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The association of metformin dose up-titration and treatment duration with adiposity, lipid profile indicators, and serum leptin levels in T2DM Iraqi patients

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ABSTRACT

Introduction: Numerous factors, including age, gender, physical inactivity, insufficient dose, noncompliance, and drug-drug interactions, may contribute to significant intraindividual variation in metformin (MET) response. This study aims to determine the effect of Met dose and treatment duration on adiposity markers and serum leptin levels in Iraqi patients with type 2 diabetes.

Methods: Between October 2021 and March 2022, a cross-sectional study at the Diabetes and Endocrinology Center in Baghdad included 150 type 2 diabetes mellitus (T2DM) patients with a disease duration of more than 1 year. Clinical and physical examinations were conducted before enrollment. We measured anthropometric variables such as body mass index, waist-to-hip ratio, and visceral adiposity index. We evaluated glycated hemoglobin, leptin, C-reactive protein, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and triglycerides (TGs) in the serum.

Results: Only the TC/HDL-c and TG/HDL-c ratios were significantly different after the data were arranged according to glycemic control level. Arrangement for MET doses and treatment duration, none of the evaluated parameters were significantly different ($p > 0.05$) between groups receiving different doses of MET for different durations, except visceral adiposity index (VAI), which shows a very slight decrease ($p = 0.046$) after more than 10 years of treatment. Pearson's correlation analysis revealed a weak and significant association between waist circumference (WC) and hip circumference and MET doses, and a weak and significant association between WC, VAI, and TG levels and treatment duration. The other markers lacked a significant relationship with MET doses or duration of treatment.

Conclusion: MET dose and duration of treatment were not significantly correlated with adiposity and lipid profiles in Iraqi patients with T2DM.

Keywords: Hemoglobin A1C; insulin level; lipid profile; metformin dose; type 2 diabetes mellitus; visceral adiposity

INTRODUCTION

There are numerous antidiabetic medications available for the pharmacological treatment of type 2 diabetes mellitus (T2DM) (1); they have a positive impact not only on glycemic control, but also on adipose tissue distribution, weight gain, and chronic low-grade inflammation (2). Metformin (MET) is a biguanide that is used as a first-line treatment for lowering hepatic glucose production and increasing peripheral insulin sensitivity (3). In addition to the lifestyle intervention program, it has been used to assist T2DM obese patients with clinical insulin resistance in losing weight and improving insulin sensitivity (4). As a result, it improves glycemic control without causing hypoglycemia and has other beneficial effects on body weight, blood pressure, and inflammation (5). Furthermore, MET, alone or in combination with other drugs, reduces abdominal visceral adipose tissues and enhances their function (5,6). MET, when added to standard care, has been shown in several studies to reduce the incidence of major cardiovascular events (cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke) in patients with T2DM who are at high cardiovascular risk (7,8). Moreover, MET therapy has been shown to have an effect on cardiovascular disorders and their consequences by downregulating microRNAs. As a result, MET's influence on their reduction could provide a potential therapeutic strategy for patients with T2DM by lowering the risk of MI (9). Many recent studies have found

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a strong link between T2DM risk and visceral fat obesity indicators such as waist circumference (WC), waist-to-hip ratio (WHR), visceral adiposity index (VAI), serum leptin levels, and body mass index (BMI) (10,11). Because of the wide variations in clinical responses to MET, approximately 35% of patients did not achieve ideal initial glycemic control on MET as monotherapy or part of a combination. MET's pharmacokinetics (PK) can be influenced by a variety of factors, which can have a significant impact on the hypoglycemic response (12). The relationships between MET's dose-dependent effects and treatment duration on visceral adiposity, glycemic control, and inflammatory markers in T2DM patients chronically treated with up-titrating doses of MET alone or in combination with other hypoglycemic agents are not well understood. While the patterns and implications of T2DM therapy intensification have been thoroughly documented globally (13), there are scanty data addressing MET up-titration in the real-world clinical context. Since MET treatment has been shown to be effective when administered at doses of 1500–2000 mg/day (14), the question remains whether MET treatment can fail due to insufficient dose optimization and up-titration. The aim of this study was to determine if MET dose up-titration and length of treatment are related to improvements in VAI, WC, WHR, serum leptin levels, and lipid profile status in Iraqi outpatients with T2DM.

