

ORIGINAL ARTICLE

Effect of Metformin on TSH Levels

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ABSTRACT

Aims and objectives: Main aim of the study was to see the effect of metformin on thyroid function parameters especially TSH. We also wanted to see factors responsible for these thyroidal effects of metformin.

Materials and methods: we selected treatment naïve type 2 diabetes and PCOS subjects. we had 72 subjects, 56 were having type 2 diabetes and 16 were having PCOS. We took their blood samples at baseline before starting metformin and 6 months after starting metformin. In both samples we checked thyroid functions and insulin resistance indices. Dose of metformin was 1 gm in type 2 DM and 500mg PCOS. We took 80 patients at beginning, 8 were lost to follow up, 72 completed the study.

Results: we found that there was no significant change in thyroid function parameters after 6 months of metformin intake. It made no difference whether patients were obese or non-obese, diabetic or nondiabetic, male or female. But on subgroup analysis it was found that in those patients in whom insulin resistance decreased, TSH was significantly decreased where as in those subjects in which insulin resistance had increased TSH did not change significantly.

Conclusion: In this study we concluded that metformin decreases TSH especially in those patients where it decreases insulin resistance also successfully.

Clinical Significance: Minor elevations in TSH may be part of metabolic syndrome and may not warrant treatment with thyroxine.

Keywords: Metformin, TSH

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INTRODUCTION

Type 2 diabetes mellitus (DM) is the predominant form of diabetes mellitus worldwide, accounting for 90% of cases globally.^{1,2} Insulin resistance is a consistent finding in patients with type 2 DM, which may be present for years before the onset of diabetes.^{3,7} Prospective studies show that insulin resistance predicts the onset of diabetes mellitus.^{3,4} Polycystic ovary syndrome (PCOS), a heterogeneous disorder of unclear etiology, when fully expressed, the manifestations include ovulatory dysfunction, androgen

excess, polycystic ovaries, and obesity.⁸ Burghen et al, 1980 were among the first to report that PCOS patients were hyperinsulinemic in response to an oral glucose tolerance test.⁹ It is now known that insulin resistance, and the development of compensatory hyperinsulinemia, is a

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frequent finding in PCOS.¹⁰

Metformin remains a time tested drug and stands as a drug of first choice in majority of the patients with type 2 DM. It is also frequently used as a treatment of PCOS especially in obese and glucose intolerant patients. In addition to antihyperglycemic action metformin has a pleiotropic effect which is exerted by metformin on arterial vessels by its effects on lipids, inflammation, hemostasis, endothelial and platelet function and vessel wall abnormalities.¹¹

One of the latest domains of function added to metformin is on thyroid functions especially TSH. Few years back Robert et al, 2006 reported that metformin appeared to suppress serum TSH to subnormal levels without resulting in biochemical or clinical hyperthyroidism.¹² Rotondi et al, also showed that metformin results in thyrotropin suppression in patients of PCOS.¹³

In this study we tried to see the effect of metformin on thyroid functions in patients of type 2 diabetes mellitus and PCOS who had never received this drug before.

PATIENTS AND METHODS

This study was conducted in the Department of Endocrinology at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar. Study was approved by the Institute Ethical Committee. Patients were recruited prospectively over a period of 1 year; each patient was part of the study for a period of 6 months.

Subjects included (1) newly diagnosed type 2 diabetes mellitus patients as per ADA statement 2013¹⁴, who were treatment naïve and (2) first time diagnosed patients of PCOS as per Rotterdam criteria 2003.¹⁵

Patients with overt hyperthyroidism or hypothyroidism were excluded from study and so were the patients who had taken metformin earlier for one reason or the other.

All the patients were put on metformin with a dose of 1gm once daily in type 2 diabetes mellitus and 500 mg once daily in PCOS patients. Height, weight, BMI and abdominal circumference of all subjects were measured at the recruitment. We measured total T3, total T4, free T3, free T4, TSH, anti-TPO antibody, serum insulin, blood sugar fasting levels at baseline and after 6 months of treatment with metformin. Lipid profile, serum creatinine, and uric acid were also measured at baseline. Insulin was measured

by immunoradiometric assay (IRMA). Analytical sensitivity of assay was 0.49µIU/ml. The range of measurement was from 0.49-300 µIU/ml. Anti-TPO antibody was measured by ELISA method. Values less than 50 IU/ml were considered negative, values between 50-75 IU/ml were considered intermediate and values more than 75 IU/ml were considered positive.

TSH was measured by hypersensitive third generation chemiluminescent immunoassay, with a range of detection from 0.01-100 µIU/ml. coefficient of variation ≤ 20%. Normal range in this assay is 0.34-5.6 uIU/ml.

