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THE EFFECT OF METFORMIN ON THYROID PROFILE IN PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME AND SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT

Polycystic ovarian syndrome and hypothyroidism are closely associated. Metformin is routinely prescribed for the treatment and has proven clinical and biological benefits. Hence this study was conducted to assess the effect of Metformin on thyroid profile in patients with polycystic ovarian syndrome and subclinical hypothyroidism, who were diagnosed according to Rotterdam's criteria. 64 patients were taken for the final analysis. Apart from and significant reductions in body weight, body mass index, Metformin caused a significant reduction in serum Thyroid stimulating hormone (TSH) from 8.24±0.63µIU/ml to 2.67±0.29µIU/ml ($P < 0.001$). Thus, from this study we conclude that Metformin can be used either as a sole therapy or as an adjuvant in women with Polycystic ovarian syndrome and subclinical hypothyroidism and clinical hypothyroidism, respectively.

KEYWORDS: ***Metformin, polycystic ovarian syndrome, hypothyroidism.***

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INTRODUCTION

Polycystic Ovarian syndrome (PCOS) is the most common endocrine disorder of the women of the reproductive age group with a prevalence of 5 to 10% worldwide[1] and about 3.7%in India[2.] It is the leading cause of anovulatory infertility and is associated with hirsutism, obesity, increased risk of diabetes mellitus and cardiovascular disease, increased reproductive morbidity, infertility, increased pregnancy loss, and an increased risk of endometrial carcinoma. Various criterias have been proposed to define PCOS including NIH criteria, Rotterdam criteria and the AES criteria, but the commonly used diagnostic criteria is Rotterdam criteria which states that PCOS is characterized by a triad of hyperandrogenism, oligomenorrhoea and polycystic ovaries. Although various hypotheses like prepubertal androgen excess[3,] inherent steroidogenic defect of theca cells, impaired dynamics of human gonadotropins, follicular arrest etc[4], have tried to explain the pathogenesis of PCOS, insulin resistance with compensatory hyperinsulinemia is the cornerstone in its pathogenesis, and is responsible for the various short and long term complications of PCOS[5.] Ever since the demonstration of Velazquez in 1994[6], insulin sensitizers occupy a unique place in the treatment of PCOS because they offer both metabolic and gynaecologic benefit[7]. Hence Metformin is being widely used to treat this disorder, both as a sole initial therapy as well as combined with other drugs, and various studies have shown that Metformin improves clinical, pathological and biochemical outcomes in women with PCOS. PCOS and hypothyroidism are closely associated with each other. Subclinical hypothyroidism occurs in about 43%[8] and clinically overt hypothyroidism is found to occur in about 22.5% of the patients with PCOS[9]. Hypothyroidism further accelerates this metabolic anomaly by augmenting the hyperandrogenism and insulin resistance seen in these patients, together with its adverse effects on ovulation and fertility. It has been recently viewed that Metformin lowers serum Thyroid Stimulating Hormone (TSH) without significantly affecting circulating T_3 and T_4 levels by various mechanisms[10].Hence this study was done to assess the effect of Metformin on thyroid profile in patients with PCOS and subclinical hypothyroidism, so that it can be either used as a sole therapy or as a valuable adjunct in managing the group of patients with co-existing disorders of thyroid function and PCOS.

