Study of the effect of metformin therapy on thyroid function in type 2 diabetic patients

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Background
Metformin, the most widely used antidiabetic drug, is considered as the cornerstone of type 2 diabetes treatments. Surprisingly, a few years ago, it has been reported that serum thyroid-stimulating hormone (TSH) level in hypothyroid patients decreased in response to metformin therapy and increased again when metformin was discontinued. This study was performed at the Diabetic Outpatient Clinic and Internal Medicine Department at Assiut University Hospital during the period between January and June 2017.
Aim
The study aimed to assess the effect of metformin treatment on TSH in type 2 diabetic patients with or without thyroid dysfunction.
Results
A total of 100 patients, with type 2 diabetes mellitus, were enrolled in the study. The patients were divided into two groups: group I included 50 patients on metformin therapy and group II included 50 patients without metformin therapy. Their age was equal to or more than 40 years; their duration of diabetic treatment was equal to or more than 5 years.
Conclusion
In conclusion, there were significant relationships between TSH levels and metformin therapy, obesity, macroangiopathy, and hyperlipidemia, as the treatment with metformin caused suppression of TSH to subnormal levels without any change in free T4 or frees T3 in diabetic patients.

Keywords:
diabetes type 2, metformin therapy, thyroid-stimulating hormone

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Introduction

Diabetes mellitus is a condition in which the pancreas no longer produces enough insulin or cells stop responding to the insulin that is produced, so that glucose in the blood cannot be absorbed into the cells of the body. Symptoms include frequent urination, lethargy, excessive thirst, and hunger. The treatment includes changes in diet, oral medications, and in some cases, daily injections of insulin [1].

There are a number of different types of diabetes, some of which are more prevalent than others. The most common form of diabetes in the general population is type 2 diabetes, which often develops from prediabetes.

Depending on the severity of type 2 diabetes, it may be managed through physical activity and meal planning, or may also require medications and/or insulin to control blood sugar more effectively.

One of the most important medications for the treatment of type 2 diabetes mellitus (T2DM) is metformin. Metformin is the first-line medication for the treatment of type 2 diabetes [2].

Metformin was discovered in 1922 [3]. It is on the WHO's List of Essential Medicines, the most effective and safe medicines needed in a health system [4].

The impact of metformin on the incidence of cardiovascular disease was more pronounced in comparison with insulin and sulfonylureas. Moreover, this agent reduced progression from impaired glucose tolerance to diabetes [5].

A meta-analysis reported a frequency of 11% in thyroid dysfunction in patients of diabetes mellitus [6].

Hormonal output from the thyroid is regulated by the thyroid-stimulating hormone (TSH) secreted from the anterior pituitary gland, which itself is regulated by the thyrotropin-releasing hormone produced by the hypothalamus [7].

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It is supposed that functional changes in the thyroid gland might have cooperation with metabolic syndrome and its related components, including, obesity, insulin resistance, lipid and glucose metabolism abnormalities, and high blood pressure [8].

Previous research has suggested that metformin could lower TSH levels, potentially exposing patients to harmful effects of subclinical hyperthyroidism [9].

Several retrospective and prospective studies in a number of patients have suggested that therapy with this agent is associated with a significant reduction in serum thyrotropin (TSH) concentrations, without relevant changes in serum thyroxine (T4) and triiodothyronine (T3) levels. This finding has been reported in diabetic patients with untreated primary hypothyroidism and in those under replacement therapy [10].

Given the widespread use of metformin in patients with type 2 diabetes and the potential negative consequences of low TSH levels, there is a need to assess the incidence and magnitude of this biochemical event in the natural setting of clinical practice.

This study aimed to assess the effect of metformin treatment on TSH in type 2 diabetic patients on thyroid function test.

Patients and methods

This is a cross-sectional comparative–case–control study. Patients participating in this study were 100 patients with type 2 diabetes attending the outpatient clinic and those admitted in the Internal Medicine Department from January to June 2017. Their age was equal to or more than 40 years; Of the patients, 55.0% were men and 45.0% were women; their duration of diabetic treatment was equal to or more than 5 years. The patients were divided into two groups: group I included 50 patients on metformin therapy and group II included 50 patients without metformin therapy.

Exclusion criteria

Patients excluded were those with recent acute illness or an acute complication of a chronic disease. Patients taking drugs known to affect thyroid function such as amiodarone, patients with a history of cancer, and those with a diagnosis of polycystic ovary syndrome were also excluded. Other excluded groups were those with a history of pituitary disorders, those with thyroid-related procedures, those with a diagnosis of gestational diabetes and those with chronic disease (kidney disease and liver disease).

