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Influence of Metformin Dose and Treatment Adherence on Glycemic Control, Adiposity, and Cardiovascular Risk Markers in Iraqi Patients with T2DM

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Abstract

Background: Numerous factors, including metformin doses and treatment adherence, may contribute to significant variations in glycemic control and adiposity markers of type 2 diabetes (T2DM) patients.
Objectives: This study aims to determine the influence of metformin dose and treatment adherence on glycemic control and adiposity markers in Iraqi patients with T2DM.
Methods: Between October 2021 and March 2022, a case-series study at the Diabetes and Endocrinology Center – Baghdad included 153 T2DM patients with a disease duration of more than one year. Clinical and physical examinations were conducted before enrolment. We measured anthropometric variables to calculate the body mass index (BMI), waist-to-hip ratio (WHR), visceral adiposity index (VAI), and other surrogate indicators. We measured glycated hemoglobin (HbA1c), leptin, C-reactive protein (CRP), total cholesterol, HDL-c, and triglycerides in the serum.
Results: Increasing metformin doses did not improve the studied parameters. Adherence to treatment significantly influences fasting glycemia, HbA1c level, and the markers of adiposity. Meanwhile, increasing metformin doses is not associated with changes in insulin resistance and cardiovascular disease risk markers.
Conclusion: Beyond metformin dose up-titration, treatment adherence affects glycemic control, visceral adiposity, and CVD risk surrogates. Metformin dose up-titration was not linked to insulin resistance and body fat contents.

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Keywords: Glycemic control, Metformin dose, Treatment adherence, T2DM, Visceral adiposity.

Introduction:

T2DM is a multisystem disorder that raises the risk of cardiovascular disease (CVD) [1]. T2DM doubles or quadruples the risk of death from cardiovascular disease or stroke and is associated with both micro- and macro-vascular complications, such as accelerated atherosclerosis leading to severe peripheral vascular an increased risk of cardiovascular disease [2]. Probably as a result of the participation of many molecular mechanisms and pathogenic pathways, these Factors lead to the designation of T2DM as a substantial risk factor for CVD. Numerous studies showed that poor glycemic management, insulin resistance (IR), and serum leptin contribute to atherosclerosis, endothelial dysfunction, oxidative stress, hypertension, and inflammatory responses [3, 4]. Long-term pharmacological treatment of T2DM may only be moderately effective. In addition to drug therapies, significant lifestyle modifications are required for effective illness management. These alterations include greater physical activity, dietary changes, stress management, and better sleeping habits. Recommendations for beginning T2DM management include a mix of effective lifestyle modifications and pharmaceutical use. Diet and exercise are the two most essential lifestyle modifications [5,6]. The American Diabetes Association (ADA) suggests prescribing

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metformin as the initial management for T2DM patients. However, the same guidelines indicate that vitamin B12 deficiency is a typical side effect found in metformin users and that these patients' vitamin B12 levels should be monitored periodically. In addition, metformin is known to cause lactic acidosis, particularly in patients with kidney disease, liver impairment, or other consequences of CVS that reduce blood oxygen levels [7, 8]. Initial therapy for patients with metformin contraindications or intolerance should be based on patient variables. When HbA1c is above the glycemic target, many patients will need dual combination medication in order to attain their glycemic target [8]. Insulin has the advantage of being effective when other agents are ineffective and should be considered as part of any combination regimen when hyperglycemia is severe, particularly if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present or if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia), even at diagnosis or early in the course of treatment. As glucose toxicity resolves, this treatment can be shortened or adjusted (e.g., by adding another oral hypoglycemic medication) [9]. If the glycemic target is not achieved after three months and the patient does not have cardiovascular disease (CVD) or chronic kidney disease (CKD), a metformin-based combination is considered by adding one of six preferred medications: sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin. The addition of a medication is defined by the specific effects of the drug and the characteristics of the patient [10]. Despite the fact that there are numerous treatment options for T2DM, including several new drug classes recommended by the ADA/EASD and the American Association of Clinical Endocrinologists (AACE) [11,12], approximately half of individuals with T2DM do not achieve blood sugar control (HbA1c > 7%) [13, 14]. The purpose of this study is to assess the effect of treatment adherence on glycemic control and adiposity markers in T2DM patients receiving escalating doses of metformin per protocol. In addition, the relationship between metformin dosages and surrogate markers of CVD risk was investigated.