MATERIALS AND METHODS

The present study was a prospective, single centre, clinical, observational study conducted in the out-patient department of Endocrinology, Government Rajaji Hospital, Madurai, after obtaining institutional ethical clearance from the Ethical committee, Government Rajaji Hospital, Madurai, in collaboration with the Institute of Pharmacology, Department of Endocrinology and the Department of Biochemistry. The informed written consent was obtained from the subjects who were willing to participate in the study. All female patients from age 15 to 40 years with polycystic ovarian syndrome and subclinical hypothyroidism were included in the study. Patients of age > 45 years, pregnant and lactating females, patient with history of allergy or hypersensitivity to the drugs, patients with PCOS, who were treated with other drugs like (Oral contraceptives, Clomiphene citrate etc) for the past 3 months, patients with PCOS, who were treated with L-Thyroxine or any other medication which affects thyroid profile for the past 3 months, patients with renal disease (serum creatinine > 1.7 mg/dl), hepatic dysfunction (as evidenced by symptomatic liver disease or abnormality in liver function tests), Chronic Obstructive Pulmonary Disease(COPD) or any other conditions with poor tissue perfusion, patients whose peripheral smear showed a picture of megaloblastic anaemia and patients who enrolled themselves for any study other than this study were excluded from the study.A total of 75 female patients were included in the study. The patients were screened for the diagnosis of PCOS based on the Rotterdam's criteria, which states that

atleast two of the following features should be present to diagnose PCOS:

- oligomenorrhoea and/or anovulation
- clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries[11].

Subclinical hypothyroidism was diagnosed by a normal serum T_3 and T_4 with elevated TSH ≤ 10 µU/ml. The patients were allocated to receive Tab. Metformin at a dose of 500 mg thrice daily orally. A total of 75 female patients were included in the study. 11 of these patients were lost to follow up (2 conceived and 9 of them could not be communicated). Hence a total of 64 patients included for the final analysis.The socio demographic data like age, sex, residential address, occupation, contact number, presenting complaints, symptoms related to thyroid dysfunction (constipation, cold intolerance, fatigue, menstrual irregularities etc), past medical history – H/O tuberculosis, epilepsy, hypertension, diabetic status, marital and menstrual history etc : were recorded. The vital signs – pulse rate, blood pressure were measured. A detailed physical examination, examination of the neck for the presence/ absence of any thyroid swelling and a detailed systemic examination were performed at the baseline and at each follow up visit. The anthropometric measurements like height, weight were recorded. The body mass index (BMI) was calculated according to the formula BMI : [Weight (kg) / Height (m^2)].Around 4 ml of blood was collected at each visit. It was added with an appropriate anticoagulant before estimation. A complete hemogram evaluation (to rule out megaloblastic anemia), liver function tests, urine examination for albumin, glucose and deposits, urine pregnancy tests etc were done at baseline. Urea was measured by Urease Glucose Deydrogenase (GLDH) method. Estimation of serum creatinine was done by Modified Jaffe's method. The levels were measured at baseline. The estimation of liver enzymes - Serum Glutamic Oxaloacatate Transaminase (SGOT), Serum Glutamic Pyruvate Transaminase (SGPT) and Alkaline Phosphatase (ALP) was done by International Federation for Clinical Chemistry (IFCC) method. Serum total and direct bilirubin was estimated by Vandenberg reaction. Serum indirect bilirubin was calculated by the formula Indirect bilirubin: [Total bilirubin – direct bilirubin]. Serum proteins were estimated by Biuret's method. Serum albumin was measured by Bromocresol green end point assay.Serum globulin was calculated by the formula Serum globulin: [Total proteins – serum albumin].The thyroid profile (TSH, T_3 and T_4) were measured by Enzyme Linked Immunosorbant Assay (ELISA) using Erba Mannheim XL Systems Packs. The levels were measured at baseline and at the end of 16 weeks.The data were analysed with SPSS statistical software package (version 16.0 SPSS Inc., Chicago, USA). The results obtained before and after Metformin therapy were analysed using student's paired't' test. P value of <0.05 was considered to be statistically significant.

