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Effects OfMetformin On Thyroid Profile In Patients Of Subclinical Hypothyroidism Attending OPD Of A Tertiary Care Hospital

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Abstract: ***Background:*** *Subclinical hypothyroidism (SCH) defined as an elevated serum Thyroid Stimulating Hormone (TSH) level with a normal serum free thyroxine (fT4) concentration [1]. SCH can progress to overt hypothyroidism. In this study we can see effect of metformin among SCH patients.*
Methodology*: The study was conducted at Midnapore Medical College. This unicentric, hospital based single arm prospective interventional study included 96 new cases of SCH patients age 18-60 years with TSH level 5-10 mIU/L and normal fT3 & fT4. Metformin prescribed 2,000 mg daily into two divided doses for 12 weeks [2]. Serum fT3, fT4 and TSH level were measured by ELISA. Statistical comparisons performed by "Paired t test".*
Results: *96 patients (15 male, 81 female) mean age was 36.18±11.57 years. Comparison of TSH levels of study subjects before starting metformin therapy and 8 weeks after therapy and also before starting metformin and 12 weeks after therapy, by "Paired t test". Significant reduction in TSH level was seen at the end of 12 weeks (P < 0.001).*
Conclusion: *Metformin can decrease TSH level in SCH patients without significant alteration of fT3 & fT4 levels. Further studies required to establish effects of metformin in long term use in SCH.*
Keywords: *Metformin, Subclinical hypothyroidism, Thyroid Stimulating Hormone.*

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I. Introduction

Anatomically thyroid gland is located at front section and of the neck. The thyroid hormones thyroxin (T4) and triiodothyronine (T3) interfere with the body metabolism as whole. In hypothyroidism, the thyroid gland produce less amount of thyroid hormone, such subjects eventually will lead to have lower metabolic rate and clinical manifestation such as overweight, fatigue, hypotension and depression. The symptoms of either hyperthyroidism or hypothyroidism can put the patient life at risk, therefore the diagnosis and management of thyroid abnormalities is a curtail task for the clinicians as well as medical diagnostic laboratories world-wide. Laboratory measurements of Thyroid Stimulating Hormone (TSH) and free thyroxin (fT4) and free tri-iodothyronine (fT3) are the key hormones in helping the clinicians to diagnose the thyroid patient abnormality.

The other undiagnosed thyroid abnormalities are either sub-clinical hyperthyroidism or sub-clinical hypothyroidism which usually can be diagnosed on the bases of laboratory blood test results. The sub-clinical hyperthyroidism or sub-clinical hypothyroidism is diagnosed when the fT4, fT3, serum concentrations are at normal range with low and high TSH serum levels respectively. Whether sub-clinical thyroid dysfunction accompanied with any metabolic disorders, it is remain to be answered and it is not fully understood. Thyroid disorder can be correlated with other metabolic abnormalities among all are dyslipidaemia, cardiovascular, liver diseases and anaemia.

We concern in this study were to see the effect of metformin among sub-clinically hypothyroid patients. Subclinical hypothyroidism (SCH) defined as an elevated serum thyrotropin (TSH) level with a normal serum free levothyroxine (fT4) concentration. Subclinical hypothyroidism (SCH) can progress to overt hypothyroidism [1]. The prevalence ofSCH increases with age, is higher in women but after sixtyyears of age prevalence in men approaches that of womenwith a combined prevalence of 10% [1,3]. Most clinicians agree that individuals with TSH level higher than 10 mIU/L should be treated with levothyroxine (LT4) but there is uncertaintyregarding usefulness of treating those with TSH levels between 5 - 10 mIU/L [4,5]. Also at the same time failure to decrease LT4 dosage in those developing subnormal TSH level while on treatment puts these patients to undesirable side effects of LT4 on bone density and cardiac function [6,7]. Metformin is a biguanide derivative oral drug used for treatment of T2DM and is commonly regarded as safe drug with no clinically relevant side effect and drug interaction with exception of folate and vitamin B12 [8] . In recent years few studies have shown TSH suppressive effect of metformin with no effect on fT4 levels [9,10]. Vigersky et al [10] observed that use of metformin for a duration varying from 2 - 8 months induced reversible suppression of TSH without a

