

Relationship between TSH, T4, T3 and Prolactin in overweight and lean Sudanese PCOS Patients

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Abstract

Objectives: to examine the role of PCOS in alteration of TSH, T4, T3 and prolactin as well as correlating the outcome to obesity.

Methods: One Hundred female patients with PCOS based on Rotterdam 2003 criteria. Together with fifty healthy volunteer females included as controls. Serum levels of Thyroid Stimulating Hormone (TSH), Thyroxine (T4), Triiodothyronine (T3) and prolactin were tested in the two groups. Body mass index (BMI) evaluated to be a part of the correlation.

Results: A significant increase was found in TSH and prolactin ($P < 0.05$) along with a significant decrease in T4 in PCOS females matched against controls ($P < 0.05$). Only lean patients showed significantly high T4 in contrast to controls ($P < 0.05$). T4 showed insignificant difference between overweight patients and controls ($P > 0.05$).

Conclusions: PCOS linked to hypothyroidism, and the latter may cause hyperprolactinemia in the same individual. Association of hyperprolactinemia and PCOS entails assessment of alternative causes of hyperprolactinemia, and this assessment should include thyroid function.

Keywords: Polycystic Ovary Syndrome, BMI, Thyroid Hormones, Prolactin

1. Introduction

Polycystic ovarian syndrome (PCOS), the major endocrinopathy of females in the reproductive age, has a prevalence of 2.2% to 26% [1],[2]. The central biochemical finding in PCOS is hyperandrogenism [1] and, females with PCOS routinely are found to have excess body fat together with showing a greater potential for developing metabolic syndrome [3]. Obesity has been recognized as a common finding in PCOS [4]. On top of that, central obesity is higher in PCOS women as opposed to controls [5]. Remarkably, serum androgens correlate with weight not only in PCOS, but also in those with simple obesity [6].

PCOS is believed to be a heterogeneous dysfunction of multifactorial etiology. It can also be linked to primary hypothyroidism in 6.3% of PCOS patients [7]. The measurement of Thyroid Stimulating Hormone (TSH) and Thyroxine (T4) levels confirms

the diagnosis of primary hypothyroidism [8]. PCOS together with thyroid disorder create independent risks of ovarian malfunction as well as pregnancy associated problems [9]. Despite that the etiology of hypothyroidism and PCOS is entirely distinct, both of these entities have many features in common [10]. An abnormal thyroid concentrations could trigger alterations in ovulation and then menstruation [11]. Initial stages of thyroid malfunction can result in delicate modifications in ovulation as well as endometrial receptivity, which consequently may have drastic influence on fertility [9]. Moreover, thyroid hormone replacement therapy in hypothyroidism leads to steady regression of the ovarian cysts, which provides a causal bond between hypothyroidism and ovarian stimulation [12].

In general, measurements of prolactin with thyroid stimulating hormone have been regarded as

significant aspects of the assessment of women with infertility[13]. On the one hand, hyperprolactinemia and hypothyroidism are positively connected[14] and the link between hypothyroidism as a trigger that ends up causing hyperprolactinemia is well recognized[15]. On the other hand, there is no evidence of a pathophysiological connection between PCOS and hyperprolactinemia which signifies that the presentation of the latter in an individual with PCOS ought to be due to other pathology and should encourage etiological investigations[16].

The intent behind this study was to look into the link between PCOS, thyroid hormones and prolactin and consequently correlated them to body weight.

2. Materials and Methods

This was a cross-sectional study carried in Khartoum state, Sudan; between June 2013 and December 2014. The study included 100 female patients suffering from PCOS. The age of involved patients was 22 - 44 years (32.610 ± 5.696 years). Control group was consisted of 50 healthy volunteer females, whose mean ages were matched (30.140 ± 5.198 years). PCOS patients further divided into lean and overweight groups according to Body Mass Index (BMI). Informed consent was obtained from each participant. Pre-prepared questionnaire including data concerning patients and their PCOS information (such as age, family history, type of treatment, and BMI) was used following the protocol of the ethical committee of Omdurman Islamic University. Venous blood sample (10 ml) was obtained at 8:00-10:00 AM in the follicular phase of the menstrual cycle from antecubital vein from patients and controls by standard venipuncture technique without venous stasis in serum separator tube (SST). After 15 minutes, serum specimens were collected in plane container after centrifugation at

