

## Evaluation of Safety and Efficacy of Metformin in Reduction of TSH Levels in Subclinical Hypothyroidism Patients

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### ABSTRACT

**Background:** The reduction of TSH levels in SCH patients with metformin alone is unclear and lack of evidence in clinical practice. Therefore we aimed to observe the efficacy of metformin with levothyroxine sodium and levothyroxine sodium alone in reduction of TSH levels in SCH patients.

**Aim:** To evaluate the safety and efficacy of Metformin in reduction of TSH Levels in subclinical hypothyroidism patients.

**Methodology:** It was a prospective observational study conducted at Department of Endocrinology, Endolife Hospital, Guntur, during the period of July 2017 to April 2018 (8 months), the study was approved from Institutional Human ethics committee. Group A 90 patients were enrolled with SCH and 30 patients are excluded due to lack of follow-up and they are not meet the inclusion criteria. After exclusion the study participants are 60. The 60 patients are divided into two groups, group A (LTX 25 mcg OD alone), group B (LTX 25 mcg+Metformin 500 mg OD). The TSH levels are measured at baseline and different intervals of baseline to first visit (45 days), first visit to second visit (45 days) and baseline to second visit.

**Results:** The safety and efficacy of metformin along with LTX observed by comparing LTX alone in TPO antibody negative individuals. The TSH levels are measured at baseline, 45 and 90 days after the treatment. Treatment improvement was observed in females as compare to males in both groups. The percentage deviation between 1<sup>st</sup> visits to 2<sup>nd</sup> visit was found to be 17.37% in males and 21.72% deviation was observed in females. The percentage deviation between 1<sup>st</sup> visits to 2<sup>nd</sup> visit was found to be 26.71% in males and 24.71% deviation was observed in females. By observing above data the prominent percentage reduction of TSH was observed in females than males in both treatment group A and B and overall the treatment Group B shows more efficacious than treatment group A.

**Conclusion:** Our study concludes that the Metformin suppresses serum TSH levels in individuals with subclinical hypothyroidism. We observed that a greater reduction of TSH was more in group B as compared to group A & also we observed that TSH levels were reduced more in female patients.

**Keywords:** Levothyroxine sodium, Metformin, TSH, Safety and efficacy

**Abbreviations:** BMI: Body Mass Index; LTX: Levothyroxine Sodium; OD: Once in a Day; PO: Per oss (Oral); SCH: Subclinical Hypothyroidism; TSH: Thyroid Stimulating Hormone; TPO: Thyroperoxidase Antibody

### INTRODUCTION

Metformin, the most widely used anti-diabetic drug, is considered as the cornerstone of type 2 diabetes treatments. Surprisingly, a few years ago it has been reported that serum TSH level in hypothyroid patients decreased in response to metformin therapy and increased again when metformin was discontinued [1]. Later this finding has been confirmed by several studies [2]. The novel effects of metformin on the thyroid were not confined to hypothyroidism. Due to lack of conclusive data regarding effect of metformin in patients of mild SCH with TSH level 5-10 mIU/L, the present study

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was planned to observe the effects of combination of metformin with Levothyroxine sodium and Levothyroxine sodium on thyroid function test (TSH) in patients with SCH. The most common symptoms reported were the problems with memory, puffy eyes, muscle cramps, muscle weakness, slowness of thinking weariness, dry skin, feeling colder, throat harshness and more constipation [3,4].

**AIM**

To evaluate the safety and efficacy of Metformin in reduction of TSH Levels in subclinical hypothyroidism patients.

**OBJECTIVES**

- To assess the levels of Thyroid Stimulating Hormone (TSH), in Subclinical hypothyroidism patients.
- To compare the results of patients who are taking Levothyroxine (LTX)+Metformin and Levothyroxine (LTX) alone.
- To monitor adverse drug reactions.

**METHODOLOGY**

It was a prospective observational study conducted at Department of Endocrinology, Endoline Hospital, Guntur, during the period of July 2017 to April 2018 (8 months), the study was approved from Institutional Human ethics committee. 90 patients were enrolled with SCH and 30 patients are excluded due to lack of follow-up and they are not meeting the inclusion criteria. After exclusion the study participants are 60. The 60 patients are divided into two groups, group A (LTX 25 mcg OD alone) % group B (LTX 25 mcg+Metformin 500 mg OD). The TSH levels are measured at baseline and different intervals of baseline to first visit (45 days), first visit to second visit (45 days) and baseline to second visit.

**Inclusion criteria**

- Subclinical hypothyroidism patients of either sex between 25-80 years of age.

- Patients with Thyroid Stimulating Hormone (TSH) between 4.2-10 mIU/L.
- Patients who are on Levothyroxine 25 mcg OD.
- Patients who are on Levothyroxine 25 mcg OD+Metformin 500 mg OD.