RESULTS

The average age group of the patients of 24.05±5.67 years.The incidence of PCOS was more common in the age group of 20 to 30 years (62.5%).(Figure I) Of the total 64 patients, 25% had BMI within normal range (18.5 to 24.9), 42.2% were overweight (25 to 29.9), 26.6% were obese (≥ 30). (Figure II) The body weight decreased from 65.16±11.32 kg to 61.97±10.30 kg (P<0.001). The BMI decreased from 26.77±4.98 kg/m^2 to 25.50±4.76 kg/m^2 (P<0.001), The T3 levels decreased from 1.81±1.65 ng/dl to 1.60±1.30 ng/dl. The T_4 levels increased from 105.74±35.15µg/dl to 119.25±94.02µg/dl. Serum TSH decreased from 8.24±0.63µIU/ml to 2.67±0.29µIU/ml (P<0.001) (Table I) (Figure III).

Age distribution of the study population

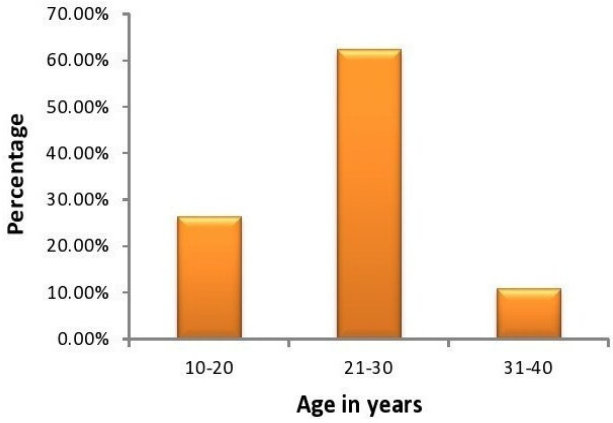

Figure I

The figure shows the distribution of the sample population according to age. The incidence of PCOS was higher in the age group of 20 to 30 years.

Before treatment BMI of the study population

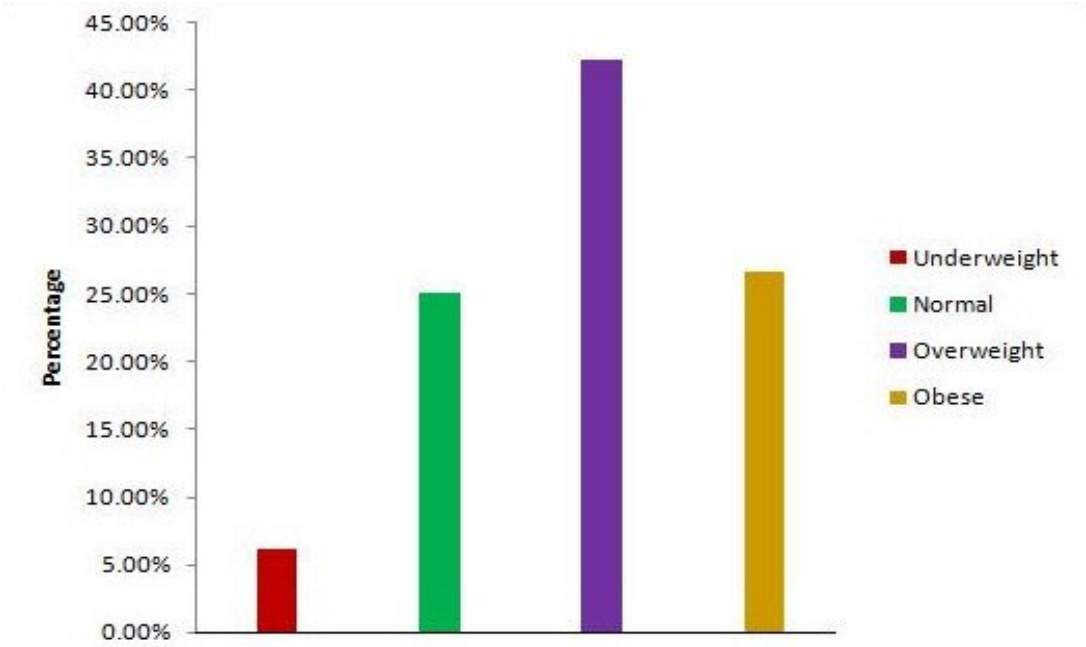

Figure II

The figure shows the BMI of the study population before treatment. It is seen from the figure that majority of the study population with PCOS were either overweight or obese.