METHODS

Out of 198 patients evaluated, 160 patients with a history of T2DM for more than a year were chosen for participation in this cross-sectional study. Only 150 T2DM outpatients (74 men and 76 women; age range, 34–73 years) who visited the Diabetes and Endocrinology Center in Baghdad for follow-up from September 2021 to January 2022 completed the study (Figure 1), and their data were incorporated. They achieved varying levels of glycemic control using up-titrating MET 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 1 year, an age range of 30-80 years, and being on MET-based treatment. Patients with type 1 diabetes (T1DM), cancer patients undergoing chemotherapy or radiotherapy, insulin users, a history of renal failure, autoimmune and hepatic diseases, major chronic disorders, and pregnancy are all 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, WC, hip circumference (HC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured in all patients. Fasting serum glucose, hemoglobin A1C (HbA1c), serum leptin levels, C-reactive protein (CRP), fasting total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), and triglyceride (TG) levels were also assessed. The VAI was determined using the gender-specific equations as previously described (16).

- Male, VAI = (WC/[39.68 + (1.88 × BMI)]) × (TG/1.03) × (1.31/HDL)
- Female, VAI = (WC/[36.58 + (1.89 × BMI)]) × (TG/0.81) × (1.52/HDL)

The WHR, TC/HDL-c ratio, and TG/HDL-c ratio, all of which have been linked to cardiovascular risks (17), were also assessed as surrogate indices of adiposity and adipose tissue function. 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 (18). 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 (19). 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 have their data made public at the time of their outpatient clinic evaluation.

The data were statistically analyzed using the GraphPad Prism 8.4.3 program (GraphPad 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 an ordinary analysis of variance (ANOVA) with Bonferroni *post hoc* analysis were used to assess group differences. The association of MET doses and treatment duration with anthropometric and biochemical indicators was evaluated using Pearson's correlation. For statistical significance, $p < 0.05$ were used.

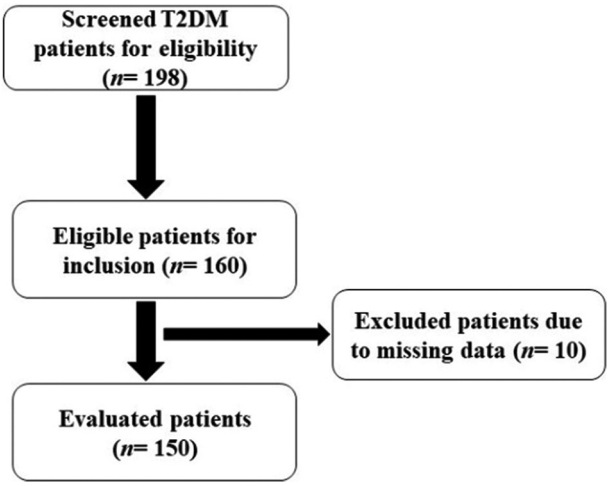

FIGURE 1. Flow chart of the study.

RESULTS

In the selected sample of patients, Table 1 indicates a relatively equal distribution of males and females (74 males and 76 females), with a mean of 55.6 ± 8.1 (34–73) years. The disease was reported to have lasted 9.2 ± 6.4 (1–36) years, and the MET-based regimen was administered for 7.08 ± 5.7 (1–31) years. The majority of participants (68, 45.3%) used 1000–1500 mg of MET/day, with 57 (38%) taking less than 1000 mg/day and 25 (16.7%) taking more than 1500 mg/day. Table 1 further shows that 52.7% of the patients included have been following the MET-based treatment for 1–5 years. The patients had insufficient glycemic and body weight control, with an HbA1c score of 9.1 ± 2.4% (5.0–15.0) and a BMI of 30.2 ± 5.4 (20–46.6) kg/m^2.

