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Research Article

The Effects of Metformin on Thyroid Function among Patients with Subclinical Hypothyroidism and Coexisting Metabolic Syndrome

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ABSTRACT

Background: The interference of metformin with thyroid function has been recently reported in several studies. In the present research, we assessed the effect of metformin on thyroid function tests in patients with subclinical hypothyroidism associated with metabolic syndrome.
Method: In a double-blind clinical trial, 60 patients were selected among who referred to outpatient endocrine clinics and met the inclusion and exclusion criteria were considered for the study. Inclusion criteria were the presence of metabolic syndrome and subclinical hypothyroidism (2.5<TSH<10 mIU/l). Screened patients used no medications interfering with TSH level. Pregnancy, GFR less than 50 ml/min and intolerance of metformin were also considered as exclusion criteria. Patients were divided into case and a placebo groups. In the case group, patients received 1000 mg/day of metformin for 12 weeks. Anthropometry, liver and thyroid function tests, and lipid profile were evaluated before and after the intervention.
Results: A total of 44 patients fully participated for the whole study period. The mean age was 44±14 years and 15 patients (34.1%) were male. The mean TSH and FT4 levels before and after intervention were 5.8±2.15, 4.8±2.7 and 1.10±0.19, 1.14±0.26, respectively. The positive TPO-ab was seen among 18 (40.9%) patients. TSH (4.12±2.07, p=0.013) and FT4 (1.18±0.23, p=0.007) levels were decreased and increased, respectively, compared to the placebo group. Furthermore, a reduction in metabolic element was observed.
Conclusion: Our data showed that metformin reduced the TSH level in subclinical hypothyroid patients, especially in patients with TSH baseline level higher than 5mIU/l and TPO-ab positive patients.

Introduction

It is generally accepted that subclinical hypothyroidism may affect some health issues including cardiovascular disorder.[1] In this regard, metabolic syndrome (MS) with an increasing incidence and complex clinical presentation is associated with insulin resistance, abdominal obesity, high blood pressure, hypertriglyceridemia and low HDL cholesterol that consequently associated with an increased risk of diabetes mellitus (DM) and cardiovascular events. Additionally, DM and thyroid function disorders are among the most common diseases in clinical practice. The hypothyroidism is a common coexisting condition in 10-30 % of the patients with DM.[2-5]

Metformin is known as an oral biguanide and safe agent with minimum or no clinically relevant pharmacologic interactions with other medications and is widely used for the treatment of T2DM, a common disorder among metabolic syndrome patients. However, the interference of metformin with thyroid function test (TFT) has been recently reported in several studies. It has been shown that it may decrease the serum levels of thyrotropin (TSH) in hypothyroid patients.[6,7] Furthermore, it has been reported that metformin decelerates tumor growth in various types of cancers including thyroid cancer.[8,9] A meta-analysis research evaluating the alteration of TSH levels in patients treated with metformin, showed that TSH levels decrease at both overt and subclinical hypothyroidism groups with no changes in euthyroid subjects.[10] In addition, Karimifar *et al.* in a double-blind placebo-control clinical trial, revealed that metformin treatment causes a decrease in the levels of serum TSH in patients with TSH level higher than 2.5 mIU/l.[11] It has been hypothesized that metformin changes the affinity and/or quantity of thyroid hormone receptors, increases the central dopaminergic tone or induces activation of the TSH receptor, and enhances the effects of thyroid hormones (TH) in the pituitary.[6,12]

Although both metformin treatment and hypothyroidism are frequent co-occurrences in DM patients, there is not sufficient data about the influence of metformin on untreated hypothyroid patients with metabolic syndrome.[3,13,14] On the other hand, TH changes have a major influence on lipid and glucose regulation. In some clinical conditions such as T2DM and nonalcoholic fatty

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liver disease, intracellular TH alterations have been observed frequently. Additionally, TH has a key role in lipid metabolism at the cellular level.[15-17]

Due to the widespread use of metformin in metabolic disorders and T2DM along with the potential negative effects on TSH levels, there is a need to evaluate the effects of this biochemical event in the natural setting of clinical practice. Therefore, in this study, we assessed the effects of metformin on patients with subclinical hypothyroidism.