**Exclusion criteria**

- Patients who are on
  - Estrogen therapy
  - Glucocorticoids
  - Dopamine
  - Bromocriptine
  - Iodine
  - Lithium and Amiodarone

**RESULTS**

**Table 1** shows age and gender wise distribution of study subjects. The 60 patients are divided into two groups, group A (LTX 25 mcg PO, OD alone) % group B (LTX 25 mcg PO and Metformin 500 mg PO, OD). In our study, total 11 males and 49 female patients with SCH and they are distributed in different age groups, age ranges from 25 to 65 years (Mean age ± SD was 37.35 ± 10.65), among them 30 patients (50%) of 5 male and 25 female in the age group of 25-35 years, 19 patients (31.67%) of 1 male and 18 female, in the age group of 36-45 years, 7 patients (11.67%) of 3 male and 4 female in the age group of 46-55 years and 4 patients (6.67%) of 2 male and 2 females in the age group of 56-65 years respectively. By observing above population SCH was found to be more prominent in females with the age range of 25-35 years.

**Table 1.** Age and gender wise distribution of study subjects.

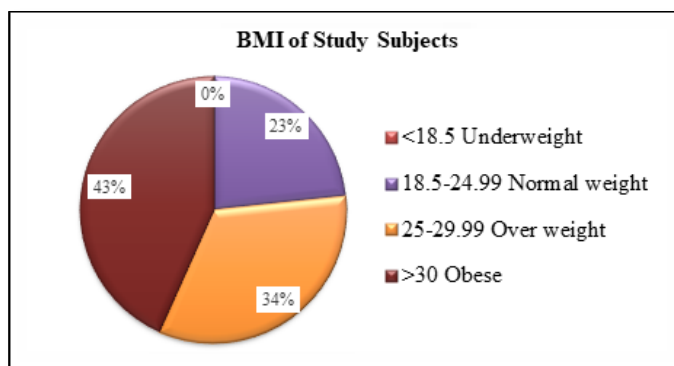
Age (Years)	No. of subjects		Total number of patients N (%)
	Males n (%)	Females n (%)	
25-35	5 (45.45)	25 (51.02)	30 (50.00)
36-45	1 (9.09)	18 (36.73)	19 (31.67)
46-55	3 (27.27)	4 (8.16)	7 (11.67)
56-65	2 (18.18)	2 (4.08)	4 (6.67)
Total	11	49	60

**Table 2** and **Figure 1** show descriptive details about the BMI of the study patients. BMI range was found to be 21.20 to 43.90 kg/m<sup>2</sup> (Mean BMI ± SD was 29.79 ± 5.452), among them 14 patients (23.33%) had normal weight with a BMI of 18.5-24.99 kg/m<sup>2</sup>, 20 patients (33.33%) were

overweight with a BMI of 25-29.99 kg/m<sup>2</sup> and 26 patients (43.33%) were obese with a BMI of >30 kg/m<sup>2</sup>. By observing BMI of the study population, SCH was found to be more common in obese and overweight patients.

**Table 2.** BMI of study subjects.

S. No.	BMI kg/m <sup>2</sup>	Category	No. of Patients (N=60)	Percentage (%)
1	<18.5	Underweight	0	00.00
2	18.5-24.99	Normal weight	14	23.33
3	25-29.99	Over weight	20	33.33
4	>30	Obese	26	43.33



**Figure 1.** BMI of study subjects.

**Table 3** shows that the percentage reduction of TSH among males and females of treatment Group A (LTX 25 mcg PO, OD) alone. Of 30 patients, 5 males (16.67%) and 25 females (83.33%). In males, the percentage reduction of TSH was found to be baseline to 1<sup>st</sup> visit (21.22%), 1<sup>st</sup> visit to 2<sup>nd</sup> visit (23.07%) and baseline to 2<sup>nd</sup> visit (38.59%), respectively. In females the percentage reduction was found to be 23.1%,

27.71% and 44.82% with respective intervals. By observing above data the prominent percentage reduction of TSH was observed in females than males. The percentage deviation between 1<sup>st</sup> visits to 2<sup>nd</sup> visit was found to be 17.37% in males and 21.72% deviation was observed in females. By observing above data the prominent % reduction of TSH was observed in females than males in treatment group A.

**Table 3.** Percentage reduction of TSH in Group A.

(Group A) LTX Alone				
Gender	% Reduction of TSH from baseline to 1 <sup>st</sup> visit	% Reduction of TSH from 1 <sup>st</sup> to 2 <sup>nd</sup> visit	% Reduction of TSH from baseline to 2 <sup>nd</sup> visit	% Deviation between 1 <sup>st</sup> to 2 <sup>nd</sup> visit
Males (n=5)	21.22	23.07	38.59	17.37
Females (n=25)	23.1	27.71	44.82	21.72

**Table 4** shows that the percentage reduction of TSH among males and females of treatment Group B (LTX 25 mcg PO+Metformin 500 mg PO OD). Of 30 patients, 6 males (20%) and 24 females (80%). In males, the percentage reduction of TSH was found to be baseline to 1<sup>st</sup> visit (16.03%), 1<sup>st</sup> visit to 2<sup>nd</sup> visit (31.72%) and baseline to 2<sup>nd</sup>

visit (42.74%), respectively. In females the percentage reduction was found to be 22.53%, 32.97% and 47.24% with respected intervals. By observing above data the prominent percentage reduction of TSH was observed in females than males. The percentage deviation between 1<sup>st</sup> visits to 2<sup>nd</sup> visit was found to be 26.71% in males and 24.71% deviation was

observed in females. By observing above data the prominent percentage reduction of TSH was observed in females than males in treatment group B. The overall percentage

reduction and efficacy was observed in Group B as compared to treatment Group B.