Meanwhile, the data in Table 1 demonstrated that 41.3% of the participants followed conservative dietary control and reported a moderate pattern of treatment protocol adherence. In Table 2, the arrangement of patients according to the status of glycemic control showed that the two groups did not show significant differences in MET doses and treatment duration, BMI, WHR, serum leptin, CRP, and TG levels ($p > 0.05$). However, the mean value of VAI was significantly increased in patients with poor glycemic control ($p = 0.038$). Both TC/HDL-c and TG/HDL-c ratios were higher in uncontrolled patients than in those with good glycemic control ($p = 0.016$ and 0.019, respectively) (Table 2). According to the results of ANOVA (Table 3), the arrangement of data according to the variation in MET doses (1000 mg/day, 1000-1500 mg/day, and >1500 mg/day) revealed non-significant differences ($p > 0.05$) between the three groups in the values of VAI, WC, WHR, serum leptin, CRP levels, and the lipid profile indicators (TG, TC/HDL-c, and TG/HDL-c). Furthermore, *post hoc* analysis revealed no significant differences between any of the groups. After data adjustment for the duration of MET administration, Table 4 shows a weakly significant decrease in the value of the VAI ($p = 0.043$) according to an ANOVA test. In addition, *post hoc* analysis using the Bonferroni test indicates that patients using MET for more than 10 years have significantly lower VAI values compared with those using MET for 1–5 years. Tables 3-4 also shows no significant variations in the values of WC, WHR, serum leptin, CRP levels, and the lipid profile indicators (TG, TC/HDL-c, and TG/HDL-c) between the three groups ($p > 0.05$). By analyzing the association between the adiposity indicators

TABLE 1. Patients characteristics and demographic data (*n*=150)

Parameter	Results
Gender, *n* (%)	
Male	74 (49.3)
Female	76 (50.7)
Age (years)	55.6±8.1 (34–73)
Disease duration (years)	9.2±6.4 (1–36)
Duration of met treatment (year)	7.08±5.7 (1–31)
1–5 years	79 (52.7)
6–10 years	41 (27.3)
>10 years	30 (20)
Met doses (mg/day)	1073±570 (500–3000)
<1000 mg/day	57 (38)
1000–1500 mg/day	68 (45.3)
>1500 mg/day	25 (16.7)
Body weight (kg)	80.6±14.4 (52–130)
BMI (kg/m^2)	30.2±5.4 (20–46.6)
WC (cm)	107.3±15.1 (47–158)
HC (cm)	109.1±12.7 (53–140)
WHR	0.98±0.1 (0.39–1.44)
VAI	7.78±6.8 (0.64–35.03)
HbA1c (%)	9.1±2.4 (5.0–15.0)
Serum leptin (ng/mL)	12.3±2.6 (6.8–25.5)
CRP (mg/dL)	6.8±10.4 (2.5–72.4)
TG (mg/dL)	184.7±104.4 (53.4–747.6)
Cholesterol (mg/dL)	173.2±41.1 (105.3–335.4)
HDL-c (mg/dL)	36.04±11.2 (7.8–85.8)
LDL-c (mg/dL)	100.2±38.2 (10.9–239.9)
TC/HDL-c	5.2±1.9 (2.1–17.0)
TG/HDL-c	5.9±5.1 (1.1–38.3)
Serum creatinine (mg/dL)	0.75±0.17 (0.37–1.7)
BP (mmHg), *n* (%)	
SBP	13.6±2.1 (10–20)
DBP	8.6±1.2 (5.0–12)
Dietary control, *n* (%)	
Free	39 (26)
Conservative	62 (41.3)
Fluctuated	49 (32.7)
Compliance with treatment, *n* (%)	
Good	34 (22.7)
Moderate	62 (41.3)
Poor	54 (36)

Values are presented as mean±SD or number and percentage. *n*: Number of patients, BMI: Body mass index, VAI: Visceral Adiposity index, WC: Waist circumference, WHR: Waist to hip ratio; CRP: C-reactive protein, TG: Triglyceride, TC: Total cholesterol, HDL-c: High-density lipoprotein cholesterol, HbA1c: Glycated hemoglobin, HC: Hip circumference, BP: Blood pressure, SBP: Systolic BP, DBP: diastolic BP, SD: Standard deviation, LDL-c: Low-density lipoprotein cholesterol

TABLE 2. Variations in the metformin doses and duration of treatment, anthropometric markers, serum levels of leptin and C-reactive protein, and lipid profile in Iraqi type 2 diabetes mellitus patients according to glycemic control (*n*=150)

Parameters	Glycemic control (HbA1c %)		*p*
	<7.0 (*n*=34)	≥7.0 (*n*=116)	
Met dose (mg/day)	979.4±478.7	1100±592.4	0.224
Duration of treatment (year)	5.72±5.9	7.5±5.56	0.124
BMI (kg/m^2)	30.9±5.9	30.0±5.2	0.412
VAI	6.12±4.5	8.3±7.4	0.038
WHR	0.98±0.07	0.99±0.11	0.36
Serum leptin (ng/mL)	12.1±2.6	12.3±2.5	0.615
Serum CRP (mg/dL)	5.9±6.8	6.9±11.2	0.521
Serum TG (mg/dL)	170.7±71.5	188.8±112	0.261
TC/HDL-c	4.6±1.6	5.4±1.9	0.016
TG/HDL-c	4.72±2.6	6.32±5.5	0.019