Materials and Methods

Patient selection

This research was a double-blind clinical trial study which was conducted on 60 patients referred to outpatient endocrinology clinics of Tabriz University of Medical Sciences (TUOMS) between January 2014 to September 2016. Three conditions were considered in the study:

(a) The inclusion criteria were similar to those which are considered in metabolic syndrome including presence of at least three of the following five components: fasting glucose ≥100 mg/dl (or receiving drug therapy for hyperglycemia); blood pressure ≥130/85 mm-Hg (or receiving drug therapy for hypertension); triglycerides ≥150 mg/dl (or receiving drug therapy for hypertriglyceridemia); HDL-C <40 mg/dl in men or <50 mg/dl in women (or receiving drug therapy for reduced HDL-C); and waist circumference ≥102 cm in men or ≥88 cm in women, (b) Subclinical hypothyroidism was also considered as normal serum free thyroxine (FT4) concentration associated with serum TSH > 2.5 mIU/l., and (c) No medications interfering with TSH level.

Subjects with pregnancy, estimated GFR < 50 ml/min, intolerance of metformin and subjects who fulfilled diagnostic criteria of diseases such as poly cystic ovarian syndrome (PCOS) and hyperprolactinemia, which could affect study results were excluded.

Data collection

A face-to-face interview was performed at the first clinical visit with all patients and a questionnaire including demographic, anthropometric, lab data and clinical data was filled up for each of them. All participants underwent a general physical exam by an endocrinologist.

Weight measurement was done by scales with an accuracy of ±100 gram, with minimal clothing and no shoes. Height measured using a stadiometer with an accuracy of ±0.5 cm. The body mass index (BMI) was calculated by dividing weight (kg) by the square of height (meters). Waist Circumference (WC) was measured in midway between the upper most border of the iliac crest and the lower border of the costal margin. Liver function tests including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total cholesterol (Chol), triglycerides (TGs), high-density lipoprotein (HDL) Cholesterol, low-Density Lipoprotein (LDL) Cholesterol, and Fasting Blood Sugar (FBS) were measured in a single laboratory.

Patients were then divided into placebo and case groups, by simple randomization method. Subjects in the case group received 500 mg metformin two times per day and subjects in the control group received the placebo similar in shape to metformin. They were followed up for 3-month time period. Diet and physical activity were also administered for all participants regarding to their metabolic syndrome status.

Statistical analysis

The results were analyzed by SPSS 20. Descriptive analysis was done. Comparisons of quantitative data with a normal distribution between two groups were performed by means of independent samples' T-test. To compare the variables that did not distribute normally the Mann-Whitney U-test was used. A P-value of lower than 0.05 ($p < 0.05$) was considered significant.

Ethic approval

The Ethical Committee of TUOMS approved the study protocol, and it is registered on the Iranian Registry of Clinical Trials website (IRCT ID: IRCT201304073565N8) in accordance with the Declaration of Helsinki. The proposal was explained to all participants and a written informed consent was obtained. Investigating endocrinologist was easily available to subjects during the study period. Moreover, they were free to quit the study at any time. The expenditures of the study were paid by the Endocrine Research Center of TUOMS. Participants did not pay any charges for laboratory tests of this study.

Table 1. Basic characteristics data of patients in metformin and placebo groups before intervention.

Variable	Metformin	Placebo	p-value
Gender(M/F) (N)	8/14	7/15	0.75
Age year (Mean±SD)	46.8±13.2	41.3±14.6	0.21
WC (cm)	104.8±9.3	101.6±6.9	0.194
SBP (mmHg)	130.7.4±24.0	133.±13.6	0.618
DBP (mmHg)	81.4±5.8	85.5±13.7	0.374
Creatinine (mg/dl)	1.00±0.14	1.00±0.19	0.773
ALT (IU/l)	28.4±15.9	37.6±6.7	0.110
AST (IU/l)	21.6±6.3	36.7±35.4	0.502
TG (mg/dl)	224.7±101.	196.60±80.4	0.314
HDL (mg/dl)	42.6±.6.7	41.0±7.5	0.284
LDL (mg/dl)	121.4±32.1	117±26.4	0.627
FBS (mg/dl)	127.1±36.6	111.4±37	0.051
TSH (mIU/l)	5.28±2.21	6.3±2.30	0.141
Free T4 (ng/dl)	1.10±0.19	1.11±0.19	0.861
TPO-ab Positive	9	9	-

WC: Waist Circumference, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, TGs: Triglycerides, HDL: High-Density Lipoprotein Cholesterol, LDL: Low-Density Lipoprotein Cholesterol, FBS: Fasting Blood Sugar, TSH: Thyroid Stimulation Hormone, T4: Thyroxin, TPO-ab: Thyroid Peroxidase Antibody.