Patients and Methods

Out of 198 patients evaluated, 160 patients with a history of T2DM for more than a year were selected for participation in this cross-sectional study. Only 153 T2DM outpatients visited the Diabetes and Endocrinology Center in Baghdad for follow-up from September 2021 to January 2022, have completed the study (Figure 1), and their data was incorporated.

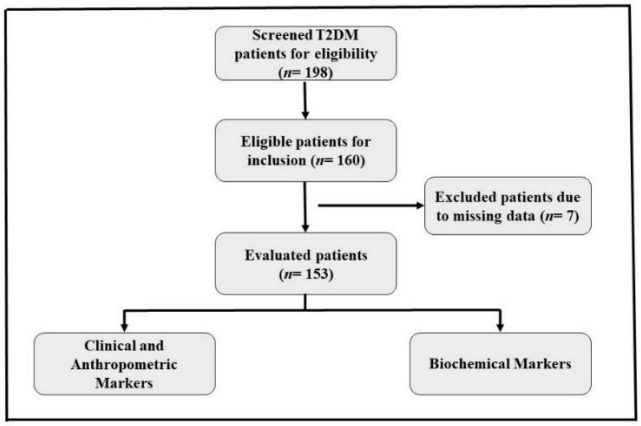

Figure 1: Flow chart of the study

They achieved varying levels of glycemic control by using up-titrating metformin doses (500–3000 mg/day) as part of the treatment protocol and for varying treatment durations (1.0–31 years). Inclusion criteria included: A previous diagnosis of T2DM according to the WHO criteria [15] for at least one year, an age range of 30 to 80 years, and being on metformin-based treatment. Patients with type 1 diabetes (T1DM), cancer patients undergoing chemotherapy or radiotherapy, insulin users, a history of renal failure, autoimmune diseases, hepatic diseases, major chronic disorders, and pregnancy were excluded. All participants were clinically evaluated and information about their medical history, demographic data, and medication history was collected, according to the study protocol. Anthropometric and clinical parameters such as BMI, waist circumference (WC), hip circumference (HC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured for all patients. Fasting serum glucose (FSG), HbA1c, serum leptin levels, C-reactive protein (CRP), fasting total cholesterol (TC), HDL-cholesterol (HDL-c), and triglyceride (TG) levels were also assessed using standard procedures. Homeostasis model assessment-insulin resistance (HOMA-IR) was estimated using the HOMA equation [16]. The visceral adiposity index (VAI) was determined using the gender-specific equations as previously described [17].

– Male VAI = [WC/(39.68 + (1.88 x BMI))] x (TG/1.03) x (1.31/HDL)

– Female VAI = [WC/(36.58 + (1.89 x BMI))] x (TG/0.81) x (1.52/HDL)

The waist-to-hip ratio (WHR), TC/HDL-c ratio, and TG/HDL-c ratio, all of which have been linked to cardiovascular risks [18], were also assessed as surrogate indices of adiposity and adipose tissue function. A body shape index (ABSI) was calculated using the following equation: $ABSI=WC/(BMI^{2/3} \times height^{1/2})$, the units of ABSI are $m^{11/6}\ kg^{-2/3}$ [19]. The body roundness index (BRI) was calculated according to the formula [20]:

BRI= 364.2 – 365.6 x √(1-(((WC/2π)^2)/((Bht/2)^2)))
Meanwhile, the other surrogate marker of adiposity, the relative fat mass (RFM), was calculated according to the following [21]: RFM (for males) = 64 − (20 × (body height/waist)) RFM (for females) = 76 − (20 × (body height/waist)) The ratio of TC or TG (mg/dl) to HDL-c (mg/dl) was used to predict the TC/HDL-c and TG/HDL-c ratios [22]. All procedures were carried out in compliance with the local committee on human experimentation's (institutional and national) ethical norms, as well as the Declaration of Helsinki (2013) and its subsequent revisions [23]. The local Research Ethics Committee of the University of Baghdad's College of Medicine gave their approval (REC-1417, Nov. 2021). All participants gave their consent to participate in the study and to have their data made public at the time of their outpatient clinic evaluation.

