levels were measured using the BT LAB® ELISA kit, following the manufacturer's recommended procedure. Fasting blood glucose was measured utilizing the RanDox® kit, which relies on the PAP enzymatic method for determining glucose levels. 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.

Table 1. Mean differences of variables in study subjects

Variables	Patients
FBG	219.46±8.80
HbA1c	8.77±0.203
Insulin	8.67±1.103
HOMA-IR	84.76±12.002
Insulin sensitivity	1.14±1.03
age	53.97±1.86
BMI	28.34±1.58

RESULTS

150 T2DM patients as shown in Table 1 with an average age of 53.97±1.86 years and a mean BMI of 28.34±1.58 kg/m2 were included in the study. Socio-demographic data as in table 2 like BMI, age, duration of disease, and diet control shows there is a difference between the two groups but statistically is non-significant (p-value ≥ 0.05).

The patients were classified into two 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% as expressed in Fig. 1.

The difference in glycemic parameters between the good and poor responders is represented in table 3. As shown by the mean difference in glycemic parameters between good and poor responders to metformin there was a highly significant difference between the two groups about the FBS, HbA1c, and HOMA-IR (p-value 0.000), (p-value 0.000), and (p-value: 0.019) respectively.

Table 2. Socio-demographic distribution of study groups

Variables	<6.5	>6.5	X^2	P value
		Diet		
No	20	57	0.00331407	0.9541
Yes	19	52		
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
BMI category				
Normal	8	33	1.61206	0.4466
Overweight	21	48		
Obese	11	28		
Gender				
Male	10	44	2.99042	0.08376
Female	30	65		

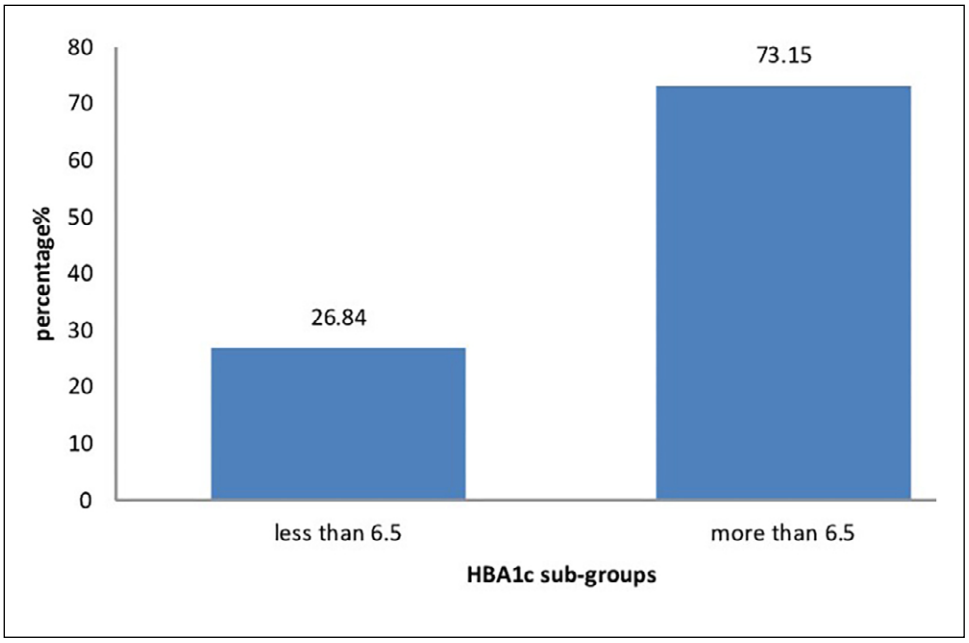

Fig. 1. The percentage of HBA1c sub-groups.

Table 3. Glycemic variables in study groups. All data is expressed as mean ± SD

Variables	<6.5	>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

Serum insulin was higher in poor responders than in good responders but this difference was statistically non-significant.

The association of BMI and glycemic control parameters is shown in table (4). Based on the data presented in table 4, the statistical analysis indicates that there is no significant difference in glycemic factors such as Fasting Blood Sugar (FBS), HbA1c, serum insulin, insulin sensitivity, and HOMA-IR when comparing patients who responded well to those who responded poorly. It's worth noting that in both groups, patients with a body mass index (BMI) greater than 30 kg/m^2, indicating overweight, exhibited higher levels of all these glycemic control parameters. Insulin sensitivity was higher in normal-weight patients (BMI<25 kg/m^2) in both groups.

The association between diet control and glycemic parameters illustrated in table 5, the result shows there is a difference in glycemic parameters (FBS, HbA1c, serum insulin, insulin sensitivity, and HOMA-IR) between good and poor responder patients as well as there is difference within the group itself but statistically non-significant. All glycemic parameters show a higher mean in patients without diet control than those with a restricted diet. The HbA1c shows a significant difference between patients with diet control and non-good responders' patients.

In this study, the correlation between the studied glycemic control parameters in two groups is clarified in table 6:

1- FBG in good responder has a positive correlation (R = 0.393) with HbA1c, which is statistically highly significant (P = 0.000). Also in poor responders, the FBG has a positive correlation (R = 0.327) with HbA1c which is statistically significant (P = 0.018). This suggests that as FBG levels increase, HbA1c levels also tend to increase.

2- In good responders, BMI has a positive correlation with FBG (R = 0.240) and HbA1c (R = 0.258) but is statistically non-significant (P = 0.292), (P = 0.113) respectively. In poor responders, BMI has a negative correlation with FBG (R =-0.041) statistically non-significant (P =0.671), while a positive correlation with HbA1c (R = 0. 0.795) statistically non-significant (P =0.782).