Values are presented as mean±SD. *n*: Number of patients, BMI: Body mass index, VAI: Visceral adiposity index, WC: Waist circumference, WHR: Waist to hip ratio, CRP: C-reactive protein, TG: Triglyceride, TC: Total cholesterol, HDL-c: High-density lipoprotein cholesterol, HbA1c: Glycated hemoglobin, SD: Standard deviation

TABLE 3. Effects of up-titrating metformin doses on the anthropometric markers, serum leptin and C-reactive protein levels, and lipid profile markers of Iraqi patients with type 2 diabetes mellitus (*n*=150)

Variables	Metformin doses (mg/day)			*p* (ANOVA)
	<1000 (*n*=59)	1000–1500 (*n*=66)	>1500 (*n*=25)	
VAI	8.37±6.6[a]	7.23±6.5[a]	8.1±7.6[a]	0.630
WC (cm)	105.8±13.3[a]	106±13.2[a]	8.1±21.4[a]	0.063
WHR	0.972±0.09[a]	0.99±0.07[a]	1.02±0.16[a]	0.179
Serum leptin (ng/mL)	12.2±2.4[a]	12.4±2.8[a]	12.1±2.5[a]	0.850
CRP (mg/dL)	5.64±7.4[a]	7.32±12.2[a]	7.75±11.0[a]	0.574
TG (mg/dL)	182.2±82.3[a]	180.8±106.9[a]	201±141.2[a]	0.682
TC/HDL-c	5.17±1.4[a]	5.04±2.3[a]	5.6±1.7[a]	0.434
TG/HDL-c	5.55±3.4[a]	5.91±5.2[a]	7.1±7.5[a]	0.449

Values are presented as mean±SD. values with non-identical superscripts [a, b]Are significantly different within the same parameter ($p<0.05$).
n: Number of patients, VAI: Visceral adiposity index, WC: Waist circumference, WHR: Waist to hip ratio, CRP: C-reactive protein, TG: Triglyceride, TC: Total cholesterol, HDL-c: High-density lipoprotein cholesterol, ANOVA: Analysis of variance, SD: Standard deviation

(VAI, WC, and WHR) and the serum leptin levels of the participants with the MET doses, Figure 2 displays a weak negative and non-significant correlation with the VAI values (r = 0.011, p = 0.891) and a weak positive and non-significant association with serum leptin levels (r = 0.011, p = 0.891). Nevertheless, WC and WHR values exhibited weak positive and significant associations with the up-titrating doses of MET (r = 0.180 and 0.190, respectively; p = 0.025 and 0.019, respectively). Assessment of the association between the up-titrating doses of MET and serum CRP levels and lipid profile indicators (TG, TC/HDL-c, and TG/HDL-c) of the participants revealed weak positive and non-significant associations (r = 0.123 and 0.029, respectively; p = 0.131 and 0.714, respectively) as shown in Figure 3. Nonetheless, serum TG levels and TC/HDL-c ratio displayed weak negative and non-significant relationships with increasing MET doses (r = 0.01 for both indicators; p = 0.904 and 0.939, respectively). By analyzing the association between the adiposity indicators (VAI, WC, and WHR) and the serum leptin levels of the participants with the duration of MET use, Figure 4 displays weak negative and significant associations between the duration of MET use and VAI values (r = –0.218, p = 0.007), whereas weak negative and non-significant associations were reported between the duration of MET use and WC and serum leptin levels (r = –0.012 and –0.015, respectively; p = 0.210 and 0.856, respectively). Nonetheless, WHR values exhibited a positive and non-significant association with the duration of MET use (r = 0.119, p = 0.134), as shown in Figure 4. Assessment of the association between the treatment duration with up-titrating doses of MET and serum CRP levels and lipid profile indicators (TG, TC/HDL-c, and TG/HDL-c) of the participants revealed weakly negative and significant associations between the duration of MET use and serum TG levels (r = 0.170, p = 0.036). Meanwhile, weakly negative and non-significant associations were reported between the duration of MET use and serum leptin levels, TC/HDL-c values, and TG/HDL-c values (r = –0.034, –0.148, and –0.157, respectively; p = 0.597, 0.072, and 0.053, respectively), as shown in Figure 5.