Statistical analysis

The data was statistically analyzed using the GraphPad Prism 8.4.3 program (GraphPad Prism Software Inc., La Jolla, CA, USA). The information was given as mean ± standard deviation (SD) or rates and proportions. The Kolmogorov-Smirnov test was used to determine the normality of the quantitative variable distribution. An unpaired Student's t-test and ordinary analysis of variance (ANOVA) were used to assess the differences between groups, with Bonferroni post hoc analysis. The association of metformin doses and treatment duration with anthropometric and biochemical indicators was evaluated using Pearson's correlation. For statistical significance, P-values of less than 0.05 were used.

Results

Demographic Characteristics of Participants: Table 1 indicates an even distribution of males and females with a mean age of 55.7±8.10 years. The mean duration of having T2DM was 9.3±6.51 years, and the Metformin-based regimen was administered for a mean of 7.1±5.63 years. Just under one-half of the participants (45.1%) used 1000-1500 mg/day of Metformin, with 38.6% taking less than 1000 mg/day and 16.3% taking more than 1500 mg/day. Table 1 further shows that 53.6% of the patients have been following the Metformin-based treatment for 1–5 years. The patients had insufficient glycemic and body weight control, with an HbA1c score of 9.13±2.38% and a BMI of 30.1±5.31 kg/m^2. Meanwhile, the data in Table 1 demonstrated that 41.2% of the participants had erratic dietary control and a moderate pattern of treatment protocol adherence. Additionally, 75.2% of the participants were treated with a combination of metformin and sulfonylurea derivatives, whereas 18.3% were treated with a combination of metformin and DPP-4 inhibitors, as shown in Table 1. The present data also indicated that 6.5% of the participants used metformin as a single medication and in an irregular manner. The current study revealed that 50.3% of the participants were hypertensive and were frequently treated with antihypertensive medications, while 18.3% had ischemic heart disease and 19.6% suffered from thyroid abnormalities in addition to T2DM.

Table 1: Characteristics of the participants (n= 153)

Parameter	Categories	Results
Gender n (%)	Male	76 (49.7)
	Female	77 (50.3)
Age (year) mean±SD (range)		55.7±8.10 (34-73)
Disease duration (year) mean±SD (range)		9.3±6.51 (1.0-31)
Metformin dose (mg/day) mean±SD (range)		1078±576.80 (500-3000)
Metformin dose (mg/day) n (%)	<1000	59 (38.6)
	1000-1500	69 (45.1)
	> 1500	25 (16.3)
Duration of Met treatment (year) mean±SD (range)		7.1±5.63 (1.0-31)
Duration of Met treatment (year) n (%)	1-5	82 (53.6)
	6-10	41 (26.8)
	> 10	30 (19.6)
Body weight (kg) mean±SD (range)		80.7±14.32 (52-130)
HbA1c (%) mean±SD (range)		9.1±2.38 (5-15)
BMI (kg/m^2) mean±SD (range)		30.1±5.31 (20.1-46.6)
Blood pressure (mmHg)	SBP mean±SD (range)	13.7±2.11 (10-20)
	DBP mean±SD (range)	8.6±1.17 (5-12)
Dietary control n (%)	Free	40 (26.1)
	Conservative	50 (32.7)
	Fluctuated	63 (41.2)
Compliance with treatment n (%)	Good	35 (22.9)
	Moderate	63 (41.2)
	Poor	55 (35.9)
Add-on drug with Met n (%)	Sulfonylurea	120 (75.2)
	DPP-4 inhibitors	33 (18.3)
	Metformin only	10 (6.5)
Comorbidities	Hypertension	77 (50.3)
	IHD	28 (18.3)
	Thyroid disorders	30 (19.6)

Values are expressed as mean±SD, numbers, percentages, and ranges. n: number of patients; HbA1c: glycated hemoglobin; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Influence of Treatment Adherence on the Outcome Variations: The study results revealed considerable variations in patients' adherence to the medication treatment procedures. There were no statistically significant variations between the daily dosages of Metformin taken by patients and the duration of therapy

(P > 0.05) (Table 2). However, based on FSG and HbA1c levels, the glycemic control status of patients with poor adherence appeared to be the worst; FSG and HbA1c levels were considerably higher in this group than in patients with good or moderate adherence (P < 0.0001). Similarly, serum TG levels were considerably higher in individuals with poor adherence to Metformin-based treatment (P = 0.017) compared to those found in patients with good treatment adherence.