change in fT4 or fT3 levels, or clinical signs of hyperthyroidism in a patient of non-alcoholic steatohepatitis who was on LT4 after radioactive iodine treatment for graves' disease and three additional hypothyroid patients (two post-surgical and one with hashimoto's disease) who developed TSH suppression when they were placed on metformin for treatment of diabetes mellitus. The present study was planned to see the effects of metformin administration on thyroid function test in patients with mild SCH.

II. Material And Methods

Patients attending the Medicine OPD (Out-Patient Department) of Midnapore Medical College and Hospital, Paschim Medinipur diagnosed drug naive SCH subjects with TSH level between 5 - 10 mIU/L were included. A written informed consent was taken from all patients. . Study was approved in written from the institutional Ethics Committee of Midnapore Medical College and Hospital, Paschim Medinipur on 18/01/2015. Study was conducted according to Good Clinical Practice Guidelines of INDIAN COUNCIL OF MEDICAL RESEARCH (ICMR).

Study Design: Unicentric, hospital based prospective, interventional study.

Study Location: The study was conducted in the department of Biochemistry, Pharmacology & "Medicine OPD (Out-Patient Department)" of Midnapore Medical College and Hospital, Paschim Medinipur.

Study Duration: The study subjects were recruited from March 2015 to February 2016.

.**Sample size:** The study was conducted in 96 consecutive newly diagnosed drug naive SCH subjects.

Sample size calculation: The sample size was estimated on the basis of a single proportion design. The target population from which we randomly selected our sample was considered 20,000. We assumed that the margin of error 05% and confidence level of 95% and incidence was 9.5%. The sample size actually obtained for this study was 92 patients. We planned to include 96 patients with 4% drop out rate.

Subjects & selection method: The study population was drawn from consecutive newly diagnosed drug naive SCH subjects with **TSH level between 5 - 10 mIU/L** attending "Medicine OPD (Out-Patient Department)" of Midnapore Medical College and Hospital, Paschim Medinipur also fulfill inclusion criteria.

Inclusion criteria:

- Patients attending Medicine OPD (Out-patient department) of Midnapore Medical College and Hospital.
- Either sex.
- Aged 18 to 60 years.
- Serum TSH level 5 to 10 mIU/L and normal fT3 & fT4.
- With written informed consent.

Exclusion criteria:

- The patients with overt hypothyroidism.
- Those taking levothyroxine and/or anti thyroid drugs, iodine, Lithium, amiodarone.
- Type II Diabetes Mellitus (T2DM).
- Irritable Bowel Disease (IBD).
- Congestive Heart Failure (CHF).
- Any addiction, pregnant and post-partum women.
- Severe anemia.
- Myocardial infarction, asphyxia, shock.
- Renal dysfunction (serum creatinine>= 1.5 mg/dl in males and 1.4 mg/dl in females, or above the upper limit of normal for age), were excluded from the study.
- H/O any thyroid surgery.

Procedure methodology

The study was carried for a time period of 12 weeks. A total of 96 patients of SCH irrespective of gender, age group from 18 to 60 years with TSH between 5 – 10 mIU/L were given 2,000 mg/day of metformin for 12 weeks. Baseline anthropometric characteristics (Body weight, free tri-iodothyronine (fT3), tetra-iodothyronine (fT4), Thyroid Stimulating Hormone (TSH) assessed at baseline at 08 weeks and at 12 weeks with routine blood test, like Hb%, TC,DC, ESR, Fasting Blood Sugar, Urea, Creatinine and Lipid profile.

Procedure Concomitant medication was not allowed with the study medication. Procainamide, digoxin, quinidine, trimethoprim, and vancomycin are all cationic drugs that have the potential to interact with metformin, but only cimetidine, which is available over the counter for heart-burn, has been implicated in one case of metformin-associated lactic acidosis (MALA). The above drugs should not be prescribed with metformin.