3- HOMA-IR has a positive non-significant correlation with FBG (R = 0. 0.159), (P =0.095).

4- Insulin sensitivity has an inverse correlation non-significant with FBG (R = -0.008), (P =0.938).

5- Age has a non-significant inverse correlation with FBG (R = -0.050), (p= 0. 0.602).

6- Serum insulin has an inverse correlation non-significant with FBG (R = -0.016), (P =0.867).

DISCUSSION

Prior research has established that being overweight or obese significantly increases the risk of inadequate blood glucose control in people with diabetes. Nevertheless, the precise impact of obesity on both metabolic

Table 4. Means differences of study variables according to BMI categories

Variables	<6.5				>6.5			
	<25	25-29.9	>30	p	<25	25-29.9	>30	P value
FBG	132.25±11.21	133.14±17.71	133.40±6.69	0.500	256.81±14.12	241.43±14.37	259.20±16.72	0.749
HbA1C	5.78±0.17	6.13±0.09	6.17±0.12	0.177	41.27±27.27	9.63±0.316	49.58±19.58	0.369
IN	6.67±1.85	7.17±2.90	7.47±2.45	0.988	6.06±1.05	10.20±2.47	6.97±2.16	0.257
IR	40.75±12.22	40.89±20.65	41.54±13.97	0.972	74.30±11.78	108.79±27.63	133.59±26.21	0.298
IS	1.23±0.09	0.95±0.13	1.20±0.122	0.358	1.11±0.07	1.10±0.07	1.05±0.09	0.339

IN:: serum insulin, IR: insulin resistant, IS: insulin sensitivity

Table 5. Differences in study variables according to diet control. All data is expressed as mean ± SD

Variables	<6.5			>6.5		P value
	no	Yes	P	No	Yes	
FBG	151.95±12.086	125.45±15.03	0.178	253.46±12.29	251.23±12.374	0.560
HbA1C	6.19±0.07	5.88±0.112	0.024	10.03±0.26	9.84±0.30	0.178
IN	5.04±0.70	4.56±3.22	0.171	10.95±1.379	10.18±2.25	0.634
IR	35.73±5.96	35.05±22.40	0.400	111.64±15.429	110.08±25.770	0.747
IS	1.04±0.090	1.11±0.138	0.665	1.12±0.06217	1.13±0.072	0.894

Table 6. The correlation coefficients among study variables in study groups

Variables		FBG	HBA1C	BMI
FBG	R		0.372	0.240
	P		0.018	0.292
HBA1C	R	0.393		0.258
	P	0.000		0.113
IN	R	-0.016-		0.121
	P	0.867		0.463
HOMA-IR	R	0.159		0.086
	P	0.098		0.601
INS	R	-0.008-		0.131
	P	0.938		0.425
Age	R	-0.050-		-0.064-
	P	0.602		0.700
Bmi	R	-0.041-	0.795	
	P	0.671	0.782	

regulation and the emergence of microvascular and macrovascular complications remains incompletely comprehended [14]. In our research, as illustrated in Tables (4), we found that individuals with a BMI of 30 kg/m^2 or higher had higher levels of glycemic parameters. This finding aligns with a separate study that also observed significant differences in HbA1c levels between individuals who were obese and those who were either pre-obese or had a normal weight [15]. In 2004, Koro et al. documented that various diabetic characteristic, such as their BMI, affected glycemic control parameters. Specifically, they found that higher HbA1c levels were related to obesity [16]. A Turkey-wide survey has unveiled a significant incidence of obesity, including severe obesity, in individuals diagnosed with type 2 diabetes. This research indicates that obesity worsens the management of blood sugar levels and increases the likelihood of cardiovascular diseases in this patient group [17]. Our study demonstrated that patients with diet control had a lower glycemic parameter as compared to those who did not. These findings consistent with multiple systematic reviews and meta-analyses have consistently found that diets emphasizing a lower glycemic index are associated with decreased fasting blood glucose levels and reduced glycation markers such as HbA1c. Additionally, these reviews have offered compelling evidence supporting the notion that the consumption of foods with a lower glycemic index substantially enhances insulin sensitivity [18].

CONCLUSIONS

The impact of BMI and diet control on metformin response in diabetic patients is a complex and multifaceted issue, while it is well-established that metformin is an effective medication for managing blood glucose levels in type 2 diabetes, the relationship between BMI, diet, and metformin response is influenced by various factors. Research suggests that individuals with higher BMIs may initially require higher doses of metformin to achieve adequate glycemic control. However, weight loss through diet control and lifestyle modifications can improve the efficacy of metformin and reduce the insulin resistance commonly associated with obesity. Additionally, dietary changes can contribute to better overall diabetes management by promoting healthier

eating habits and weight reduction. However, a personalized and comprehensive approach to diabetes care, including regular medical supervision and ongoing lifestyle modifications, remains the cornerstone of successful diabetes management.

LIMITATION OF STUDY

To draw more robust conclusions about the impact of BMI and diet control on diabetic patients using metformin, you may consider conducting a longitudinal cohort study or a randomized controlled trial (RCT) with appropriate controls and follow-up periods. These study designs can help establish causation, control for confounding variables, and provide insights into the temporal relationships between variables. It's important to note that the impact of diet control and BMI on T2DM can vary from person to person, and individualized care is essential. A healthcare provider or registered dietitian can work with patients to develop a personalized diabetes management plan that takes into account their unique needs, preferences, and medical history. Additionally, regular monitoring and follow-up are crucial to assess progress and make any necessary adjustments to the treatment plan.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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