Table 2: Association of adherence to treatment with up-titrating metformin doses on the glycemic control and serum levels of insulin, leptin, CRP, and TG of Iraqi patients with T2DM (n=153)

Variables	Adherence to treatment			P-value (ANOVA)
	Good (n=35)	Moderate (n=63)	Poor (n=55)	
Met Dose (mg/day)	937.1±483.33[a]	1205.0±641.82[a]	1009.0±507.42[a]	0.05
Duration of treatment (year)	6.5±5.42[a]	6.6±5.42[a]	8.1±5.97[a]	0.289
FSG (mg/dl)	147.1±35.32[a]	187.5±58.00[b]	248.3±84.22[c]	<0.0001
HbA1c (%)	7.3±1.38[a]	8.8±2.13[a]	13.8±4.66[b]	<0.0001
Serum insulin (ng/ml)	16.1±11.31[a]	22.0±27.69[a]	15.0±11.52[a]	0.125
Serum Leptin (ng/ml)	12.6±2.77[a]	12.3±2.72[a]	12.1±2.37[a]	0.613
Serum CRP (mg/dl)	4.9±1.78[a]	7.2±12.28[a]	7.3±11.12[a]	0.504
Serum TG (mg/dl)	142.4±59.22[a]	190.6±114.88[a]	205.0±108.13[b,a]	0.017

Table 3: Patients' adherence to treatment with up-titrating metformin doses and the anthropometrics characters, cardiovascular risk markers, and insulin resistance of patients with T2DM (n=153)

Variables	Adherence to treatment			P-value (ANOVA)
	Good (n=35)	Moderate (n=63)	Poor (n=55)	
BMI (kg/m^2)	29.0±4.72[a]	31.4±5.85[a]	29.4±5.10[a]	0.056
VAI	5.3±4.87[a]	7.8±7.86[a]	9.4±6.23[b,a]	0.019
WHR	1.0±0.11[a]	1.0±0.14[a]	1.0±0.08[a]	0.312
RFM	37.7±8.79[a]	38.0±10.21[a]	40.9±8.75[a]	0.173
BRI	6.6±2.03[a]	7.1±2.87[a]	7.1±2.58[a]	0.636
ABSI	0.5±0.12[a]	0.4±0.13[a]	0.5±0.11[a,b]	0.019
TC/HDL-c	4.4±1.27[a]	5.4±2.31[b]	5.5±1.58[b]	0.016
TG/HDL-c	3.9±2.12[a]	6.7±6.07[b]	6.4±4.77[b]	0.019
HOMA-IR	4.8±3.61[a]	8.0±9.55[a]	7.5±5.82[a]	0.104

Values are presented as mean±SD; n: number of patients; FSG: fasting serum glucose; HbA1c: glycated hemoglobin; CRP: C-reactive protein; TG: triglycerides; Bonferroni post hoc test: values with non-identical superscripts (a,b,c) are significantly different within the same parameter (P<0.05).As shown in Table 3, the remaining biochemical markers (serum levels of insulin, leptin, and CRP) were not substantially impacted by the level of adherence (P = 0.125, 0.613, and 0.504, respectively). Regarding the effect of treatment adherence level on anthropometric characteristics, Table 3 demonstrates that VAI values were significantly higher in patients with poor adherence levels (P = 0.019), whereas BMI and WHR values did not differ significantly between patients with different adherence levels (P = 0.056 and 0.312, respectively). The influence of treatment adherence level on the surrogate markers of cardiovascular risk (RFM and BRI) revealed no significant differences between patient groups (P = 0.173 and 0.636, respectively); however, the value of the other surrogate marker (ABSI) was significantly higher in patients with poor adherence level (P = 0.019). In the present study, the variations in the treatment adherence levels led to significant elevations of the lipid profile indicators (TC/HDL-c and TG/HDL-c) in patients with poor adherence levels (P = 0.016 and 0.019, respectively), whereas the value of the insulin resistance marker (HOMA-IR) was not significantly affected by the variations in the treatment adherence levels (P = 0.104), as shown in Table 3. Values are presented as mean±SD; n: number of patients; BMI: body mass index; VAI: visceral adiposity index; WHR: waist-to-hip ratio; RFM: relative fat mass index; BRI: body roundness index; ABSI: a body shape index; TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment of insulin resistance; Bonferroni post hoc test: values with non-identical superscripts (a,b) are significantly different within the same parameter (P<0.05). The assessment of the relationship between increasing Metformin doses and the insulin resistance marker (HOMA-IR) values revealed a modest negative correlation that is not statistically significant (r = 0.001, P = 0.246) (Figure 2A). Pearson's correlation analysis of the association between up-titrating doses of Metformin and the values of RFM and ABSI, which are surrogate markers of cardiovascular risk, reveals weak negative and non-significant correlations (r = -0.034 and -0.146, respectively; P = 0.68 and 0.07, respectively); whereas the other surrogate marker (BRI) exhibited a weak positive and non-significant association with the up-