Free T3, Free T4, total T3 and total T4 were measured by chemiluminescent immunoassay on Beckman Coulter immunoassay system. Patient test results are determined automatically by the system software using a weighted four parameter logistic curve (4PLC) math model. The range of detection for free T3 was 0.88 to 30 pg/ml. This assay exhibits total imprecision ≤ 12%. Normal range of free T3 in this assay is established as 2.5-3.9 pg/ml. Range of detection for free T4 was 0.256-0 ng/dL. Normal range for free T4 with this assay is established as 0.61-1.12 ng/dl. For total T3 range of detection was 0.1-8 ng/ml, with imprecision less than 10%. Established normal range for total T3 is 0.87-1.78 ng/ml. Range of total T4 detection was 0.5-30 µg/dl with an imprecision of less than 10%. Established normal range for total T4 by this assay is 6.09-12.23 µg/dl.

We also calculated HOMA-IR and QUICKI indices using standard formulas. $HOMA-IR = \text{Fasting insulin (mIU/ML)} \times \text{Fasting glucose (mg/dl)} / 405$,

$QUICKI = 1 / (\log \text{fasting insulin} + \log \text{fasting glucose})$

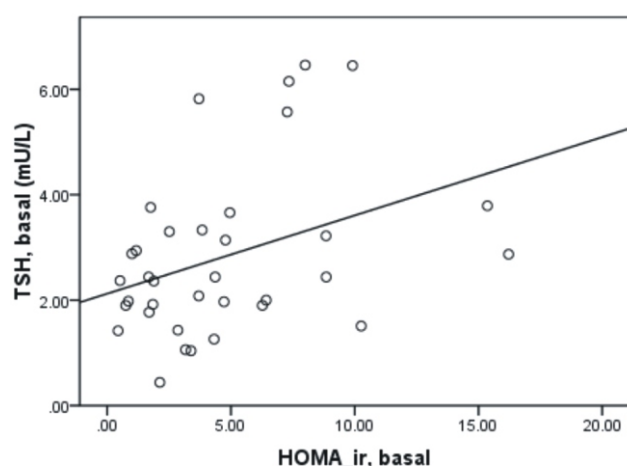
RESULTS

Of the 80 subjects recruited, only 72 completed the study, but the characteristics of 8 subjects who didn't follow were similar to those who completed the study. Of these 72 study subjects, 56 were patients of type 2 DM while the remaining 16 subjects were having PCOS. All the subjects were diagnosed first time and were treatment naïve. Age of the subjects ranged from 17 to 65 with a mean of 40.76 ± 11.72 years (median, 43). Understandably subjects with PCOS were significantly younger than those with type 2 DM. Relevant parameters at baseline are shown in table 1.

Table 1: Baseline anthropometric and laboratory parameters of the study subjects

Parameter	T2DM (mean ± SD)	PCOS (mean ± SD)	All subjects
Age (years)	46.79 ± 2.21	23.19 ± 3.66	40.76 ± 11.72
BMI (Kg/m ²)	25.95 ± 2.35	22.69 ± 2.06	25.23 ± 2.65
HOMA IR	4.91 ± 4.02	2.86 ± 2.04	4.45 ± 3.76
QUICKI	0.32 ± 0.04	0.35 ± 0.06	0.33 ± 0.05
Cholesterol (mg/dl)	193.86 ± 25.53	173.56 ± 23.40	189.35 ± 26.32
Triglycerides (mg/dl)	215.14 ± 37.13	175.19 ± 28.04	206.26 ± 38.90
LDL (mg/dl)	112.64 ± 18.45	98.81 ± 12.31	109.57 ± 18.15
HDL (mg/dl)	43.64 ± 4.047	46.25 ± 3.73	44.22 ± 4.10
T3 (ng/ml)	1.07 ± 0.26	1.19 ± 0.22	1.10 ± 0.25
T4 (µg/dl)	8.59 ± 1.80	7.40 ± 0.88	8.32 ± 1.71
TSH (uIU/ml)	3.38 ± 2.10	3.10 ± 1.54	3.32 ± 1.98
FT3 (pg/ml)	2.78 ± 0.31	3.05 ± 0.29	2.84 ± 0.32
FT4 (ng/dl)	0.91 ± 0.16	0.79 ± 0.08	0.88 ± 0.16

We observed that TSH was having a positive linear relation with HOMA IR, more the insulin resistance, higher were the TSH levels.

