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Predictors of Metformin Side Effects in Patients with Newly Diagnosed Type 2 Diabetes Mellitus

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Abstract

Introduction Metformin has become the first-line agent for the treatment of type 2 diabetes mellitus (T2DM) in several international guidelines. Up to 25% of patients suffer from gastrointestinal side-effects, with approximately 5% unable to tolerate metformin at all.

Objective We aimed to study the effect of variables that may influence the development of metformin side effects and/or intolerance.

Method A prospective study was conducted from April 1, 2021 to March 30, 2022. One-hundred and forty-eight patients newly diagnosed with T2DM were enrolled in the study, and divided into two groups—those who were escalate to the maximum dose of metformin over 2 weeks ($n = 43$) and the other group over 4 weeks ($n = 105$). We studied the variables that may affect the development of side effects including age, gender, body mass index (BMI), lipid profile, glycemic level, and the use of other antidiabetic medications besides the duration of dose escalation.

Results Total number of patients who developed side effects was 59 (39.9%). Twenty-four (55.8%) and 35 (33.3%) patients were put in the rapid and slow escalation groups, respectively. Twenty-six (17.6%) patients developed diarrhea that was the most common side effect. Two (2.7%) men and ten women (13.5%) had stopped metformin due to severe side effects developed after initiation ($p = 0.016$). The mean BMI for the patients who discontinued metformin was 34.7 ± 4.1 kg/m^2 in the rapid escalation arm and 31.6 ± 3.3 kg/m^2 in the slow escalation arm ($p = 0.003$). The mean of fasting blood glucose for the patients who discontinued metformin in the rapid and slow escalation arms was 200.6 ± 25.6 and 173.4 ± 36.5 mg/dL, respectively ($p = 0.022$).

Conclusion The severity of metformin side effects is higher in women than in men, making more women to discontinue the drug. Besides, a higher fasting blood sugar and BMI are associated with a higher rate of discontinuation. A rapid dose escalation is associated with a higher frequency of side effects. Diarrhea is the commonest side effect encountered.

Keywords
- diabetes mellitus
- metformin
- side effects
- intolerance
- dose escalation

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Introduction

According to the World Health Organization, diabetes mellitus (DM) is a chronic, progressive disease characterized by high levels of glucose in the blood. Type 2 diabetes mellitus (T2DM) accounts for 90% of all cases of diabetes, a condition caused by either decline in pancreatic B cell function or peripheral insulin resistance.[1] Diabetes risk factors include (genetic, metabolic, and environment that interact with each other leading to its prevalence. T2DM risk factors are divided into nonmodifiable risk factors (ethnicity and family history/genetic predisposition) and modifiable risk factors (obesity, low physical activity, and an unhealthy diet).[2,3] The prevalence of T2DM in 2019 in the Middle East was 12.2% and is estimated to increase to 15.7% by 2045. In Iraq, the prevalence of T2DM in 2018 was ranging from 8.5 to 13.9%.[4] T2DM can be managed with different strategies (lifestyle modification, the use of insulin, or the antidiabetic medications administration) together with monitoring of blood glucose.[5]

Metformin—dimethylbiguanide—is an oral glucose-lowering medication. Its origin was based on a plant extract commonly named as goat's rue or French lilac, the Galega officinalis.[6] Since its discovery early in the last century, it became well known for its blood glucose lowering effects, in animals initially, when Jean Sterne extensively studied it and later developed the glucophage in the fifties of last century.[7] Its good reputation, regarding both the efficacy and safety profiles, placed it at the top of most T2DM management guidelines recommendations.[8] Although one can recall some past bumps through its history, when, at some point, it was shadowed by phenformin, which had contributed to serios lactic acidosis until the 1970s when it was withdrawn.[9] Several large randomized control trials had proven that metformin improves glycemic control and has a good safety profile and is not associated with hypoglycemia besides its low cost.[10] Metformin, like any medications, has side effects, and up to 25% of patients may suffer from side effects mostly gastrointestinal with approximately 5% could not tolerate metformin.[11]

The most noticeable metformin side effects include nausea, vomiting, bloating, dyspepsia, metallic taste, abdominal pain, abdominal cramps, and/or changes in intestinal motility, leading to loose stools and overt diarrhea that becomes, sometimes, intractable. The etiology behind metformin intolerance is still unclear.[12]

The aim of this article was to study the effect of variables that may influence the development of metformin side effects and/or intolerance and the frequency of each side effect.