They were subjected to the following:

(1) Full history that include patient age, sex, diabetes duration, BMI, waist circumference, waist-to-hip ratio and those under treatment for diabetes with special stress on metformin therapy as regards the duration of usage and dose of metformin.
(2) Clinical examination was done to each patient to detect the presence or absence of diabetic complications (diabetic retinopathy, nephropathy, neuropathy, ischemic heart disease, cerebrovascular disease, peripheral artery disease), fundus examination, and neurological examination.
(3) Thyroid assessment by physical examination.
(4) Vital sign [pulse and blood pressure (mmHg)] will be measured.

Laboratory measures

Laboratory measures included random plasma glucose level, plasma lipid levels, glycated hemoglobin (HbA1c), thyroid function test (FT3, FT4, and TSH), renal and liver Function, urine analysis to detect albuminuria, ECG to detect ischemic heart disease, and complete blood count.

Ethical considerations

The study was conducted in accordance with the principles of the Ethics Committee. Serum samples were obtained after receiving informed consent from each patient.

Statistical analysis

Data were collected and analyzed using SPSS (SPSS Inc., Chicago, Illinois, USA) (Statistical Package for the Social Sciences, version 24, continuous data were expressed in the form of mean±SD or median (range) while nominal data was expressed in the form of frequency (percentage). c^2 test was used to compare the nominal data of different groups in the study, while Student's t test was used to compare the mean of two different groups and analysis of variance test for more

Table 1 Anthropometric measurements of the studied patients

	With metformin therapy (*N*=50)	Without metformin therapy (*N*=50)	*P* value
Waist circumference (cm)	90.65±2.99	93.32±3.87	0.04*
Waist-to-hip ratio	0.81±0.12	0.83±0.22	0.01*
Mean BMI (kg/m^2)	24.21±5.09	27.89±3.98	0.02*
Range	18.4–32.09	17.98–34.76	

Data are presented as mean±SD. **P* value was significant if <0.05.

than two groups. Pearson's correlation was used to determine the correlation between serum TSH and duration of metformin use. *P* value was significant if less than 0.05.

Results

In Table 1, there were significant decrease in the waist circumference, waist-to-hip ratio, and mean BMI ($P<0.05$) in patients under metformin therapy versus those without metformin therapy. According to clinical data of enrolled patients, goiter was presented in three (6%) patients without metformin therapy and in two (4%) patients who were under metformin therapy.

It was noticed that 47 (94%) patients on metformin therapy had no clinical manifestation of thyroid dysfunction while three (6%) had positive clinical manifestations of thyroid dysfunction. As regards the laboratory finding in those patients; 39 (78%), 10 (20%), and one (2%) patients had euthyroidism, hypothyroidism, and hyperthyroidism, respectively . As regards those without metformin therapy; 45 (90%) of those patients had no clinical manifestation of thyroid dysfunction while five (10%) had positive clinical manifestations of thyroid dysfunction. As regards the laboratory findings in those patients; 35 (70%), 12 (24%), and three (6%) patients had euthyroidism, hypothyroidism, and hyperthyroidism, respectively (Table 2).

It was noticed that majority (62%) of those patients with thyroid dysfunction were women while majority (61%) of those patients without thyroid dysfunction were men ($P=0.02$).

It was noticed that the prevalence of hypothyroidism was significantly higher in female patients in comparison to male patients (63.6 vs. 36.4%; $P=0.04$), but there was no significant difference present between male and female patients as regards the prevalence of hyperthyroidism ($P=0.98$; Tables 3 and 4).

Baseline laboratory data of both groups are shown at Table 5. It was noticed that complete blood picture, liver function tests, and kidney function tests had no significant differences between both groups ($P>0.05$) with the exception of lipid where those patients on metformin therapy had significantly lower cholesterol, triglycerides, and low-density lipoprotein and had significantly higher high-density lipoprotein in comparison to those without metformin therapy ($P<0.05$). Also, patients with metformin therapy had significantly lower HbA1c.

Table 2 Thyroid dysfunction of the studied patients

Items	With metformin therapy (*N*=50)	Without metformin therapy (*N*=50)	*P* value
Clinical manifestations			0.04*
No symptoms[a]	47 (94)	45(90)	
Positive symptoms[a]	3 (6)	5 (10)	
Laboratory data			0.02*
Euthyroid[a]	39 (78)	35 (70)	
Hypothyroid[a]	10 (20)	12 (24)	
Subclinical	8 (16)	10 (20)	
Overt	2 (4)	2 (4)	
Hyperthyroid (overt)[a]	1 (2)	3 (6)	

Data are presented as *n* (%). Patients with no symptoms of any thyroid dysfunction. Patients have symptoms of any thyroid dysfunction. Patients with normal TSH and T4. Patients with elevated. TSH and normal T4. Patients with elevated TSH and low T4. Patients have low TSH and raised T3, T4. **P* value was significant if <0.05.