**FIGURE 1:** Positive linear relationship between TSH and HOMA IR ($r=0.4$, $p=0.03$)

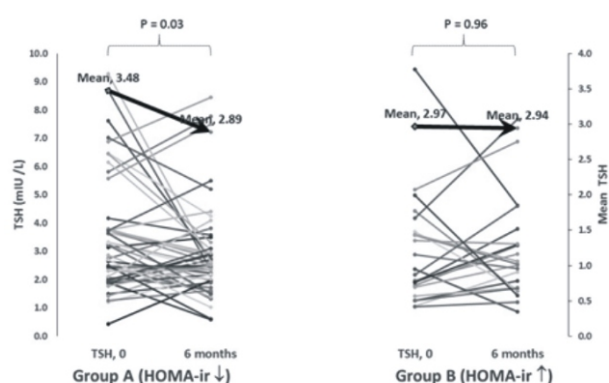
After 6 months of treatment with metformin the mean TSH values were 2.9 ± 1.64 μ IU/ml. Mean total T4 levels were 7.54 ± 1.26 μ g/dl and mean total T3 levels were 1.12 ± 0.26 ng/ml. Mean free T4 levels were 0.84 ± 0.11 ng/dl, while mean free T3 levels were 2.83 ± 0.31 pg/ml (figure 2). Mean HOMA-IR was 3.41 ± 2.66 and mean QUICKI was 0.198 ± 0.015 .

Overall the mean TSH values decreased from 3.32 to 2.9 μ IU/ml after treatment with metformin, but the difference was not statistically significant when compared by paired t test ($p=0.07$). However, total T4 values decreased

significantly from 8.32 to 7.5 μ g/dl ($p=0.03$). There was no significant difference between baseline total T3 and post therapy total T3 ($p=0.548$). There was also no difference between basal and post therapy free T3 ($p=0.848$). Again there was no difference between basal and post therapy free T4 levels ($p=0.128$). (table 2)

Table 2: Thyroid function parameters and insulin resistance markers before and after treatment.

Parameter	Baseline	After 6 months	p value
Total T3 (ng/ml)	1.10 ± 0.25	1.12 ± 0.26	0.55
Total T4 (µg/dl)	8.32 ± 1.71	7.55 ± 1.26	0.03
Free T4 (ng/dl)	0.88 ± 0.16	0.85 ± 0.11	0.13
Free T3 (pg/ml)	2.84 ± 0.32	2.83 ± 0.32	0.85
TSH (µIU/ml)	3.32 ± 1.98	2.90 ± 1.65	0.07
QUICKI	0.33 ± 0.05	0.33 ± 0.04	0.18
HOMA-IR	4.45 ± 3.76	3.41 ± 2.66	<0.01

**Figure 2** A comparison of change in TSH between two groups where HOMA-IR decreased and increased respectively.

DISCUSSION

The primary aim of present study was to observe effect of metformin on TSH. We also tried to assess the relation between indices of insulin resistance and parameters of thyroid function, especially TSH. We also tried to find whether any thyroïdal effects of metformin were related to changes in markers and/or indices of insulin resistance.

We selected the first time diagnosed patients of type 2 DM and PCOS who were historically euthyroid and not taking any medications that could affect TSH levels. Age of subjects ranged from 17 to 65 years. Mean age for T2DM patients was 45.79 ± 7.63 years whereas that of PCOS subjects was 23.19 ± 3.66 years. Out of 72 subjects (40 females), 39 (54%) had BMI of 25 kg/m^2 or more. Baseline HOMA-IR of our subjects ranged from 0.2 to 16.2, with a mean of 4.45 ± 3.76 (median, 3.4), with a significant linear correlation with age ($r = 0.33$) and body weight ($r = 0.24$). Baseline QUICKI ranged from 0.26 to 0.51 with a mean of 0.33 ± 0.05 (median, 0.32); correlating significantly with age ($r = -0.29$; $p = 0.014$) only. Correlation of body weight and BMI with HOMA-IR is a well-known fact proven beyond doubt in many studies.¹⁶