TABLE 4. Effects of metformin use duration on the anthropometric markers, serum leptin, and C-reactive protein levels, and lipid profile markers of Iraqi patients with type 2 diabetes mellitus (n=150)

Variables	Duration of using metformin (year)			p (ANOVA)
	1–5 years (n=79)	6–10 years (n=41)	>10 years (n=30)	
VAI	8.87±7.6[a]	7.55±6.64[a,b]	5.2±3.94[b]	0.043
WC (cm)	109±15.2[a]	105.2±15.4[a]	105.5±14.3[a]	0.311
WHR	0.98±0.09[a]	0.98±0.11[a]	1.01±0.02[a]	0.276
Serum leptin (ng/mL)	12.1±2.1[a]	13.0±3.6[a]	11.98±2.0[a]	0.154
CRP (mg/dL)	7.43±12.3[a]	5.4±4.7[a]	6.6±10.2[a]	0.592
TG (mg/dL)	200.5±110.7[a]	174.3±93.9[a]	156.0±95.4[a]	0.103
TC/HDL-c	5.41±2.1[a]	5.03±1.6[a]	4.8±1.3[a]	0.243
TG/HDL-c	6.6±5.6[a]	5.77±4.9[a]	4.9±3.2[a]	0.177

Values are presented as mean±SD. Values with non-identical superscripts [a,b]Are significantly different within the same parameter (p<0.05).
n: Number of patients, VAI: Visceral adiposity index, WC: Waist circumference, WHR: Waist to hip ratio, CRP: C-reactive protein, TG: Triglyceride, TC: Total cholesterol, HDL-c: High-density lipoprotein cholesterol, ANOVA: Analysis of variance, SD: Standard deviation

DISCUSSION

This is the first study to our knowledge to explore the relationship between MET up-titration and treatment duration with improvements in adiposity and lipid profile indicators in Iraqi T2DM patients on MET-based combination therapy. Weight reduction, adiposity indices, lipid profile markers, and even glycemic control are not substantially

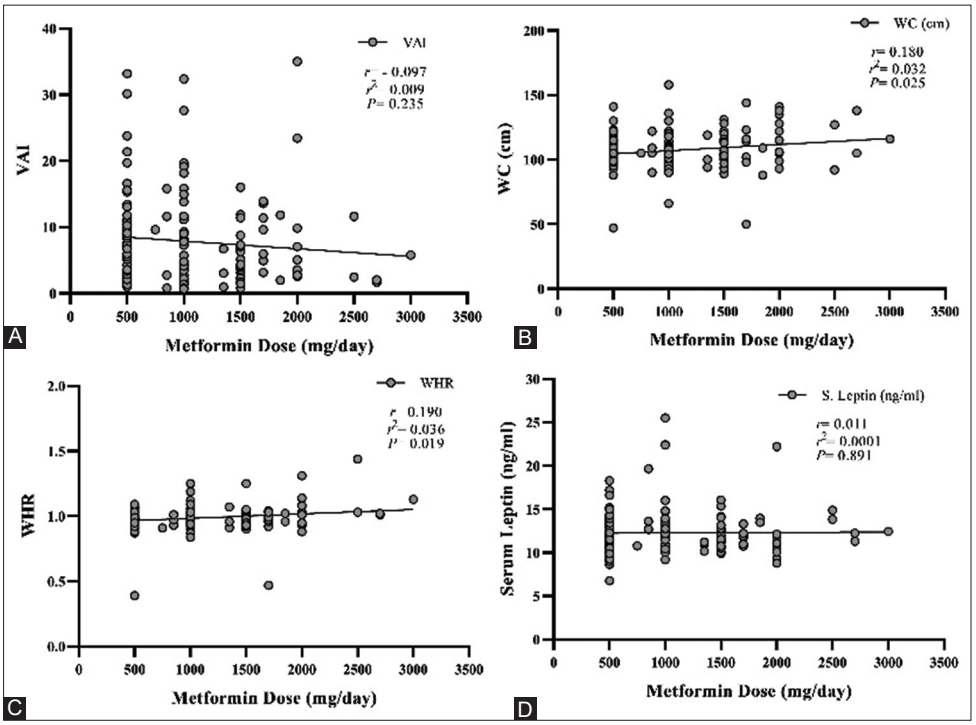

FIGURE 2. Correlation of metformin dose up-titration with (A) VAI, (B) WC, (C) WHR, and serum leptin levels (D) of Iraqi patients with T2DM
VAI: visceral adiposity index; WC: waist circumference; WHR: Waist to hip ratio; *r*: Pearson's Correlation Coefficient.