Results

Among 60 patients selected initially, 44 subjects remained in the study for the whole time. Table 1 shows the basic characteristics data of patients who participated in this study before intervention. No significant differences were observed between groups in baseline condition.

Table 2. Change in study variables after intervention in metformin and placebo groups.

Variable	Groups					
	Metformin			Placebo		
	Before Mean±SD	After Mean±SD	P-value	Before Mean±SD	After Mean±SD	P-value
WC (cm)	104.8±9.3	103.5±8.8	0.011	101.6±6.9	100.4±7.1	0.016
SBP (mmHg)	130.7.4±24.0	135.5±20.9	0.483	133±13.6	132±9.7	0.255
DBP (mmHg)	81.4±5.8	82±9.2	0.837	85.5±13.7	83.3±6.6	0.722
Creatinine (mg/dl)	1.00±0.14	-	-	1.00±0.19	-	-
ALT (IU/l)	28.4±15.9	24.2±9.9	0.163	37.6±6.7	31.9±17.2	0.174
AST (IU/l)	21.6±6.3	20.7±5.7	0.590	36.7±35.4	23.02±6.7	0.380
TG (mg/dl)	224.7±101.	191.7±80.2	0.013	196.60±80.4	172.9±49.8	0.015
HDL (mg/dl)	42.6± 6.7	44.7±8.9	0.272	41.0±7.5	43.5±8.7	0.006
LDL (mg/dl)	121.4 ±32.1	101.1±30.7	0.001	117±26.4	114.4±18.1	0.374
FBS (mg/dl)	127.1±36.6	107.4±28.2	0.0001	111.4 ±37	111.9±62.2	0.094
TSH (mIU/l)	5.28±2.21	4.12±2.07	0.013	6.3±2.30	5.41±3.33	0.249
Free T4 (ng/dl)	1.10±0.19	1.18±0.23	0.007	1.11 ±0.19	1.09±0.30	0.647
TPO-ab positive	9	9	-	9	8	-

WC: Waist Circumference, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, TGs: Triglycerides, HDL: High-Density Lipoprotein Cholesterol, LDL: Low-Density Lipoprotein Cholesterol, FBS: Fasting Blood Sugar, TSH: Thyroid Stimulation Hormone, T4: Thyroxin, TPO-ab: Thyroid Peroxidase Antibody.

The mean age of patients was 44±14 years. 15 (34.1%) of them were male and 29 (65.9%) of them were female. The means of TSH (mIU/l) and free T4 (ng/dl) before intervention were 5.8±2.15 and 1.10±0.19, respectively. The TPO-ab positive was seen among 18 (40.9%) patients. Table 2 illustrates characteristics of subjects regarding metformin treatment vs. placebo before and after intervention.

The results in Table 2 show a significant reduction in WC, FBS and LDL cholesterol after a three-month treatment with metformin. Analyzing the obtained results within the intervention group showed that both TSH and FT4 levels changed significantly. The TSH level decreased from 5.28±2.21 to 4.12±2.07 (P-value<0.013), while the FT4 level increased from 1.10±0.19 to 1.18±0.23 (P-value<0.007).

In order to omit the effect of confounding factors, such as hyperprolactinemia, PCO etc., we adjusted data for gender in both metformin and placebo groups after intervention. Results are shown in Table 3. In the metformin group, no significant changes were observed in variables except FBS while in the placebo group only DBP and TG variables were changed significantly in the end of the study.

For further evaluation of the effects of metformin we analyzed the TSH and FT4 changes in the metformin group in two subgroups of patients with TSH<5 or TSH>5 mIU/l in the baseline. We determined P-values before and after adjusting data for gender in both subgroups. As shown in Table 4 a significant reduction was observed in TSH level only in the subgroup with TSH>5 mIU/l before (p=0.026) and after (p=0.001) adjusting data for gender. Additionally, no significant changes in FT4 were observed in both subgroups.

Table 3. Changes in P-values in metformin and placebo groups after data adjustment for gender.