titrating doses of Metformin (r = 0.137, P = 0.09), as shown in Figure 3B, C, and D).

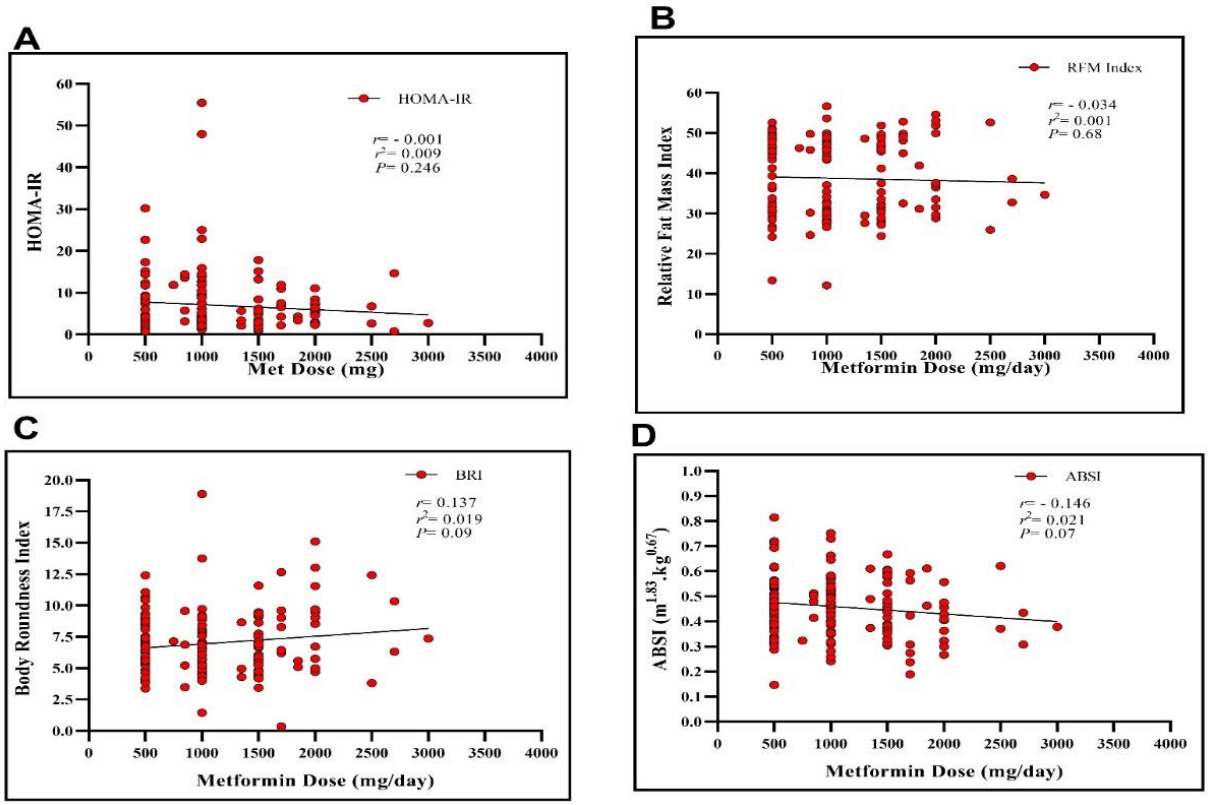

Figure 2: Correlation of Metformin dose up-titration with (A) HOMA-IR values, (B) RFM index, (C) BRI index, and (D) ABSI values of Iraqi patients with T2DM. HOMA-IR: homeostatic model assessment of insulin resistance; RFM: relative fat mass; BRI: body roundness index; ABSI: a body shape index; r: Pearson's correlation coefficient.