Analysis of blood sample for fT3, fT4 and TSH were done by ELISA in the Clinical Biochemistry Laboratory of the Biochemistry department. Recruitment would cease, once the desired recruitment target is fulfilled – estimated 9 months from study inception. The entire study, including data analysis and report preparation, is expected to be completed within 12 months of inception.

Adverse events recorded during the study included treatment emergent events reported spontaneously by subjects at any time during the study or for one week after completing the scheduled course of study medication, or those elicited as clinical signs by the investigators during the scheduled visits. Adverse laboratory test results were also to be considered as adverse events. Statistical comparisons were performed using "Paired t test". Data were considered statistically significant at $p < 0.05$.

The prescribed doses of metformin in Medicine OPD (Out-Patient Department) of Midnapore Medical College and Hospital for SCH patients were as follows:
Metformin prescribed 2,000 mg daily into two divided doses for 12 weeks.

Statistical analysis

Data was analyzed using SPSS version 16 (SPSS Inc., Chicago, IL). Student's *t*-test was used to ascertain the significance of differences between mean values of two continuous variables all data was processed and analyzed at the Department of Pharmacology, Midnapore Medial College and Hospital, Paschim Medinipur. A period of 3 months is envisaged for the data entry, clarification, and analysis and report preparation.

Archiving of study documents was done by the Principal Investigator in his office at the Department of Pharmacology, Midnapore Medial College and Hospital, Paschim Medinipur, for a period of two (2) years following completion of the study. The study completion date would be taken as the date of submission of final report summary to the Institutional Ethics Committee.
The level $P < 0.05$ was considered as the cutoff value or significance.

III. Result

Out of ninety six (96) patients fifteen (15) were male and eighty one (81) were female with mean age of 36.18 ± 11.57 years. There was statistical significant difference in TSH between at the baseline and 8 weeks after therapy (P = <0.001). Comparison of the TSH levels of the study subjects before starting metformin therapy and 8 weeks after the therapy (Table no. 1) and also before starting metformin therapy and 12 weeks after the therapy (Table no. 2), by *"Paired t test"*. Significant reduction in serum TSH was seen at the end of 12 weeks (P < 0.001) with mild effects on fT4 and fT3 levels. None of the patient develop clinical or biochemical hypoglycemia during the study period. Hemoglobin concentration after administration of metformin was decreased both in 8 weeks and after 12 weeks (Figure no. 1) which is statistical significant (p = < 0.001). Clinical global impression of patientimproved significantly, weight reduction; improve physical health, emotional wellbeing and social functioning

Table no. 1: Comparison of the TSH levels of the study subjects before starting metformin therapy and 8 weeks after the therapy, by *"Paired t test"*

No of samples	TSH levels before therapy (Mean ± SD)	TSH levels 8 weeks after therapy (Mean ± SD)	t value	P value	Significance of difference
96	7.36±1.24	6.51±1.06	15.99	<0.001	Significant

Table no. 2: Comparison of the TSH levels of the study subjects before starting metformin therapy and after end of the therapy, by *"Paired t test"*

No of samples	TSH levels before therapy (Mean ± SD)	TSH levels after end of therapy (Mean ± SD)	t value	P value	Significance of difference
96	7.36±1.24	6.06±0.99	18.78	<0.001	Significant

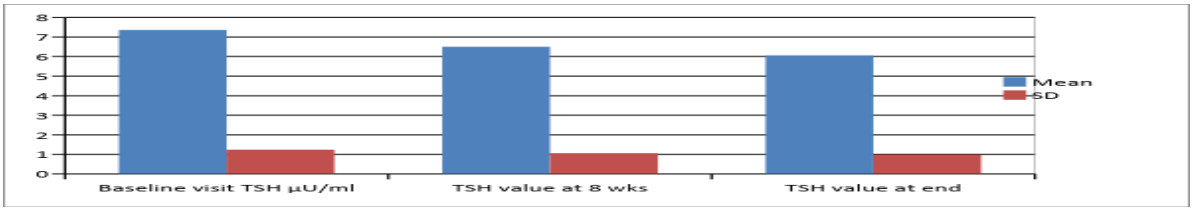

Figure no. 1: Comparison of TSH levels at the beginning of the study with the TSH levels at 8 weeks after and at the end of the metformin therapy.