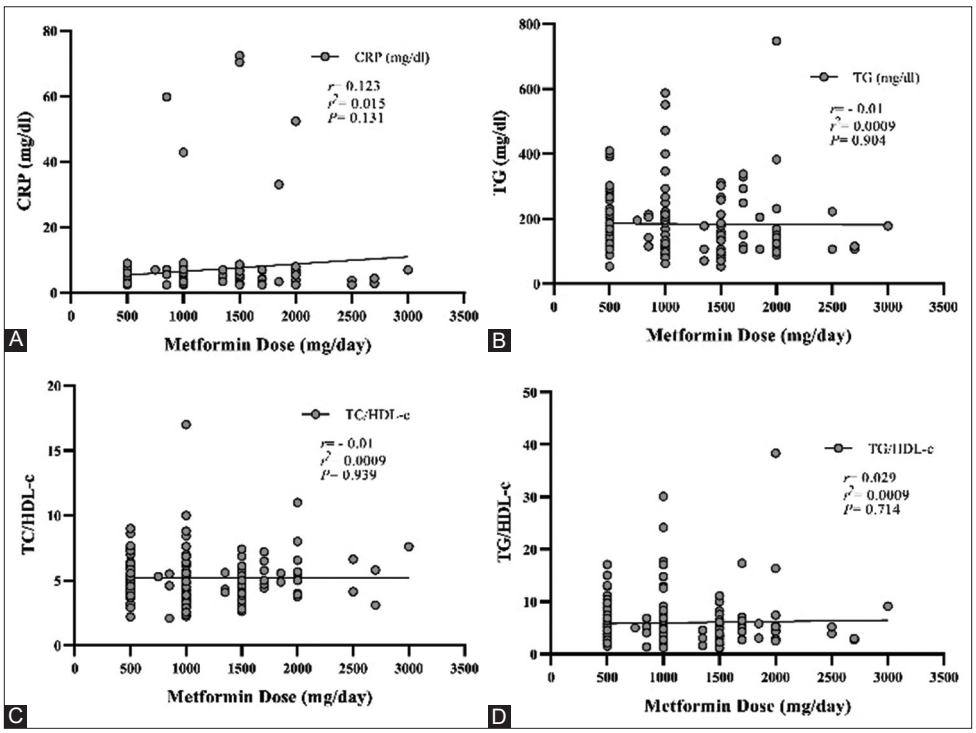

FIGURE 3. Correlation of metformin dose up-titration with (A) CRP levels, (B) TG levels, (C) TC/HDL-c ratio, and TG/HDL-c ratio (D) of Iraqi patients with T2DM

CRP: C-Reactive Protein; TG: Triglyceride; TC: Total cholesterol; HDL-C: High density lipoprotein cholesterol; *r*: Pearson's correlation coefficient.