Method

Patients and Setting

A prospective study was conducted in Faiha Specialized Diabetes, Endocrine and Metabolism Center in Basrah city from April 1, 2021 to March 30, 2022. Data were collected from the patients attending the center and from patients referred from private specialized endocrinology clinics (as mentioned in the acknowledgment) using the same inclusion and exclusion criteria. One hundred and forty-eight patients with newly diagnosed T2DM on any one of the following criteria: (non-fasting blood glucose more than 200 mg/dL (>11.1 mmol/L), fasting (8 hours or longer) blood glucose more than or equal to 126 mg/dL ($\geq$ 7.0 mmol/L), or glycated hemoglobin (HbA1c) more than or equal to 6.5%[13], in patients who had symptoms suggestive of DM (polyuria, polydipsia and weight loss), their age 35 years old and above. Patients with abnormal renal function (raised serum creatinine level $\geq$ 1.5 mg/dL in men, and more than 1.4 mg/dL in women), pregnancy, liver cirrhosis, peptic ulcer disease, congestive heart failure, inflammatory bowel disease, and patients with gastrointestinal surgery were excluded. In this study, we divided the patients into two groups, those who escalated their metformin dose to the maximum (2000 mg/day) over 2 weeks (500 mg twice daily [bid] in the first week and 1000 mg bid in the second week), while the other group escalated over 4 weeks (500 mg once daily in the first week and increase the dose by 500 mg weekly). Anthropometric data were collected from the patients through careful history and clinical examination; patients were sent for HbA1c, fasting, and/or random blood glucose and lipid profile; a questionnaire involving all the required data was filled by physicians who volunteered to help. Verbal consents were taken from all patients prior to enrollment. We studied the effect of the above variables on the development of the side effects including the use of other antidiabetic medications.

Statistical Analysis

We used the statistical package for the social sciences (SPSS v23); for the comparison of the continuous variables, Student's *t*-test was used, and for the categorical variables Pearson's chi-squared or Fisher's exact test was used when appropriate. Receiver operator characteristics (ROC) curve statistics were used to extract a cutoff value of some continuous variables. A *p*-value of less than 0.05 was considered as a level of significance.

Results

►**Table 1** shows the general characteristics of the patients at the beginning of our study. Of the 148 enrolled patients, 72 (48.6%) were men and 74 (51.4%) women. Forty-three (29%) patients were in the rapid escalation arm and 105 (71%) in the slow escalation arm.

Out of all the enrolled patients, 59 (39.9%) developed one or more of the metformin side effects (gastrointestinal tract [GIT] and non-GIT), and the frequency of each side effect can be seen in ►**Fig. 1**. While diarrhea was the most frequently observed side effect seen in 26(17.6%) patients, myalgia was observed in the least 2 patients (1.4%). The effect of escalation methods on the frequency of side effects can be seen in ►**Table 2**. Higher frequencies of side effects occurred in the rapid escalation arm in comparison to the slow escalation arm, with the exception of chest discomfort (although statistically not significant).

Some of the features of the 59 patients who developed side effects can be seen in ►**Table 3**. Although no single factor

was significantly associated with the development of the metformin side effects between both arms, generally they tend to occur more in women. In 12(8.1%) patients, the side effects were rather more severe that obligated them to discontinue metformin; some features of these patients are illustrated in ►**Table 4**. Ten women (13.5%) versus two men (8.1%) had discontinued metformin due to the development of severe side effects ($p = 0.016$). Patients who discontinued metformin had a higher BMI (mean = 34.70 ± 4.05 kg/m^2) than those who did not (mean = 31.64 ± 3.29 kg/m^2) ($p = 0.003$) and were having a higher basal fasting blood sugar (200.60 ± 25.57 vs. 173.36 ± 36.48; $p = 0.022$).

From the area under the curve retrieved from the ROC curve drown for the BMI against the development of metformin discontinuation (►**Fig. 2**), we can see that patients with BMI 32.2 kg/m^2 and above were more likely to be intolerant to metformin (sensitivity = 75%, specificity = 72%; odds ratio [OR] = 6.930 with 95% confidence interval = 1.462–32.844;, $p = 0.004$).