Free Thyroxine (fT4) levels of the study subjects at base line visit is 1.30±0.28 ng/dl (Mean and SD) and after 8 weeks of metformin therapy fT4 increase 1.38±0.27 ng/dl (Mean and SD) (Table no 3) which is statistically significant (p<0.001) and after 12 weeks of metformin treatment fT4 increase further 1.41 ± 0.27pg/dl (Mean and SD) (Table no. 4). It is statistically significant (< 0.001) but not clinically. (Figure no. 2)

Table no. 3: Comparison of the fT4 levels of the study subjects before starting metformin therapy and 8 weeks after the therapy, by *"Paired t test"*

No of samples	fT4 levels before therapy (Mean ± SD)	fT4 levels 8 weeks after therapy (Mean ± SD)	t value	P value	Significance of difference
96	1.30±0.28	1.38±0.27	-15.25	<0.001	significant

Table no. 4: Comparison of the fT4 levels of the study subjects before starting metformin therapy and after end of the therapy, by *"Paired t test"*

No of samples	fT4 levels before therapy (Mean ± SD)	fT4 levels after end of therapy (Mean ± SD)	t value	P value	Significance of difference
96	1.30±0.28	1.41±0.27	-9.32	<0.001	significant

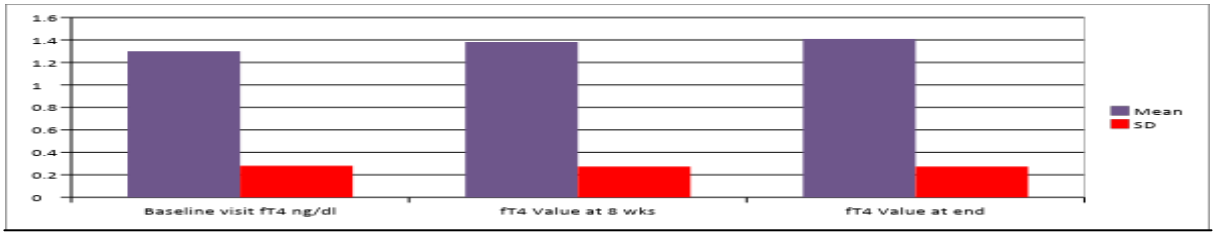

Figure no. 2: Comparison of free-t4 levels at the beginning of the study with the free-t4 levels at 8 weeks after and at the end of the metformin 56herapy

Free Tri-iodothyronine (fT3) levels of the study subjects at base line visit is 2.33±0.57pg/ml (Mean and SD) and after 8 weeks of metformin therapy fT3 increase 2.60±1.9 pg/ml (Mean and SD) (Table no. 5) which is statistically not significant (p=0.162) and after 12 weeks of metformin treatment fT3 bring down further 2.45±0.56 pg/ml (Mean and SD) (Table no. 6). It is statistically significant (< 0.001) (Figure no. 3) but not clinically.