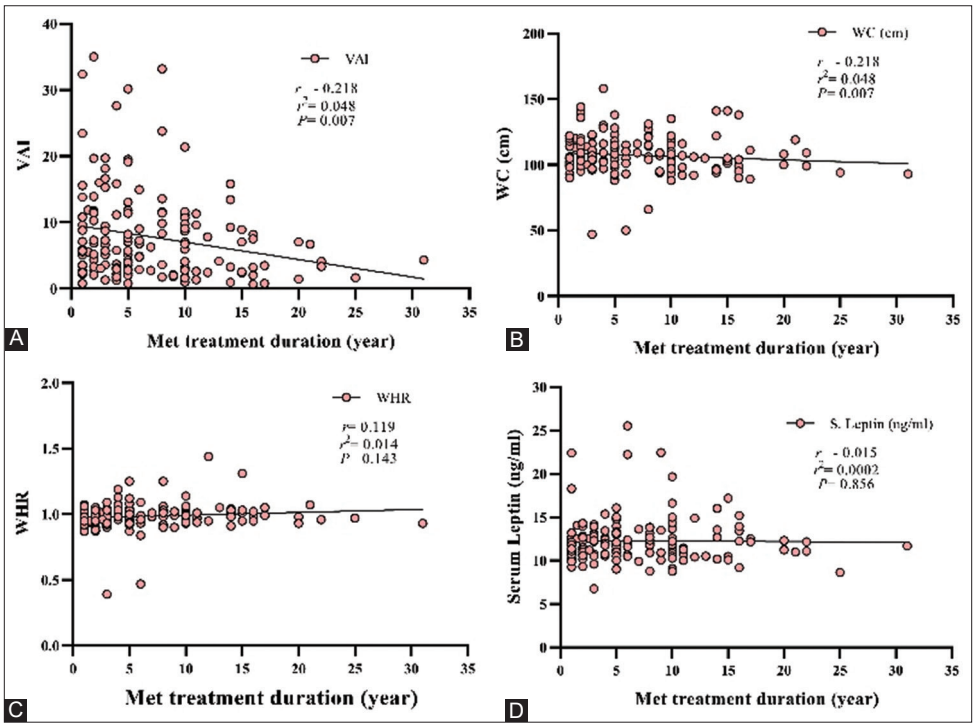

FIGURE 4. Correlation of metformin treatment duration with (A) VAI, (B) WC, (C) WHR, and serum leptin levels (D) of Iraqi patients with T2DM

VAI: Visceral adiposity index; WC: Waist circumference; WHR: Waist to hip ratio; *r*: Pearson's correlation coefficient.

associated with up-titration MET dosages and treatment duration, according to our findings. On the other hand, MET up-titration was associated with non-adherence to therapy and insufficient dietary management (as side events). Multiple diverse factors can influence a T2DM patient's treatment journey at the start of treatment, during treatment, and at the end of treatment (20,21). Examples of these factors include the patient, therapy, health-care system, economy, social support network, and psychosocial issues. Knowing which aspects are especially significant to T2DM patients is crucial because patient-centered care that respects individual preferences and barriers is beneficial for enhancing treatment results (22). They might take their prescribed medications for a longer period of time if their wants and expectations are better met. In this study, we looked at the relationship between adiposity and lipid profile indicators and up-titrating MET dosages and therapy duration. The results show a non-significant association,

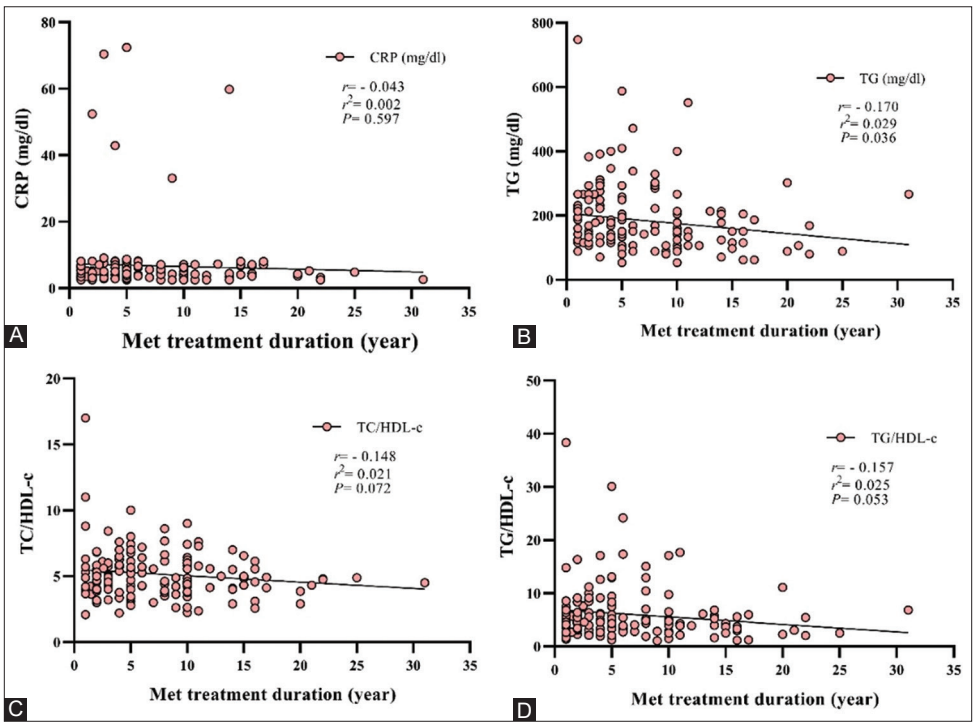

FIGURE 5. Correlation of metformin treatment duration with (A) CRP levels, (B) TG levels, (C) TC/HDL-c ratio, and TG/HDL-c ratio (D) of Iraqi patients with T2DM