While data from the area under the curve retrieved from the ROC curve (►**Fig. 3**) drown for the FBG against discontinuation of metformin, we can see that patients with FBG of 180 mg/dL and below were less likely to be intolerant to metformin (sensitivity = 90%, specificity = 74%; OR = 22.629 with 95% confidence interval = 2.763–185.304, $p = 0.001$).

Discussion

Oral hypoglycemic drugs were reported as a common cause of side effects especially gastrointestinal[14] the mechanism behind these side effects was still in a controversy and the studies' results were conflicting.[15–17] Moreover, these symptoms were very common in diabetic patients and normal people in the community making the relationship difficult to prove. And even in patients with diabetes, the frequency and severity were subjected to a significant interindividual variation that may hinder a genetic predisposition.[11]

To our knowledge, this was the first study ever looking for the effect of escalation time on the development of metformin

Table 1 General characteristics of the patients at the beginning of the study,[a] $n = 148$

	Rapid escalation $n = 43$	Slow escalation $n = 105$	p-Value
Age (years)	50.4 ± 8.1	48.5 ± 5.8	0.103
Male gender	22(51.2)	52(49.5)	0.856
Female gender	21(48.2%)	53(50.5%)	
BMI (kg/m^2)	32.1 ± 5.1	31.8 ± 2.5	0.685
FBS (mg/dL)	184.7 ± 41.2	172.2 ± 34.3	0.083
RBG (mg/dL)	262.1 ± 103.2	225.3 ± 100.2	0.387
TG (mg/dL)	208.2 ± 81.1	210.8 ± 36.4	0.838
Total cholesterol (mg/dL)	205.1 ± 52.6	213.9 ± 36.1	0.465
HbA1c %	9.7 ± 2.1	9.5 ± 1.1	0.575
SU	13(30.2)	38(36.2)	0.622
DPP4i	12(27.9)	22(21.0)	0.361
TZD	6(14.0)	7(6.7)	0.303
Insulin	10(23.3%)	8(7.6%)	0.008

Abbreviations: BMI, body mass index; FBG, fasting blood glucose; RBG, random blood glucose; TG, triglycerides; HbA1c, glycated hemoglobin; SD, standard deviation; SGLT2i, sodium/glucose cotransporter-2 inhibitors; SU, sulphonylureas; DPP4i, dipeptidyl peptidase type 4 inhibitors; TZD, thiazolidinedione.
Note: Data were expressed either as mean ± SD or *n* (%).
[a]Four patient were on SGLT2i in the rapid escalation arm, while no one in the slow arm.

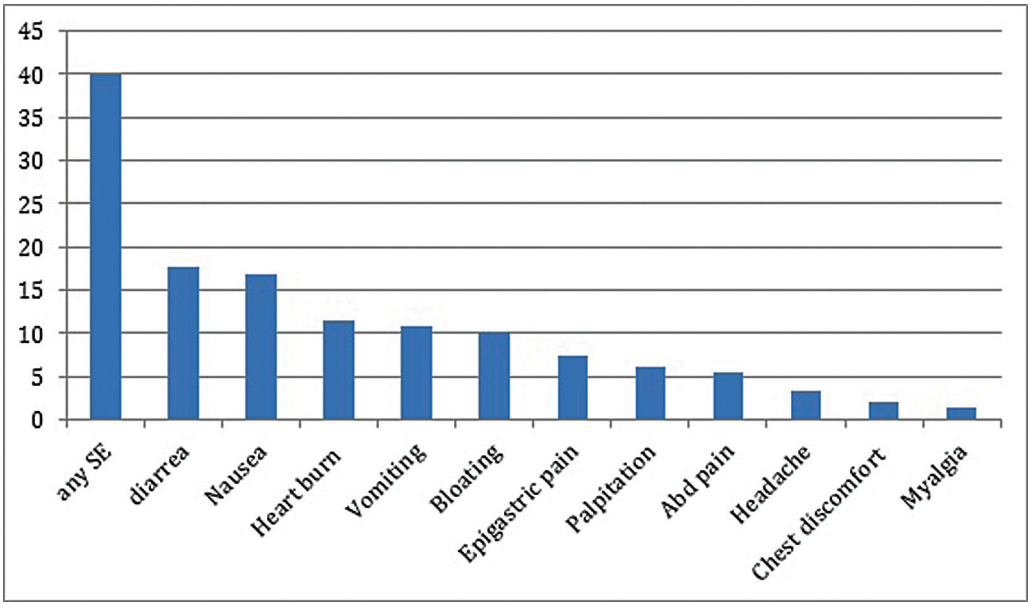

Fig. 1 Percentages of metformin side effects.