Serum TSH of the study population before and after treatment

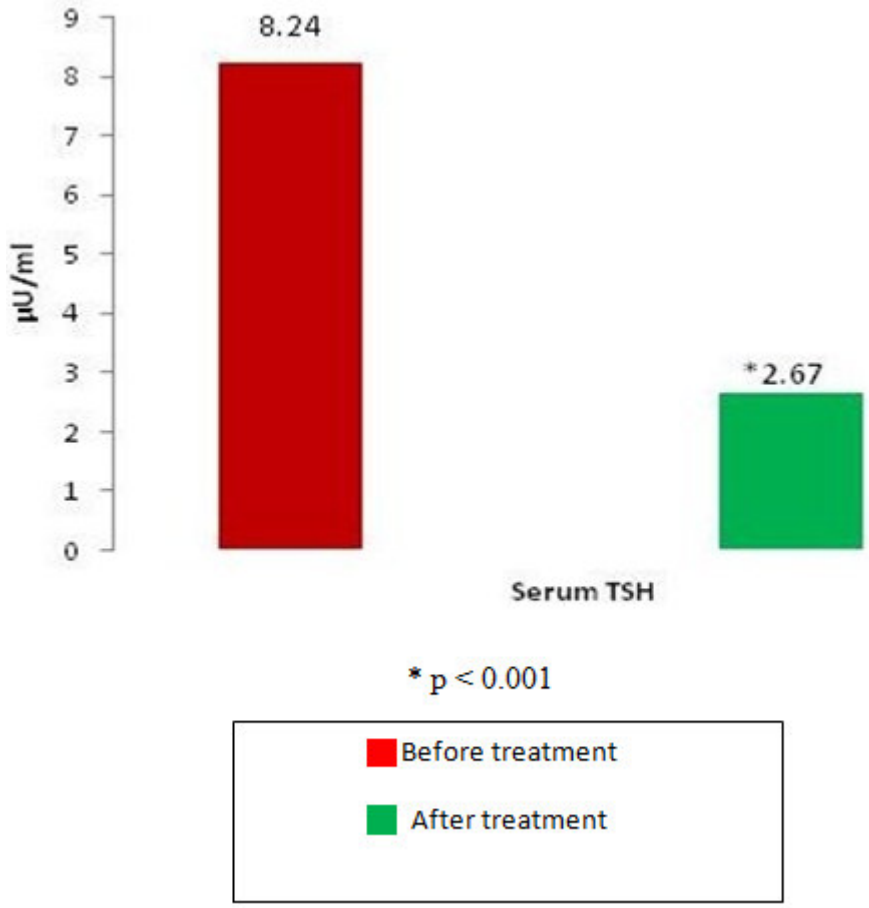

Figure III

The figure shows the change in serum Thyroid stimulating hormone (TSH) after treatment with Metformin for a period of 16 weeks, and it was found to be statistically significant.

Table I

Clinical characteristics and thyroid function of the patients (mean ± S.D) before and after treatment with Metformin.

Sl.No	PARAMETER	BASELINE	4 MONTHS	P-Value
1.	Body weight (kg)	65.16±11.32	61.97±10.30	P<0.001
2.	Body mass index (kg/m^2)	26.77±4.98	25.50±4.76	P<0.001
3.	Serum T_3 (ng/dl)	1.81±1.65	1.60±1.30	P>0.196
4.	Serum T4(µg/dl)	105.74±35.15	119.25±94.02	P>0.288
5.	Serum TSH(µU/ml)	8.24±0.63	2.67±0.29	P<0.001