Table no. 5: Comparison of the fT3 levels of the study subjects before starting metformin therapy and 8 weeks after the therapy, by *"Paired t test"*

No of samples	fT3 levels before therapy (Mean ± SD)	fT3 levels 8 weeks after therapy (Mean ± SD)	t value	P value	Significance of difference
96	2.33±0.57	2.60±1.9	-1.4	0.162	Not significant

Table no. 6: Comparison of the fT3 levels of the study subjects before starting metformin therapy and after end of the therapy, by *"Paired t test"*

No of samples	fT3 levels before therapy (Mean ± SD)	fT3 levels after end of therapy (Mean ± SD)	t value	P value	Significance of difference
96	2.33±0.57	2.45±0.56	-13.75	<0.001	significant

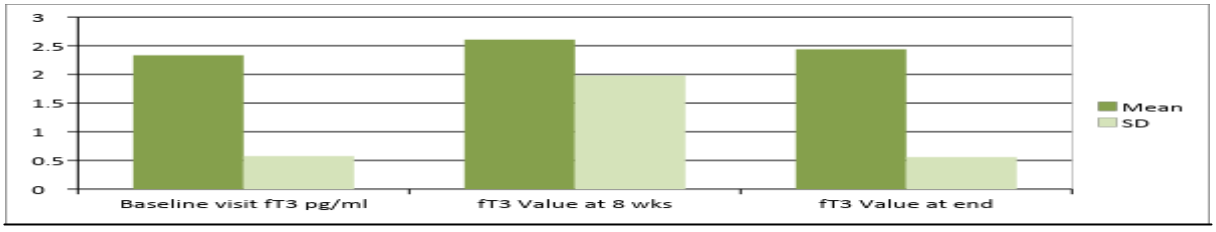

Figure no. 3: Comparison of free-T3 levels at the beginning of the study with the free-T3 levels at 8 weeks after and at the end of the metformin therpay

IV. Discussion

Subclinical hypothyroidism has been detected with increasing frequency in recent years and is causing major controversies concerning management and treatment. Treatment of patients with a serum TSH level between 5 - 10 mIU/L is remains controversial [5,6]. The strongest arguments for levothyroxine therapy are the

high risk of progression to overt hypothyroidism, the possible improvement of quality of life, and the possibility that SCH is a cardiovascular risk factor but the potential risks of therapy include development of subclinical hyperthyroidism, which may occur in 14% to 21% of individuals treated with levothyroxine [5,6,7,8].

Various studies have shown the effects of metformin on thyroid profile of the hypothyroid/subclinical hypothyroid patients stating a TSH lowering effect of the drug [11,12,13].

The various suggested mechanism of action responsible for this TSH lowering effect of metformin include an increase in number or sensitivity of thyroid receptors, an increase in dopaminergic tone, and activation of TSH receptors. Cappelli et al [13] hypothesized that metformin may enhance the inhibitory modulation of thyroid hormones on central TSH secretion. Such an effect would not modify circulating FT3 or TSH levels when the closed loop control system is normally functioning, but may well explain the reduction of circulating TSH levels observed in subjects with altered thyroid hypophyseal feedback. Another explanatory hypothesis could be that metformin ameliorates the thyroid function reserve in those patients with hypothyroidism both treated and untreated. They concluded that metformin administration in diabetic patients with hypothyroidism, both with L-T4 therapy and untreated, is associated with a significant reduction in the serum levels of TSH, with no change in FT4. No effect is detectable in patients with an intact pituitary thyroid axis. However, these hypotheses would require that metformin be able to cross the blood brain barrier but since metformin is a low molecular mass water-soluble molecule (168 Da) its penetration across blood brain barrier has not been studied. Also, if metformin produced subtle increases in the absorption of L-T4 from the gastrointestinal tract, then suppression of serum TSH might be predicted. In the present study as well in other studies the reduction in TSH level is not associated with changes in fT4 and fT3 levels suggesting that increase in LT-4 absorption is unlikely mechanism for this TSH lowering effect of metformin. It is known that there is a complex interaction between thyroid hormones and adipose tissue where TSH and thyroid hormone may participate in adipocyte differentiation and lipolysis regulation whereas various adipocyte cytokines may interact with hypothalamic-pituitary-thyroid axis [14,15].

V. Conclusion

Our present study shows that metformin suppresses serum TSH levels without affecting fT3 and fT4 levels in individuals. However to substantiate the results of present study and to explore the potential mechanism for this observed effect, further studies with a large sample size and longer duration of follow-up are needed.

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