**Table 4.** Percentage reduction of TSH in Group B.

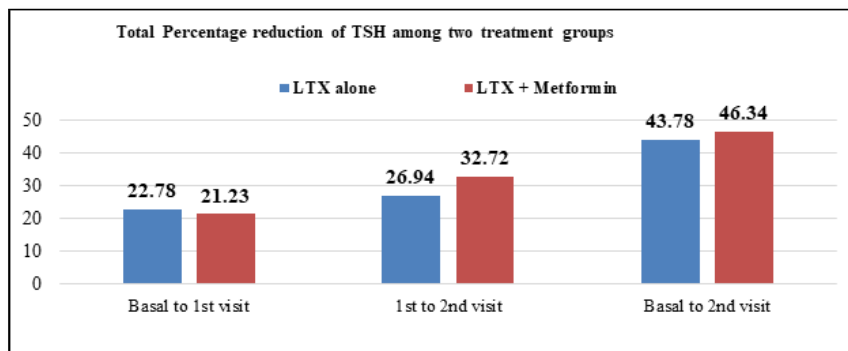
<b>(Group B) LTX+Metformin</b>				
<b>Gender</b>	<b>% Reduction of TSH from baseline to 1<sup>st</sup> visit</b>	<b>% Reduction of TSH from 1<sup>st</sup> to 2<sup>nd</sup> visit</b>	<b>% Reduction of TSH from baseline to 2<sup>nd</sup> visit</b>	<b>% Deviation between 1<sup>st</sup> to 2<sup>nd</sup> visit</b>
Males (n=5)	16.03	31.72	42.74	26.71
Females (n=25)	22.53	32.97	47.24	24.71

**Table 5** and **Figure 2** shows that, Of 60 patients, 30 Group A (50%) and 30 Group B (50%).the percentage reduction of TSH was found to be 22.78%, 26.94% and 43.78% between

the baseline to 1<sup>st</sup> visit, 1<sup>st</sup> visit to 2<sup>nd</sup> visit and baseline to 2<sup>nd</sup> visit, respectively. In Group B, it was found to be 21.23%, 32.72% and 46.34% between the baseline to 1<sup>st</sup> visit, 1<sup>st</sup> visit to 2<sup>nd</sup> visit and baseline to 2<sup>nd</sup> visit, respectively.

**Table 5.** Total percentage reduction of TSH between Group A and B.

<b>Group</b>	<b>% Reduction of TSH from baseline to 1<sup>st</sup> visit</b>	<b>% Reduction of TSH from 1<sup>st</sup> to 2<sup>nd</sup> visit</b>	<b>% Reduction of TSH from baseline to 2<sup>nd</sup> visit</b>
Group (A)	22.78	26.94	43.78
Group (B)	21.23	32.72	46.34



**Figure 2.** Total percentage reduction of TSH between Group A and B.

The student T-test was applied for these two groups and it was found to be, calculated t value shows that there is significant difference within each group during their baseline to first visit, first to second visit and baseline to second visit. We are not observed any adverse drug reactions or drug related problems during our study period.

**DISCUSSION**

The age range of 25-44 years was found in the study which was done by Rajput [5], whereas in our study the SCH Patients were lies between the age of 25-35 years old, off which most of are obese and overweight. Subclinical hypothyroidism has been detected with increasing frequency

in recent years and is causing major controversies concerning management and treatment. In the present study patients of subclinical hypothyroidism who are more obese, and are TPO antibody negative responded favorably to LTX and Metformin therapy at 24 weeks as compared to individuals of SCH with LTX alone. Our findings that TSH lowering effect is observed only in individuals who were TPO antibody negative are in contrast with observation made by Capelli et al. [6] who showed that significant reduction in TSH level was seen in those patients on Metformin who had a baseline TSH higher than 2.5 mIU/l independent of presence or absence of TPO antibodies.

## CONCLUSION

Our study concludes that the Metformin suppresses serum TSH levels in individuals with subclinical hypothyroidism. We observed that a greater reduction of TSH was more in group B (Levothyroxine+Metformin) as compared to group A (Levothyroxine alone) after 2<sup>nd</sup> visit. There is a significant difference within each group during their baseline to 1st visit, 1<sup>st</sup> to 2<sup>nd</sup> visit and baseline to 2<sup>nd</sup> visit. And we also observed that TSH levels were reduced more in female patients.

## CONFLICT OF INTEREST

None

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