3000 rpm for 5 minutes. The serum stored frozen (-20°C) in a tightly sealed tube for only 2 weeks and then analyzed. Specimens should be allowed to come to room temperature and then mixed thoroughly by gentle inversion before assaying. Then thyroxine (T4), triiodothyronine (T3), thyrotropin (Thyroid Stimulating Hormone, TSH) concentrations, as well as the prolactin (PRL) were measured by automated Enzyme-Linked Immunosorbent Assay (ELISA) kit as described by Kazerouni *et al*[17] and Lennartsson *et al*[18]. Within the Division of Medical Laboratory, VRC Center, Khartoum, two levels of control material and analyses were performed by according to the manufacturer.

1.1. Methods of BMI estimation

The BMI calculates a value indicative of the fat content of the body by dividing the body weight by the square of body height following the method adopted by Ibrahim *et al*[2]. The BMI categories as follow:

Underweight is less than 18.5, normal weight is 18.5 - 24.9, overweight is 25 - 29.9, and overweight is 30 or higher.

1.2. Statistical analyses

All data was analyzed using the Statistical Package for Social Sciences (SPSS) software computer program version 11.0 (SPSS, Chicago, IL). Data were expressed as mean \pm standard deviation (SD) following analyzes using student t-test, which was performed for comparison between control and patient groups. A value of $P < 0.05$ was considered significant.

2.Result

As in table 1, comparing to control, results of PCOS patients showed a significant increase in TSH and prolactin and significant reduction in T4. Serum T3 registered insignificant rising in PCOS females when compared to controls.

Table 1: Comparison of results between PCOS and control group:

	TSH (mIU/L)	T3 (ng/dL)	T4 ($\mu\text{g/mL}$)	PRL (ng/ml)
Control	2.698 \pm 0.5682	1.100 \pm 0.2013	8.421 \pm 0.8236	11.000 \pm 5.683
PCOS	5.669 \pm 1.562	1.451 \pm 0.3936	6.357 \pm 1.226	21.270 \pm 6.328
P value	<0.001	>0.05	<0.01	<0.001

The results was expressed in Mean \pm SD; PRL= prolactin; PCOS=polycystic ovary syndrome

The PCOS females were classified according to BMI into two groups: overweight patients and lean patients. TSH levels increased significantly in overweight and lean PCOS females when compared to control females. PCOS T4 level of lean patients was decreased significantly when

compared to control group. PRL levels showed significant changes between control and overweight PCOS, also significant changes between control and lean PCOS as well as between overweight PCOS and lean PCOS groups.

Table 2: Comparison of PCOS results between overweight and lean patients:

	TSH (mIU/L)	T3 (ng/dL)	T4 (μg/mL)	PRL (ng/ml)
Control	2.698 \pm 0.5682	1.100 \pm 0.2013	8.421 \pm 0.8236	11.000 \pm 5.683
overweight PCOS	6.254 \pm 1.497	1.525 \pm 0.4672	6.689 \pm 1.117	24.098 \pm 5.009
Lean PCOS	5.083 \pm 1.410	1.377 \pm 0.2889	6.024 \pm 1.250	18.442 \pm 6.284
P value [significance]	a b	-	b	a b c

The results was expressed in Mean \pm SD; PRL= prolactin; PCOS=polycystic ovary syndrome; a=comparison between control and overweight; b= comparison between control and lean; c=comparison between overweight and lean.

3. Discussion

Polycystic ovary syndrome (PCOS), a common endocrinopathy of women of reproductive age, is associated with the early appearance of multiple risk factors for cardiovascular disease, such as abdominal obesity[19].