Table 2 Frequency of metformin side effects in the whole studied patients[a]

		Total	Rapid escalation	Slow escalation	*p*-Value
	Any side effect	59(39.9%)	24(55.8%)	35(33.3%)	0.011
GIT related					
	Epigastric pain	11(7.4%)	4(9.3%)	7(6.7%)	0.402[b]
	Diarrhea	26(17.6%)	15 (34.9%)	11(10.5%)	<0.001
	Bloating	15(10.1%)	9(20.9%)	6(5.7%)	0.005
	Nausea	25(16.9%)	12(27.9%)	13(12.4%)	0.22
	Vomiting	16(10.8%)	8(18.6%)	8(7.6%)	0.051
	Abd pain	8(5.4%)	3(7.0%)	5(4.8%)	0.424[b]
	Heart burn	17(11.5%)	9(20.9%)	8(7.6%)	0.021
Non-GIT					
	Chest discomfort	3(2.0%)	0(0.0%)	3(2.9%)	0.354[b]
	Palpitation	9(6.1%)	7(16.3%)	2(1.9%)	0.003[b]
	Headache	5(3.4%)	4(9.3%)	1(1%)	0.025[b]
	Myalgia	2(1.4%)	1(2.3%)	1(1.0%)	0.498[b]

Abbreviation: GIT, gastrointestinal tract.
[a]No patients in our study had complained of dyspepsia, constipation, flushing, or distension.
[b]F-test.

side effects; any previous advice about gradual escalation was delivered from clinical observations and was advised for escalation of the dose over a period of 4 weeks.[18] Though, in our clinical practice, we were frequently facing patients who escalated their metformin rapidly on their own without complaining from serious side effects, which made us thinking about including the study of this factor and its effect on the development of metformin side effects.

The frequency of metformin side effects differs between the studies and as more than one third of our patients

Table 3 Factors associated with the development of metformin side effects, $n = 59$

	Rapid escalation $n = 24$	Slow escalation $n = 35$	*p*-Value
Age (years)	51.29 ± 7.81	48.17 ± 8.305	0.152
Male gender	10/22(45.5%)	11/52(21.2%)	0.420[a]
Female gender	14/21(66.7%)	24/53(45.3%)	
BMI (kg/m^2)	32.05 ± 5.77314	32.38 ± 3.35	0.780
FBG (mg/dL)	188.53 ± 44.98	174.55 ± 54.111	0.356
RBG (mg/dL)	253.89 ± 106.107	231.86 ± 120.763	0.704
TG (mg/dL)	202.20 ± 55.966	200.47 ± 69.745	0.948
Cholesterol (mg/dL)	219.27 ± 36.266	202.65 ± 41.553	0.288
HbA1c %	9.44 ± 1.86	9.19 ± 1.52	0.569
SU	12(50.0%)	10(28.6%)	0.095
DDP4	5(20.8%)	8(22.9%)	0.854
TZD	4(16.7%)	3(8.6%)	0.293[b]
SGLT2	2(8.3%)	0(0.0%)	0.161[b,c]
Insulin	4(16.7%)	4(11.4%)	0.418[b]

Abbreviations: BMI, body mass index; DPP4i, dipeptidyl peptidase type 4 inhibitors; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; RBG, random blood glucose; SD, standard deviation; SGLT2i, sodium/glucose cotransporter-2 inhibitors; SU, sulphonylureas; TG, triglycerides; TZD, thiazolidinedione.
Note: Data were expressed either as mean ± SD or *n*(%).
[a]Percentages were calculated by dividing the number of patients who did develop side effects by the number of those who did not in each field.
[b]F-test.
[c]Already there are no patient on SGLT2i in the slow arm.