Variable	Groups	
	Metformin	Placebo
WC (cm)	0.274	0.496
SBP (mmHg)	0.569	0.412
DBP (mmHg)	0.203	0.030
Creatinine (mg/dl)	-	-
ALT (IU/l)	0.627	0.064
AST (IU/l)	0.649	0.078
TG (mg/dl)	0.139	0.020
HDL (mg/dl)	0.143	0.753
LDL (mg/dl)	0.116	0.730
FBS (mg/dl)	0.001	0.212
TSH (mIU/l)	0.112	0.621
Free T4 (ng/dl)	0.931	0.512
TPO-ab positive	-	-

WC: Waist Circumference, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, TGs: Triglycerides, HDL: High-Density Lipoprotein Cholesterol, LDL: Low-Density Lipoprotein Cholesterol, FBS: Fasting Blood Sugar, TSH: Thyroid Stimulation Hormone, T4: Thyroxin, TPO-ab: Thyroid Peroxidase Antibody.

To investigate the effect of the TPO-ab on the TSH and FT4 variations, metformin treated patients were divided into TPO-ab positive and TPO-ab negative subgroups.

Table 4. The TSH and FT4 level before and after treatment with metformin.

Groups	TSH≤5mIU/l (n=11)		TSH>5mIU/l (n=11)	
Factor	**TSH (mIU/l)**	**FT4 (ng/dl)**	**TSH (mIU/l)**	**FT4 (ng/dl)**
Pretreatment (Mean ± SD)	3.67±0.84	1.17±0.21	7.21±1.74	1.02±0.12
Post treatment (Mean ± SD)	2.97±1.88	1.25±0.25	5.49±1.37	1.10±0.17
P-value before adjusting data for gender	0.236	0.06	0.026	0.07
P-value after adjusting data for gender	0.796	0.848	0.001	0.756

n = number of patients

Table 5. The TSH and FT4 levels before and after treatment with metformin (based on TPO-ab).

Groups	TPO-ab positive (n=9)		TPO-ab negative (n=13)	
Factor	**TSH (mIU/l)**	**FT4 (ng/dl)**	**TSH (mIU/l)**	**FT4 (ng/dl)**
Pretreatment (Mean±SD)	6.68±1.88	1.03±0.16	4.32±1.91	1.15±0.19
Post treatment (Mean±SD)	5.21±1.83	1.06±0.20	3.36±1.94	1.27±0.21
P-value before adjusting data for gender	0.03	0.46	0.14	0.006
P-value after adjusting data for gender	0.009	0.746	0.374	0.372

n = number of patients

As shown in Table 5, a significant reduction of TSH was observed only in the TPO-ab positive subgroup before as well as after adjusting data for gender. In contrast to TSH changes, FT4 showed a significant increase in the TPO-ab negative subgroup only before adjusting data for gender.

Finally, because the baseline FBS between two groups before intervention is near significant (p=0.051, Table 1), we did a correlation analysis to determine the relationship between FBS changes and TSH/FT4 variations in both groups before and after intervention. Furthermore, we found the relationship between TSH changes and FT4 variations. The obtained results are shown in Table 6.

Table 6. Correlation analysis of FBS and thyroid function test.

Group	Variable	TSH	FT4
Intervention	FBS	0.2	0.141
	TSH	-	-0.452
Placebo	FBS	0.043	0.028
	TSH	-	-0.289

As it is shown in Table 6, in the intervention group there was a mild but not a significant positive association between FBS changes and TSH/FT4 variations, respectively (R=0.2, p=0.373; R=0.141, p=0.530). Similarly, in the placebo group there was a very mild but not a significant positive association between FBS changes and TSH/FT4 variations, respectively (R=0.043, p=0.850; R=0.028, p=0.901).

Discussion

Despite several studies about the role of metformin on thyroid profile still there is not a definite conclusion in this regard. In the present study, the results showed that 1000 mg per day metformin can probably improve both subclinical hypothyroidism and metabolic syndrome characteristics.

Metformin as an anti-diabetic drug is commonly used for T2DM. The mechanisms of its action are not completely understood; nevertheless, it may be related to its role in improving insulin sensitivity. Recent studies have indicated that metformin decreases the TSH level.[6,10,18,19] Furthermore, other researchers reported that metformin may have effects on the size and development of nodule(s) in thyroid gland.[20,21] In recent years, the prevalence of subclinical hypothyroidism has increased, becoming an important issue regarding management and treatment in general medical practice. Notably, there is not a consensus about treatment of hypothyroid patients.[22, 23]