The present study revealed significantly high TSH level in PCOS patients in contrast to controls ($p < 0.001$). Based on Garber *et al*[20], this indicates the diagnosis of hypothyroidism in PCOS patients. This outcome was in keeping with Janssen *et al*[21] who documented a high mean level of TSH in PCOS patients. Besides this, hypothyroidism could be the reason behind PCOS in those patients. Muderris *et al*[22] stated that severe prolonged hypothyroidism contributes to bigger ovarian size and/or cyst formation, and additionally, restoration inserum hormone levels owing to accomplishment of euthyroidism, induces a reduction in ovarian size, resolve of ovarian cysts together with reversal of the polycystic ovary syndrome-like characteristics. At the same time, the study was consistent with Ghosh *et al*[23] who, in intending to analyze the part of hypothyroidism in the causation of PCOS, proposed that hypothyroidism resulted in reducing of sex hormone binding globulin level and increment of testosterone level.

Concurrently, the present study revealed a significantly lower T4 level in PCOS patients as compared to controls ($P < 0.01$). However, Janssen *et al*[21] identified normal thyroid hormone levels in subjects with PCOS. As outlined by Carvalho *et al* and Schussler[24],[25], alterations in transporter proteins give rise to altered levels of total T4 irrespective of thyroid status. Based on this consideration, this low T4 cannot be explained by isolated thyroid abnormality.

The additional finding in this study when comparing PCOS group with control was significant high prolactin level in PCOS patients ($p < 0.001$). Most likely, there is no causative relationship between PCOS and hyperprolactinemia, and the reason behind this hyperprolactinemia could be hypothyroidism. Those results were close to that report of Robin *et al*[16], who stated that in clinical practice, it is not uncommon to discover

hyperprolactinemia in context of clinical, hormonal ultrasound features of PCOS. Furthermore, at present, there is no proof of a pathophysiological connection between the above two entities. Likewise, Filho *et al*[26] stated that hyperprolactinemia is not a laboratory manifestation of PCOS. Conversely, Grubb *et al*[27] stated that hypothyroidism predisposes to hyperprolactinemia.

The classification of PCOS into two groups of overweight and lean patients (according to BMI), unveiled significant lower level of T4 among lean compared to overweight PCOS patients ($p < 0.05$), at the same time as T4 level in overweight PCOS patients displayed no significant difference as opposed to controls. Additionally, we found significant high TSH level in both groups versus control ($p > 0.05$). This suggests the diagnosis of primary hypothyroidism in lean PCOs patients and subclinical hypothyroidism in overweight PCOS patients. Silva[28] stated that body composition and thyroid hormones are considered closely linked given that the thyroid hormones are known to take part in the regulation of basal metabolism and thermogenesis as well as playing a significant role in lipid metabolism. Dahiya *et al*[29] confirmed that PCOS individuals with BMI of 30 .14 \pm 3 .24 are significantly lower in fT4 in comparison to control. But then, to our knowledge, nobody has compared the level of T4 between lean and overweight PCOS patients. Diamanti-Kandarakis[30] believed that no matter what the degree of obesity, women with PCOS usually tend to have central (abdominal) distribution of body fat. Basing on Iuhas *et al*[31], obese women with PCOS have no greater buildup of visceral fat distinct from weight/age-matched controls. Ortega *et al*[32] pointed out that Thyroid hormone receptor (TR) gene expressions were significantly higher in subcutaneous when equated with omental fat depot from obese women but not in non-obese subjects. Moreover, Zandieh-Doulabi *et al*[33] noticed a relationship between hypothyroidism and increased TR mRNA and thus protein expression. Consequently, low T4 in lean PCOS patients could be stemming from high level of TR in abdominal fat.

Prolactin level was significantly high in overweight PCOS patients as opposed to lean patients

as well as to controls. This finding agreed with Shibli-Rahhal and Schlechte[34] who described an association between prolactin and obesity. On top of that, Greenman *et al*[35] stated that weight loss was seen in 70% of prolactinomas patients and in 90% of who normalized their prolactin. Yet, one should bear in mind that this hyperprolactinemia developed in the context of PCOS and hypothyroidism.

In conclusion, the data suggest that hypothyroidism related to PCOS, and this hypothyroidism could result in hyperprolactinemia in the same patients. These imply that patients with hyperprolactinemia and PCOS should be evaluated for causes of hyperprolactinemia, and this evaluation should include thyroid function. Equally, Degree of obesity in PCOS patients could be a key factor that influences thyroid hormones level.

More studies should be carried to reveal the precise relationship of obesity, hypothyroidism and hyperprolactinemia in the context of PCOS.

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