Table 4 Factors associated with discontinuation of metformin

	Yes	No	*p*-Value
Number	12(8.1%)	136(91.9%)	NA
Age (years)	49.17 ± 5.54	49.02 ± 6.71	0.942
Male gender	2(2.7%)	72(97.3%)	0.016
Female gender	10(13.5%)	64(86.5%)	
BMI (kg/m^2)	34.70 ± 4.05	31.64 ± 3.29	0.003
FBG (mg/dL)	200.60 ± 25.57	173.36 ± 36.48	0.022
RBS (mg/dL)	207.33 ± 19.35	252.82 ± 107.22	0.479
TG (mg/dL)	205.50 ± 108.45	210.38 ± 47.60	0.852
Cholesterol (mg/dL)	207.20 ± 26.03	210.38 ± 45.40	0.879
HbA1c %	9.79 ± 1.07	9.54 ± 1.49	0.562
SU yes	6(11.8%)	45(88.2%)	0.237
No	6(6.2%)	91(93.8%)	
DDP4 yes	2(5.9%)	32(94.1%)	0.450[a]
No	10(8.8%)	104(91.2%)	
TZD yes	2(15.4%)	11(84.6%)	0.284[a]
No	10(7.4%)	125(92.6%)	
SGLT2 yes	0(0.0%)	4(100.0%)	0.710[a]
No	12(8.3%)	132(91.7%)	
Insulin yes	2(11.1%)	16(88.9%)	0.641
No	10(7.7%)	120(923%)	

Abbreviations: BMI, body mass index; DPP4i, dipeptidyl peptidase type 4 inhibitors; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; RBG, random blood glucose; SGLT2i, sodium-glucose cotransporter type 2 inhibitor; SU, sulphonylureas; TG, triglycerides; TZD, thiazolidinediones.
[a]F-test.

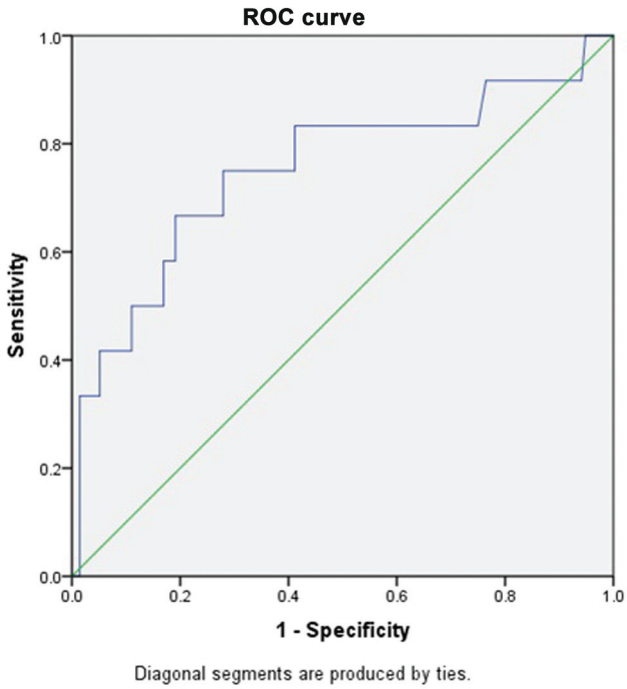

Fig. 2 Receiver operator characteristics (ROC) curve for the effect of body mass index on metformin discontinuation rate.

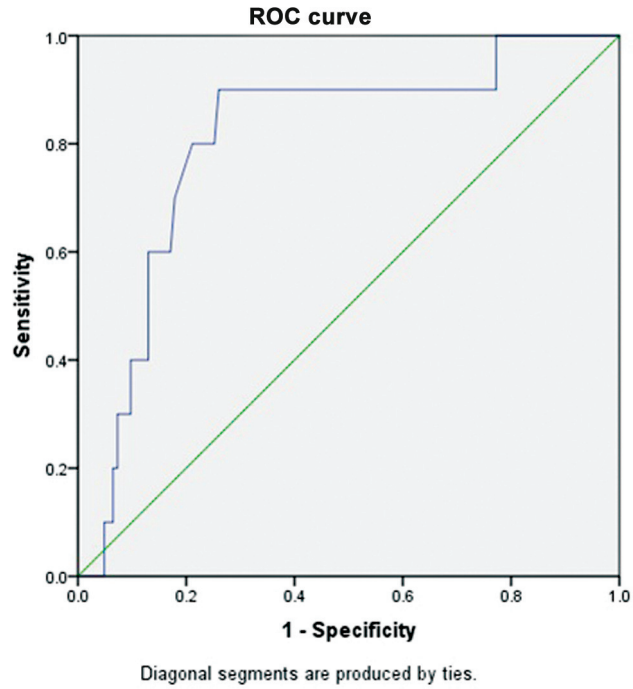

Fig. 3 Receiver operator characteristics (ROC) curve for the effect of fasting blood glucose on metformin discontinuation rate.