CRP: C-reactive protein; TG: Triglyceride; TC: Total cholesterol; HDL-C: High density lipoprotein cholesterol; *r*: Pearson's correlation coefficient.

which could be attributable to a lack of knowledge about other factors beyond glycemic control. The decision to start, continue, or stop using a T2DM medication was found to be influenced by an increase in body weight and adiposity. Many studies have found that patients who lose weight are more likely to take their medication and stick to their T2DM treatment plan (23). T2DM patients with a higher BMI may have a lower HRQoL (24). Furthermore, it has been reported that weight gain is significantly associated with lower rates of overall treatment satisfaction (25). This could explain the current study's reported high rate of noncompliance with the treatment protocol and lack of awareness of their dietary control. Chung et al. (2018) discovered a non-linear relationship between MET dosages and glucose-lowering effects, confirming the negative relationship between systemic MET exposure and glucose-lowering benefits at high doses (26). As a result, irrational MET dose up-titration may fail to improve therapeutic outcomes such as weight loss and lower cardiovascular risk indicators, as reported in the current study. Moreover, clinical research found that delayed-release MET was more effective than comparable doses of a more bioavailable extended-released version of MET, implying that the stomach plays a role in MET's glycemic control action (27). Because the patients utilize varied formulations of MET, this adds an additional factor that could alter the association between MET dosage and therapeutic outcomes seen in the current study. In addition, decreased efficacy may be the result of non-adherence to an optimum treatment schedule. MET has a lower rate of treatment adherence than other oral anti-hyperglycemic medications (28), and poor adherence to MET-based protocols has been linked to poor therapeutic outcomes (29). Thus, both clinical inertia on the part of clinicians and non-adherence on the side of patients may contribute to MET-based therapeutic failure. Our findings were consistent with those of Sivitz et al., who reported that increasing MET doses was associated with greater therapeutic outcomes. However, participants who did not change their MET dose, and even those who did, also had adequate glycemic control outcomes, which may indicate that improved medication adherence and/or lifestyle behavior contributed as well (30). Numerous data points document contradictory findings regarding MET's influence on blood leptin levels. Ida et al. found no reduction or elevation in blood leptin levels in T2DM patients treated with MET in 2017 (31). However, a MET-induced decrease in blood leptin levels has been associated with decreased BMI and obesity, as well as improved insulin resistance (32). In the current investigation, no significant variations in blood leptin levels were seen between T2DM patients receiving varied MET doses over various time periods. Meanwhile, serum leptin levels are unrelated to MET dosage titration and duration of therapy. Other oral hypoglycemic medications have already been shown to cause weight gain or fat buildup (33). MET, on the other hand, has been shown to help people lose weight (34). As a result, it appears that differences in the activities of these drugs, which were administered with MET, may have influenced the outcomes. The possible effect of MET appears to be hidden when both genders are considered together. Wei et al. (2021), in agreement with our findings, found that oral hypoglycemic medications, including MET, had no effect on leptin concentrations in T2DM patients (35). In 2018, Pangeta et al. reported positive and significant associations between glycemic control and the atherogenic indices of T2DM patients (36). Various doses of MET (1000–2550 mg/day) generate significant changes in lipid profile indicators after a maximum of 3 months of treatment in a prospective controlled clinical trial setting (37,38). In the current investigation, which mirrors the real-world clinical practice

situation, no significant variations in lipid profile indicators were seen following the arrangement for MET dosage titration and treatment duration. When the current data were analyzed according to HbA1c levels; however, it was discovered that glycemic control was associated with improved TC/HDL-c and TG/HDL-c ratios that were independent of MET dose and length of treatment. In addition, the current investigation failed to demonstrate a sufficient and significant correlation between MET dose up-titration and treatment duration and the lipid profile indicator. This conclusion can be related to the high prevalence of treatment non-adherence and poor dietary control documented in the recruited patients.

Study limitations

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. In addition, we excluded patients receiving MET monotherapy due to a 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

In real-world clinical practice, the present study did not observe a sufficient and significant association between MET dose up-titration and treatment duration with the indicators of adiposity and lipid profile in Iraqi patients with T2DM, which could be attributed to insufficient control of treatment-related factors.

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DATA SHARING STATEMENT

Supplementary data will be provided by the corresponding author based on a reasonable request.

SOURCE OF FUNDING

No source provided.

DECLARATION OF INTERESTS

The authors declare no conflicts of interest.

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