Table 3 Thyroid dysfunction of the studied patients based on sex

	With thyroid dysfunction (*N*=26)	Without thyroid dysfunction (*N*=74)	*P* value
Male	10 (38)	45 (61)	0.01*
Female	16 (62)	29 (39)	

Data are presented as *n* (%). **P* value was significant if <0.05.

Table 4 Prevalence of type of thyroid dysfunction based on sex

	Hypothyroidism (*N*=22)	Hyperthyroidism (*N*=4)	Euthyroidism (*N*=74)
Male	8 (36.4)	2 (50)	45 (61)
Female	14 (63.6)	2 (50)	29 (39)
P value	0.04*	0.98	0.02*

Data are presented as *n* (%). **P* value was significant if <0.05.

Table 5 Baseline laboratory data of the studied patients

Laboratory data	With metformin therapy (*N*=50)	Without metformin therapy (*N*=50)	*P* value
Complete blood picture			
TLC ($\times 10^9$/ml)	6.89±1.89	5.31±1.87	0.65
Hemoglobin (g %)	12.58±2.37	12.78±3.89	0.16
Platelets ($\times 10^9$/ml)	258.58±45.09	279.17±55.09	0.17
Liver function tests			
Bilirubin (μmol/l)	11.58±3.89	11.02±4.11	0.73
Direct bilirubin (μmol/l)	3.01±0.86	4.01±3.99	0.45
AST (U/l)	56.12±12.09	60.23±15.97	0.23
ALT (U/l)	76.11±10.09	81.34±12.34	0.13
Protein (g/dl)	7.61±0.85	7.91±1.04	0.32
Albumin (g/dl)	3.7±0.57	3.41±0.38	0.21
Kidney function tests			
Urea (μmol/l)	11.63±6.59	12.12±6.54	0.76
Creatinine (μmol/l)	1.37±0.48	1.33±0.58	0.45
Lipid profile			
Cholesterol (mg/dl)	175.52±29.4	181.01±33.91	**0.03**
Triglycerides (mg/dl)	81.96±15.18	89.23±12.09	**0.04**
HDL (mg/dl)	55.11±12.81	49.90±14.24	**0.02**
LDL (mg/dl)	53.01±18.92	58.41±15.42	**0.02**
HbA1c (%)	7.11±1.01	9.04±0.99	0.04

Data are expressed in the form of mean±SD. ALT, alanine transaminase; AST, aspartame transaminase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TLC, total leukocytic count. **P* value was significant if <0.05.

Table 6 Thyroid dysfunction based on glycosylated hemoglobin

HbA1c (%)	With thyroid dysfunction (*N*=26)	Without thyroid dysfunction (*N*=74)	*P* value
<7	7(26.9)	48 (64.86)	0.02
7.1–8	6 (23.1)	15 (20.3)	
>8	13 (50)	11 (14.8)	

Data are presented as *n* (%). HbA1c, glycated hemoglobin.

Table 7 Thyroid function tests in both the studied groups

Laboratory data	With metformin therapy (*N*=50)	Without metformin therapy (*N*=50)	*P* value
Serum thyrotropin (mU/l)	3.78±0.87	5.67±1.04	**0.03**
Serum triiodothyronine (ng/dl)	110.23±20.56	114.89±25.98	0.65
Serum thyroxine (μg/dl)	5.23±0.34	6.28±0.46	0.31

Data are expressed in the form of mean±SD. TSH, thyroid-stimulating hormone.

It can be noted from Table 6 that the prevalence of thyroid dysfunction increased with poor glycemic control where it was low (26.9%) as those patients were with HbA1c less than 7% while the highest (50%) frequency was in those patients with HbA1c more than 8% (*P*=0.02).