Previous studies have reported the effects of autoantibody in developing of subclinical hypothyroidism. In this regard, TPO-ab should be taken into account. In the present study, the positive TPO-ab was not different between two groups following before and after metformin treatment. Previous reports revealed that high rate of insulin resistance and autoimmunity occurs in patients who are overweight. They concluded that the TSH lowering effect of metformin may be more favorable among TPO-ab negative subjects.[24,25] On the other side Karimifar *et al.*[11] in a RCT on 89 patients obtained comparable results to the current research and indicated that metformin may not affect thyroid autoimmunity in a brief period of treatment. We illustrated that metformin could decrease the TSH level especially in positive TPO-ab and TSH > 5 mIU/l patients. Regarding to FT4, a significant increase was observed in the TPO-ab negative subgroup after metformin treatment. This increase in FT4 level was not observed after adjusting data for gender. However, FT4 changes were not noticeable in TSH≤5mIU/l, or in TSH>5mIU/l and TPO-ab positive subgroups. Rajput *et al.*[26] showed that suppressive effects of metformin are associated with negative anti-TPO while Capelli *et al.*[3] claimed that these suppressive metformin effects would be independent of the anti-TPO status. Furthermore, some of the previous studies reported that the suppressive effects of metformin occur when the TSH level is relatively high. In a meta-analysis done by Lupoli *et al.*[10] on previous studies, it is reported that metformin reduces the TSH level in subjects with either overt hypothyroidism or subclinical hypothyroidism. However, this effect of metformin was not seen in euthyroid subjects. In this meta-analysis there was no discussion about the effect of anti-TPO factor on reducing TSH level by metformin. Some previous studies revealed that the suppressive effect of metformin on TSH occurs in the specific level of TSH. Cappeli *et al.*[3] and Karimifar[11] emphasized the association of this effect with the baseline of TSH more than 2.5mIU/l. Santos-Palacios *et al.*[19] in a retrospective study on 278 patients revealed that metformin has a lowering effect on TSH level when TSH level is higher than 2.98 mIU/l.

Similar to previous studies, our results showed that metformin is effective primarily in patients with a relatively higher TSH level.[3,11,19] Furthermore, our results affirmed that metformin is effective on subjects with TPO-ab positive. Similarly to the previous studies done by other researchers, our study showed that there is no significant change in the level of FT4 after adjusting data for gender. As mentioned previously different results were reported about the association between the effect of metformin and TPO-ab status. There is no significant

positive association between FBS reduction and TSH/FT4 variations for both intervention and placebo groups.

The mechanism of metformin on thyroid profile is complex and its effects are related to the insulin resistance in most organs such as liver, skeletal or adipose tissues. Metformin may work on thyroid hormone receptors and on hypothalamic-pituitary-thyroid axis activity.[27,28] In animal studies, it has been demonstrated that metformin can pass through the brain-blood barrier (BBB), although there is not enough data on human subjects. In general, at the molecular level, metformin may generate its effects via adenosine monophosphate-activated protein kinas (AMPK) and subsequent inhibition of mammalian targets of rapamycin (mTOR), which is involved in supplying of cellular energy and regulation of TRH/TSH pathway.[8,9,29,30] In other study Krysiak *et al.* indicated the proper role of gender on metformin effects in hypothalamic-pituitary-thyroid axis activity.[31] Furthermore, previous studies showed that the levels of TSH in obese patients were slightly more than in normal population.[14,32-34] This association could be bilateral, however this phenomenon needs further investigations to be fully understood. It is reported that some little variations in thyroid function within laboratory reference ranges may contribute to weight gain. On the other hand, FT4 and BMI have an inverse correlation, even when FT4 remains in the normal range.[32,35] The main difference between the current research and previous studies is the coexistence of metabolic syndrome and subclinical hypothyroidism.

These outcomes are in part related to metformin. The role of metformin in insulin resistance-related diseases is accepted. Taghavi *et al.* also reported that administration of 1500 mg/d of metformin causes a significant decrease in TSH level after six months in PCOS obese women with no similar effects on FT4 and T3.[36] The role of metformin on the nonalcoholic fatty liver disease without glucose intolerance or diabetes is not accepted commonly by most researchers.[37]

Conclusion

Metformin as an anti-diabetic drug has various metabolic effects on different organs via different pathways including hypothalamic-pituitary-thyroid axis activity. In this study, obtained results showed that metformin decreases the TSH level particularly in patients with a TSH level higher than 5 mIU/l and TPO-ab positive. Our results show an increase in FT4 for the metformin group. This effect was not observed after adjusting data for gender. Increasing in FT4 level would be due to reduction in BMI. However, further research would be required to investigate the effects of metformin on the thyroid function test.

Conflict of interests

The authors claim that there is no conflict of interest.

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