developed one or more side effects, other studies found it to be as high as 53.3%.[19]

Diarrhea continues to be the most frequently encountered side effect in about sixth of the patients followed by nausea with comparable frequencies of diarrhea in other studies,[20,21] but much less than the observation of Florez et al who found it to be reaching to the half.[22]

Heartburn, vomiting, and bloating were seen in around tenth of the patients, a percentage quite smaller than what was seen by other studies: 52, 25, and 35%, respectively.[22–24]

Epigastric and abdominal pain were seen in less than 10% of the patients, and in contrast to other side effects, epigastric pain was higher than what was noticed previously.[21]

Patients also reported some nongastrointestinal side effects of metformin, such as palpitation, headache, chest discomfort, and myalgias, but none of these have reached 10% in prevalence, similar to the findings of previous investigators.[24,25]

Most of the patients who developed side effects were around the age of 50 years, Flory et al found that patients aged between 50 and 65 years were 8% less likely to have side effects than patients more than 65 years old, although their results were not statically significant.[26]

Obesity was evident in the patients who developed metformin side effects, although this was in contrast to the finding of Guo et al who found that the proportion of patients who reported more than one side effect did not differ significantly between BMI groups.[27]

As a common finding, women reported side effects more than men did, although statistically not significant in our study.[28]

Some of these side effects were severe enough to obligate the patients to discontinue metformin, at a rate slightly higher than the finding of Bouchoucha et al.[29] Most of them were females as in the observations of previous investigators who found, besides, women were prescribed lower doses of metformin to avoid discontinuation.[28,30–32] One explanation for this gender difference could be attributed to fact that women may be more eager to read about drug information including side effects than men did, which may cause reporting biase.[33] Or it can be attributed to pharmacokinetics differences between genders that may result from differences in body fat percentage and its effect on the drug distrbution.[34] Likely wise, this could be the explanation behind the higher BMI of the patients who discontinued metformin in our study.

We failed to find studies investigating the effect of glycemia or lipid profile on the development of the metformin adverse effects to compare it with our results regarding both the frequency of side effects and the rate of discontinuation of metformin, which will merit the need for further investigations and studies in the future. And apart from hypoglycemia which accompanies sulfonylureas and insulin, the coadministration of other anti-diabetic medications had no effect on the patterns of side effects.

Surprisingly, other gastrointestinal symptoms like constipation, flushing, dyspepsia, abnormal taste, and distension were not reported by any patients in our cohort.

Whether the side effects mentioned by the patients were due to undiagnosed gastrointestinal diseases or due to metformin itself was hardly to be confirmed, making it one of the limitations of the study. Another limitation of the study was that we have only studied (from medication-wise) the effect of antidiabetic medications and have not included other medications that may contribute to these symptoms. But as we have asked the patients to report only new symptoms they felt after metformin use, we proposed that these symptoms were due to metformin use.

Conclusion

Metformin side effects (gastrointestinal and to a lesser extent nongastrointestinal) were common in our population. Diarrhea was the most frequently noticed side effect. Women exhibit side effects to metformin more than men did, and were more likely to discontinue the drug due to higher severity of the side effects. Patients who titrated their medication in a short period were more prone for the development of side effects in comparison with those who titrated it over a longer period. Female gender, higher BMI, and higher FBG were associated with more metformin discontinuation events.

Authors' Contributions

Data collection was performed by M.G.C. Results and statistical analyses were done by N.T.Y.A. The study was designed by S.S.H. and A.A.M. was responsible for literature review and discussion.

Compliance with Ethical Principles

The research was approved by the ethical committee at Faiha Specialized Diabetes, Endocrine and Metabolism Center in Basrah.

Funding and Sponsorship

None.

Conflict of Interest

None declared.

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