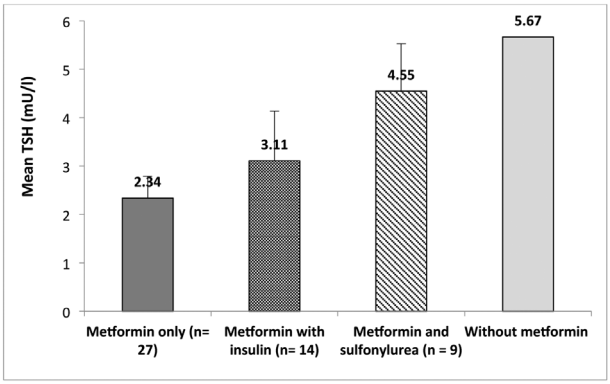
Thyroid functions are shown in Table 7. It was noticed that the level of serum triiodothyronine and serum thyroxine in patients with metformin therapy (110.23 ±20.56 ng/dl and 5.23±0.34 μg/dl, respectively) had insignificant differences in comparison to those without metformin therapy (114.89±25.98 ng/dl and 6.28±0.46 μg/dl, respectively).

The mean level of serum thyrotropin (TSH) in patients with metformin therapy (3.78±0.87 mU/l) was significantly lower in comparison to those without metformin therapy (5.67±1.04 mU/l; *P*=0.03).

It was noticed that serum thyrotropin was significantly lower on those patients on metformin therapy only (2.34±0.98 mU/l) in comparison to those on metformin with insulin (3.11±1.03 mU/l) and those on metformin and sulfonylurea (4.55±0.45 mU/l) (*P*=0.02) (Fig. 1).

It can be noted from Table 8 that the level of thyroid hormones was insignificant between those patients

Figure 1



Mean level of TSH in patients with metformin therapy based on regimens of therapy. TSH, thyroid-stimulating hormone.

with metformin use of more than 10 years and those patents with metformin use of less than 10 years.

Discussion

The clinical implication of a TSH-lowering property for metformin could be important as an adjunct in the pharmacological treatment of thyroid cancer. In patients receiving thyroxine therapy for TSH suppression, the risk of arrhythmias and bone loss is a hindering factor and the use of a medication with TSH-lowering effects and a more than acceptable safety profile would be an attractive alternative. Furthermore, the increased prevalence of hypothyroidism in patients with DM is another factor illustrating the clinical relevance of metformin's effect on thyroid function tests [11].

In this study it was noticed that the mean BMI was significantly lower in those with metformin therapy (P=0.02) than those without metformin therapy. This agrees with Díez and Iglesias [12] who reported that the metformin group had significantly less obese patients than the group of patients not taking this drug.

Also, in this study the waist circumference (P=0.04) and the waist-to-hip ratio (P=0.01) were significantly lower in those patients with metformin. This agrees with Nurcheshmeh *et al.* [13], who reported a significant reduction in waist circumference after a 3-month treatment with metformin.

In this study, goiter was seen in three patients of those without metformin therapy and in two patients of those with metformin therapy. This agrees with Ittermann *et al.* [14] and Blanc *et al.* [15], who reported that diabetic patients treated with metformin had a smaller

Table 8 Thyroid function tests based on the duration of metformin use

Laboratory data	>10 years	<10 years	*P* value
Serum thyrotropin (mU/l)	3.99±0.32	3.44±1.23	**0.3**
Serum triiodothyronine (ng/dl)	103.34 ±24.98	117.09 ±32.04	0.22
Serum thyroxine (μg/dl)	5.13±0.22	5.28±0.33	0.31

thyroid volume and a lower risk for the formation of thyroid nodules when compared with controls. These results suggested that metformin exerts an antiproliferative activity, providing a rationale for an innovative therapy of thyroid-proliferative diseases with metformin.

In this study there were both clinical manifestations of thyroid dysfunction and laboratory data had significant differences between both groups (P<0.04, 0.02). It was noted that the mean level of serum thyrotropin (TSH) in patients with metformin therapy was significantly lower in comparison to those without metformin therapy (P<0.03); in contrast, the level of serum triiodothyronine and serum thyroxine in patients with metformin therapy had insignificant differences in comparison to those without metformin therapy.

This agrees with Chakraborty *et al.* [16], who reported that metformin is considered as a first-line drug for the treatment of T2DM, and metformin-suppressed TSH to subnormal levels, without changes in free T4 and T3 levels. Prospective studies in patients with diabetes and hypothyroidism on stable LT4 treatment showed that during metformin administration for 3 months, TSH levels were significantly lower than basal TSH concentrations with reverse effects occurred on discontinuation of metformin.