Discussion:

At any BMI, abdominal obesity and T2DM are substantial cardiovascular risk factors [24]. In 2020, Zhao and co-workers reported that the surrogate marker of abdominal adiposity, ABSI, was linearly associated with an increased risk of T2DM across the entire ABSI range, independent of gender, age, smoking status, alcohol intake, fatty liver, SBP, BMI, FPG, HbA1c, HDL-cholesterol, and triglycerides [19]. In the present cross-sectional study, we evaluated the ability of seven non-invasive, low-cost, and easily predicted anthropometric indicators, including BMI, WC, VAI, WHR, RFM, ABSI, and BRI, to define CVD risk factors in T2DM patients receiving titrated doses of Metformin based on the dose range and treatment duration. Except for WC and WHR, which showed weak relationships with increasing Metformin doses, our findings indicate that increasing the Metformin dose does not correlate with improvements in these parameters. In the past decade, the BMI was utilized as a representative index in studies on obesity and related disorders. However, BMI is not regarded to be associated with the deleterious effect of intra-abdominal fat on mortality and morbidity, particularly in persons who may have a "normal" BMI but a disproportionately high intra-abdominal fat content [25]. Consequently, adiposity measures have been proposed as alternatives that help mitigate the shortcomings of BMI. A recent systematic study revealed that independent of total adiposity, all indices of central adiposity, including WC, WHR, VAI, BRI, RFM, and ABSI, were substantially and positively linked with an increased cardiovascular risk [26]. However, the current investigation reveals that therapy-induced changes in adiposity indicators are mostly influenced by dietary choices, physical activity, and most significantly, treatment adherence level. Nonetheless, until recently, researchers have been unable to discover the best indicators that may be used to monitor treatment outcomes in T2DM patients that are favorably associated with apparent glycemic control status. Numerous studies have revealed that the greatest predictor among adiposity markers varies according to multiple parameters, including age, sex, ethnicity,

dietary habits, and the type of metabolic illness, and adiposity markers are the predictors most strongly related to diabetes mellitus [27,28]. In this regard, ABSI and BRI have recently drawn considerable interest in relation to the development of cardiovascular disease and other undesirable consequences. ABSI demonstrated a greater link with early mortality than BMI or WC, according to preliminary investigations [29]. However, later studies revealed contradictory results on the efficacy of the ABSI to predict chronic disease and mortality [30]. Consistent with previously reported findings, the values of these markers revealed inconsistent changes after the treatment of T2DM patients with Metformin-based protocols, as demonstrated by the present investigation. In controlled trials and cross-sectional analyses, the incorporation of independent metabolic indicators such as serum levels of TG and HDL-c that were considered for VAI calculation resulted in the preserved ability for treatment follow-up in terms of cardiovascular risk changes and even enhanced ability to predict metabolic outcomes at treatment follow-up stages and routine monitoring in clinical practice [31]. Overall, the current study strongly suggests that anthropometric adjusted surrogate markers of adiposity should not be recommended over WC for high-risk patient identification for DM treatment-associated risk management strategies in the general population, and especially in overweight-obese individuals, unless they are strengthened by the inclusion of additional plasma risk markers, specifically lipid profile. To the best of our knowledge, our study is the first to offer comparisons across a vast array of accessible measures of body adiposity to predict the results of metformin dose titration in T2DM patients. In general, the current findings are similar to prior reports in smaller populations with specific illness conditions and with less thorough cross-sectional analyses [32]. Other studies have revealed varying levels of predictive power without direct comparison to gold-standard biomarkers such as waist circumference and body mass index [33]. Finally, we would like to stress that the current results may be confined to the population under study, and they should not be immediately transferred to other populations, especially those with considerable changes in age, ethnicity, and disease conditions. In 2016, A placebo-controlled trial demonstrated that long-term treatment with metformin stabilizes BMI and improves body composition in adolescents with obesity and insulin resistance compared to placebo [34]. In this age range, the authors recommended that Metformin be considered a safe supplementary medication in conjunction with lifestyle modification. The results of the current study contradicted those of the previous study, which may be attributable to the difference in the age range of participants and the targeted disorder. In accordance with the actual conditions of clinical practice during the care of T2DM patients, under which this study was conducted and the sample of patients was chosen, the age group studied was determined based on the majority of patients who routinely visit the Specialized Diabetes and Endocrinology Center for health care, as well as the infrastructure requirements necessary to provide standard health services to those patients. Under these conditions, several factors influence the control of the illness therapy and have overlapping effects, necessitating an attempt to evaluate the results based on the impact of each of these elements separately. The primary limitation of this study is that it is a single-center study, which means that the results may not be representative of all Iraqi T2DM patients. Additionally, we excluded patients receiving Met monotherapy due to the small number of cases. However, we analyzed a relatively large sample of patients treated with Met-based combinations that included dose up-titration for different periods.