DISCUSSION

This study was undertaken in 64 female patients with confirmed diagnosis of PCOS and subclinical hypothyroidism. Metformin was prescribed at a dose of 500 mg thrice daily, and the evaluation was performed at the end of 4^{th} month (16^{th} week). Obesity increases some features of PCOS such as hyperandrogenism, hirsutism, infertility and pregnancy complications. Both obesity and insulin resistance increase diabetes mellitus type 2 and cardiovascular diseases. Moreover, obesity impairs insulin resistance

and exacerbates reproductive and metabolic features of PCOS. It is well known that obesity is associated with anovulation, pregnancy loss and late pregnancy complications (pre-eclampsia, gestational diabetes). Obesity in PCOS is also linked to failure or delayed response to the various treatments including clomiphene citrate, gonadotropins and laparoscopic ovarian diathermy [12]. Metformin showed significant benefits in reducing body weight ($p < 0.05$). by decreasing insulin resistance, modulating the levels of various peptides involved in controlling appetite like ghrelin, neuropeptide YY and adipokines, via hypothalamic Adenosine Mono Phosphate Kinase (AMPKinase)[13], and by its beneficial effects on lipid profile, which include decreased fatty acid synthesis by phosphorylation and inactivation of Acetyl-CoA-Carboxylase (ACC) by AMPKinase and also by inhibition of fatty acid oxidation [14]. PCOS and hypothyroidism are closely associated. The thyroid hormones regulate the expression of genes like Glucose transporters (GLUT – 4), Phosphoglycerate kinase (PGK) and mitochondrial uncoupling protein (UCP – 1) and Peroxisome Proliferator Activated Receptor co-activator 1 alpha (PCG-1 α), all of which are involved in normal glucose homeostasis and fatty acid oxidation. Thus the deficiency of thyroid hormones may augment the insulin resistance seen in PCOS .Also they can accelerate hyperandrogenism by decreasing sex hormone binding globulin (SHBG), and also accelerates the metabolic and cardiovascular complication seen in these women[15]. Metformin lowers serum TSH levels significantly, whereas the change in circulating T_3 and T_4 levels was not significant. This might be due to the possible increase in number and sensitivity of the thyroid receptors, sensitisation of the cells of the anterior pituitary to the effects of thyroxine, augmentation of the central hypothalamic dopaminergic response in TSH secretion, and a direct effect of Metformin, through the hypothalamic AMPKinase, through the recruitment of various co-regulators, on TSH secretion. Thus the potential beneficial effect of Metformin on thyroid profile could be of great use in treating the patients with PCOS associated with hypothyroidism[16].

CONCLUSION

Metformin, apart from its beneficial effects on clinical and biochemical parameters, causes a significant fall in serum TSH. Hence it can be used as a sole therapy in women with PCOS and subclinical hypothyroidism, and as a valuable adjuvant with L-Thyroxine in women with PCOS and overt clinical hypothyroidism.

Strength of the study

Selection of patients based on rigid inclusion criteria, close monitoring and supervision by specialists, recordings done by a single observer under the supervision and guidance of senior professors, and regular follow up of all the patients during the study.

Limitations of the study

A smaller sample size, failure to assess the effect of Metformin in patients with clinical hypothyroidism who are L-Thyroxine therapy and the possible synergistic effect with L-Thyroxine, and failure to assess the effect of Metformin on TSH suppression beyond 16 weeks.

Future implications

This study evokes interest in the possibility of treating thyroid dysfunction with co-existing diabetes and metabolic syndrome by a single drug. And patients with subclinical hypothyroidism can be treated with Metformin, either alone or in combination with L-Thyroxine. Also, Metformin has demonstrated cancer protective effect owing to its antiproliferative and apoptotic effects, and increasing sensitivity to cancer chemotherapeutic agents. In addition, because of its TSH suppressing effect, it can be used as an adjuvant therapy in patients who require suppressive chemotherapy with L-Thyroxine after surgery for well differentiated thyroid cancer.

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CONFLICTS OF INTEREST

Conflict of interest declared none.

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