Cappelli *et al.* [17] in their study evaluated thyroid hormone profiles by studying the interaction between metformin and circulating thyroid function parameters in patients who were started on metformin. A pilot study of diabetic hypothyroid patients showed a baseline reduction of TSH level after 6 months. Similarly, a large cohort study carried out on diabetic patients showed a significant fall in TSH level in euthyroid patients on LT4 substitution and subclinical hypothyroid patients who did not receive LT4 treatment, except in euthyroid patients after 1 year on metformin. This study concluded that the TSH-lowering effect of metformin is only seen in untreated hypothyroid patients and with LT4 replacement therapy irrespective of the thyroid function test [11].

In contrast, there is some recent evidence that the relation between TSH values and metformin treatment may not be independent [12].

In this study the majority (62%) of those patients with thyroid dysfunction, specially hypothyroidism were women while the majority (61%) of the patients without thyroid dysfunction were men ($P<0.02$). This agrees with Ravishankar *et al.* [18], who reported that thyroid disorders are more in women (36%) than men (22%). In both, the general population and diabetic patients with thyroid diseases were reported to be more common in women than in men.

This also agrees with Khurana and Malik [19] who reported the prevalence of thyroid disorders especially hypothyroidism was more in women as compared with men (71.87 vs. 28.12%), which when evaluated statistically was significant ($P<0.05$).

In this study, microangiopathic complications in patients with metformin therapy were: five (10%) patients, four (8%), and seven (14%) patients had retinopathy, nephropathy, and neuropathy, respectively, while such complications occurred in 12 (24%), 13 (26%), and 16 (32%) patients, respectively, of those without metformin therapy. It was noticed that three (6%), two (4%), and two (4%) of those with metformin therapy had coronary artery disease, cerebrovascular disease, and peripheral vascular disease, respectively, while such complications occurred in 10 (20%), two (4%), and seven (14%) patients of those without metformin therapy. All these complications were significantly higher in those patients without metformin therapy with the exception of cerebrovascular disease. This agrees with Díez and Iglesias [12] who reported that patients taking metformin were less prone to have microangiopathy, macroangiopathy, and hypertension.

In this study it was found that the prevalence of thyroid dysfunction increased with poor glycemic control ($P<0.02$), which agrees with Vikhe *et al.* [20], who found that the prevalence of thyroid dysfunction was increased in poor glycemic-controlled diabetic patients as HbA1c was divided into four groups. A significant association between the presence of thyroid dysfunction and glycemic control is noted. Poorly controlled T2DM patients carried increased risk (27.9%) of development of thyroid dysfunction compared with well-controlled diabetic groups (14.7%) ($P<0.012$).

In this study, serum thyrotropin was significantly lower on those patients on metformin monotherapy in comparison to those on metformin with insulin or those on metformin and sulfonylurea ($P<0.02$).

This is disagrees with Díez and Iglesias [12] who reported serum TSH concentration was not different in patients, who were classified according to their antidiabetic treatment modality, that is, diet [148 mU/l (109–210 mU/l)], oral antidiabetics [149 mU/l (103–214 mU/l)], and insulin therapy [141 mU/l (101–212 mU/l)]. Nevertheless, their study found no significant differences in TSH levels in patients who were on therapy with sulfonylureas, meglitinides, or thiazolidinedione in relation to patients not taking these drugs.

In this study, the level of thyroid hormones (T3 and T4) had no significant difference between those patients with metformin use more than 10 years and those patients with metformin use of less than 10 years. This agrees with Alevizaki [21], who reported nonsignificant difference between changes in TSH with the duration of treatment of diabetes with metformin. Also, Fournier *et al.* [22] showed that the use of metformin is not associated with an increased risk of low TSH levels and has no pattern with the duration of use. The observed nonsignificantly lower TSH level in T2DM patients who have been on metformin for 10 years or more compared with patients with fewer years supports the report of Cappelli *et al.* [23], who reported nonsignificantly lower mean TSH level in euthyroid T2DM patients after 12 months of metformin use.

Conclusion

In conclusion, we found significant relationships between TSH levels and metformin therapy, obesity, macroangiopathy, and hyperlipidemia. However, the use of metformin was associated with an increased risk of low TSH levels in patients with treated hypothyroidism, with the highest risk after treatment initiation. Metformin appeared to have no effect on TSH levels in euthyroid patients. Further prospective studies in large samples of euthyroid patients with diabetes are needed to clarify the effect of different doses and duration of treatment with metformin on thyroid function test.

Recommendations

Our study recommends a wide range of skill studies that include more patients, and more clinical and

laboratory parameters to evaluate the effect of metformin therapy on thyroid function in type 2 diabetic patients. Clinicians should consider the effect of metformin when they interpret thyroid function to avoid any appropriate treatment or adjustment of LT4 dosage.

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Conflicts of interest
There are no conflicts of interest.

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