Conclusion:

Beyond the variation of metformin doses, adherence to the treatment protocol significantly influences glycemic control, visceral adiposity, and the surrogate markers of CVD risk. However, up-titrating metformin doses were poorly associated with insulin resistance and body fat indicators.

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Author's contributions:

Zainab S. Abdulrahman: Conducting biochemical and clinical measurements and data collection, analysis of data, and preparation of the article draft.

Mohammed Q. Alatrakji: First Supervisor; study design, data interpretation, and reviewing the draft manuscript.

Ahmed A. Al-Maliky: Second Supervisor; clinical guidance, and reviewing the draft manuscript.

Khalid I. Hussein: Clinical consultation and guidance, evaluation, and interpretation of the clinical outcomes.

Saad A. Hussain: Concept design, study protocol design, data acquisition, and approval of the final draft of the manuscript.

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تأثير جرعة الميتفورمين والإلتزام بالعلاج على التحكم في نسبة السكر في الدم والسمنة وعلامات مخاطر القلب والأوعية الدموية لدى المرضى العراقيين الذين يعانون من داء السكري النوع الثاني

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الخلاصة
الخلفية: قد تساهم العديد من العوامل، بما في ذلك جرعات الميتفورمين والإلتزام بالعلاج في إختلافات كبيرة في التحكم في نسبة السكر في الدم وعلامات السمنة لمرضى السكري من النوع الثاني.
الهدف: تهدف هذه الدراسة إلى تحديد تأثير جرعة الميتفورمين والإلتزام بالعلاج على التحكم في نسبة السكر في الدم وعلامات السمنة لدى المرضى العراقيين الذين يعانون من هذا المرض.
المنهجية: بين سبتمبر 2021 ومارس 2022، شملت دراسة مقطعية في مركز السكري والغدد الصماء - بغداد 153 مريضا من مرضى T2DM الذين تزيد مدة مرضهم عن عام واحد. وأجريت فحوص سريرية وبدنية قبل التسجيل. قمنا بقياس المتغيرات الأنثروبومترية مثل مؤشر كتلة الجسم، ونسبة الخصر إلى الورك، ومؤشر السمنة الحشوية وغيرها من المؤشرات البديلة. قمنا بتقييم الهيموغلوبين السكري، اللبتين، البروتين التفاعلي، الكوليسترول الكلي، HDL-c، والدهون الثلاثية في مصل الدم.
النتائج: لم تحسن زيادة جرعات الميتفورمين المعايير المستهدفة. يؤثر الإلتزام بالعلاج بشكل كبير على نسبة السكر في الدم، ومستوى HbA1c ، وعلامات السمنة. وفي الوقت نفسه، فإن زيادة جرعات الميتفورمين لا ترتبط بالتغيرات في مقاومة الأنسولين وعلامات خطر الإصابة بأمراض القلب والأوعية الدموية.
الإستنتاج: بغض النظر عن زيادة جرعة الميتفورمين، يؤثر الإلتزام بالعلاج على التحكم في نسبة السكر في الدم، والسمنة الحشوية، ومعايير مخاطر الأمراض القلبية الوعائية. لم تكن زيادة جرعة الميتفورمين مقترنة بمقاومة الأنسولين ومحتويات الدهون في الجسم.
الكلمات المفتاحية: التحكم في نسبة السكر في الدم، جرعة الميتفورمين، الإلتزام بالعلاج، داء السكري النوع الثاني، السمنة الحشوية.