The mean TSH of our study subjects at baseline was $3.32 \pm 1.98 \text{ } \mu\text{IU/ml}$, which corresponds well to the range for normal euthyroid population.¹⁷ There was a positive linear correlation between TSH and markers of insulin resistance (HOMA-IR) especially in those subjects who had free T4 in upper half of normal range. Similar correlations have been shown in previous studies. In a recent study from South-India, Vyakaranam et al, reported that TSH positively correlated with insulin and HOMA-IR.¹⁸ Singh et al, also have noticed this positive correlation of TSH with indices of insulin resistance, but only in overt hypothyroid group of their study and not in euthyroid and subclinical hypothyroidism subjects.¹⁹ Their study was primarily aimed at observing this correlation only. In another study association of TSH with insulin resistance and androgen parameters in PCOS patients was studied by Dittrich R et al.²⁰ The authors observed that women with TSH of $>2.5 \text{ mU/l}$ had higher BMI, higher insulin and higher testosterone concentrations. In another study higher levels of TSH were found to be associated with higher LDL cholesterol and lower HDL cholesterol levels and thereby

were associated with increased cardiovascular risk.²¹

After 6 months of therapy with metformin we found an overall decrease in mean TSH levels (3.32 vs $2.91 \text{ } \mu\text{IU/ml}$). The level of suppression we observed was just marginally short of statistical significance ($p=0.07$). There are studies though, that have observed a statistically significant suppression of TSH by metformin. Carlo Capelli et al, in their study observed that metformin causes suppression of TSH in hypothyroid patients, both treated and untreated, but they failed to show this effect in euthyroid subjects.²² They hypothesized that metformin may increase the inhibitory modulation of T4 on TSH secretion and this effect may not be valid in case of a normal hypothalamo-pituitary-thyroid axis, thus explaining the lack of effect on euthyroid patients where axis is normally operating. Mario Rotondi et al, in their study on PCOS subjects with and without hypothyroidism observed that metformin caused TSH suppression of statistical significance in only hypothyroid subjects and had no effect on TSH in euthyroid subjects.²³ Vigersky et al, reported suppression of TSH to below normal in 4 hypothyroid patients who were on treatment and well controlled, but there were no clinical features of thyrotoxicosis in these patients.²⁴ Another reason that in our study suppression of TSH did not achieve statistical significance may have been a relatively small sample size.

One unique observation from our study is significant decrease in total T4 after 6 months of treatment with metformin, but there was no change in free T4. None of the studies mentioned above have noticed a suppression in total T4. This effect noticed in our study may be due to possible effect of metformin on the protein binding of thyroxine as has been postulated before also.^{24,25}

We did not find any difference in change in thyroid function on the basis of their BMI (obese vs non-obese), gender (male vs female) and diagnosis (T2DM vs PCOS). Oleadri SE et al, in their study on subjects with abdominal obesity did not find any variation in TSH levels on treatment with metformin. There is no study in literature that has compared head to head, changes in TSH among males vs females, or diabetes vs PCOS.

We also observed that TSH was significantly decreased in those subjects in whom HOMA-IR has decreased as compared to those subjects where HOMA-IR has increased.

Though there are no such studies till date who have shown correlation of thyroidal effect of metformin with changes in HOMA-IR, but many studies have shown TSH to be related to insulin resistance.¹⁸⁻²¹ These studies have shown more insulin resistance in subclinical hypothyroidism as compared to euthyroid population.¹⁸ Singh et al, found that TSH progressively increased through low to high BMI and through increasing levels of serum insulin.¹⁹ Ours is the first study which shows that TSH suppression of metformin may be dependent on decrease in insulin resistance.

There have been various hypotheses regarding the mechanism of action of metformin in the context of TSH suppression, which include:²⁵⁻²⁶ 1) Metformin may increase the affinity or number of thyroid hormone receptors 2) There may be an increase in dopaminergic tone resulting in TSH suppression 3) Change in bioavailability of thyroid hormone by altering protein binding 4) Metformin may cause constitutive activation of TSH receptor. However, to elucidate the exact mechanism of action is beyond the scope of current study.

The positive points of our study are that it is a prospective study as compared to majority of the studies mentioned previously, which were retrospective in nature. Also in our study, participants were not taking any other medication except metformin, where as in other studies patients were on multiple other drugs including thyroxine. Majority of our patients tested negative for anti-TPO antibody, only 5 out of 72 tested positive. This makes possibility of autoimmune influence on the thyroid functions less likely; any change in TSH would be more likely due to time and/or metformin. Majority of previous studies have not checked for anti-TPO antibody. We have used baseline values as control though, it would have been ideal to have separate controls. Another limitation of our study is a marginally small sample size.

CONCLUSION

In conclusion, we observed a positive correlation between serum thyrotropin levels and indices of insulin resistance. There was a decrease of thyrotropin (TSH) level with metformin treatment at 6-months follow up that is statistically significant only in subjects in whom HOMA-IR also decreased. We also found that total T4 levels were decreased significantly after treatment with metformin, but this effect was not dependent on change in HOMA-IR, and needs to be studied further. How exactly the changes in

HOMA-IR bring about changes in TSH levels remains a topic of interest for further research.

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