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Assessment of Leptin And Thyroid Stimulating Hormone In Women With Polycystic Ovary Syndrome

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Abstract

Objective: Polycystic ovarian syndrome (PCOS) is a disorder characterized by chronic anovulation, hyperandrogenism, hyperinsulinemia, and often presence of obesity. Leptin is an adipocyte‑derived hormone encoded by *'ob'* gene. Circulating leptin correlates strongly with obesity. Obesity has been linked to thyroid dysfunction. The purpose of this study was to find out the association if any between serum leptin and thyroid hormones levels in clinical scenario of PCOS.

Methods: A comparative study including 30 women diagnosed as PCOS and 30 age and BMI matched healthy women as controls was conducted. The age group for the study was 18-35 years. Fasting blood samples were drawn to measure serum leptin, triiodothyroxine(T_3), thyroxine(T_4) and thyroid stimulating hormone(TSH). BMI was also calculated.

Results: Significant positive correlations between leptin levels and BMI in cases and controls (ρ= 0.683, $p < 0.001$; ρ= 0.485, $p = 0.007$ respectively) were observed. Mean BMI, leptin, T_3, T_4 and TSH were found elevated in the PCOS population compared to controls but they were not statistically significant. No significant correlation was found between leptin and TSH.

Conclusion: The present study showed that a positive correlation exists between serum leptin and BMI both in cases and controls. This correlation couldn't be demonstrated between TSH, and BMI and similarly between leptin and TSH both in cases and controls.

Keywords: PCOS, Leptin, TSH

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age group and is the leading cause of female infertility [1].

The rate of prevalence of PCOS varies between 5 to 10% [2]. According to ESHRE/ASRM consensus workshop at Rotterdam in 2003, the diagnosis of PCOS is based on the presence of any two of (1) chronic anovulation, (2) clinical/ biochemical parameters for hyperandrogenism, and (3) polycystic ovaries on ultrasonography [3]. This major dysovulatory infertility condition in women is also associated with comorbidity such as obesity, insulin resistance and dyslipidemia. Obesity is seen in 70 % of the patients, while insulin resistance is seen in 84-94 % of the patients [4]. The associated possible cause of insulin resistance is known in terms of polymorphism of Insulin Receptor Substrate (IRS).

Leptin is a 167 amino acid protein with molecular weight 16kDa, a product of obese gene (ob), produced mainly by the adipocytes. Leptin levels are directly proportional to the fat mass. It is involved in the regulation of appetite and energy expenditure via hypothalamic mediated effects [5]. Both the granulosa and theca cells of the human ovarian follicle have leptin receptors and it has been shown that granulosa cells can secrete leptin, which indicates a direct paracrine role for leptin at the ovarian follicular level. Moreover, elevated leptin level is a common feature in obese subjects, and it has been suggested that it could represent an additional factor involved in the development of insulin resistance and in the impairment of ovarian function, particularly in women with PCOS [6].

Thyroid function is linked to energy expenditure, and its hormone increases metabolic rate, thus being a major regulator of energy homeostasis. Alterations in thyroid status often result in changes in body weight and energy metabolism, with hyperthyroidism increasing thermogenesis and hypothyroidism decreasing basal metabolic rate and body temperature [7]. Since leptin and thyroid hormones have similar effects on thermogenesis and energy metabolism, the present research attempted to find out the association if any between serum leptin and thyroid hormones levels in clinical scenario of PCOS.

Materials and methods:

The study was carried out on 30 PCOS subjects in the age group of 18 to 35 years and 30 voluntary age and BMI matched healthy women with normal menstrual cycle as controls. The study was conducted at Kempegowda Institute of Medical Sciences & Hospital. The diagnosis of PCOS was fulfilled as per Rotterdam criteria. Presence of at least two criteria from clinical, hormonal and abdominal USG category was considered diagnostic of PCOS. Patients with diabetes mellitus, hypertension, dyslipidemia, renal and liver failure, thyroid disorders and other endocrine disorders and patients receiving hormonal/non-hormonal treatment for PCOS were excluded from the study. The institutional ethical committee approved the study protocol. Informed consent was obtained from all the participants.

A pre-structured and pre-tested proforma was used to collect the data. Baseline data including age, BMI, detailed medical history, clinical examinations and relevant investigations were included as part of the methodology. Serum leptin, T_3, T_4 and TSH were measured in all participants from blood samples collected after 12 hours of fasting. Serum leptin was measured by Sandwich ELISA method (Diagnostic

Biochem Canada Inc. Cat.No. CAN-L-4260;Version:8.1;August 2009). T_3, T_4 and TSH were measured by electrochemiluminescence immunoassay (Elecsys 2010 analyzer, Roche Diagnostics). Body mass index (BMI) was calculated as the ratio of weight (Kg) to height squared (m^2).

Statistics analysis

SPSS software version 13.0 was used for statistical analysis. Comparisons between groups were performed using the Mann-Whitney test. Correlation analysis between BMI, serum leptin and TSH were done using Spearman's rank order correlation coefficients. A P value < 0.05 was considered statistically significant.

Results

Results on continuous measurements are presented as Mean ± SD. The basic characteristics and the mean distributions of biochemical parameters are depicted in Table 1 of the cases and controls. There was no significant difference in age between two groups. Slightly higher mean was recorded in BMI, Leptin, T_3, T_4 and TSH in cases than in controls but the difference in mean between the two groups was not statistically significant (P>0.05). Correlation of leptin with BMI and TSH is depicted in Table 2. Significant positive correlation between leptin levels and BMI in cases and controls (ρ= 0.683, p < 0.001; ρ= 0.485, p = 0.007 respectively) was found in our study, which is shown in figure 1. No significant correlation could be found between leptin and TSH in cases (ρ= - 0.139, p = 0.465) or controls (ρ= - 0.058, p = 0.762). Similarly, no significant correlation could be found between BMI and TSH in cases (ρ= 0.244, p = 0.193) or controls (ρ= - 0.094, p = 0.621).

Discussion

The consequences of the polycystic ovary syndrome extend beyond the reproductive axis; women with the disorder are at substantial risk for the development of metabolic, endocrine and cardiovascular abnormalities.

Serum leptin is found to be keenly interrelated with estrogens, progesterone, and androgens. PCOS features are often linked to leptin and its receptor. These facts thus make PCOS women the useful subjects to assess the interregulatory phenomena between leptin and ovarian function. Expression of leptin receptors in granulosa cells, which synergies with glucocorticoids to promote steroidogenesis, indicates that leptin exerts direct regulatory action in ovarian folliculogenesis [8]. In our study, higher mean serum leptin was recorded in PCOS subjects compared to controls but the difference between them was not statistically significant (P>0.05). The results of the present study showed that a significant positive correlation exists between serum leptin and BMI both in PCOS subjects (p < 0.001) and controls (p = 0.007) suggesting that leptin is secreted from adipocytes into circulation and by acting as a sensing hormone to hypothalamus informing the brain about abundance of body fat. This finding was consistent with study done by Chakrabarti J[8], Tayfun Alper et al[9] and

Javed Mohiti-Ardekani et al[10]. Study done by Chakrabarti J showed that irrespective of BMI, PCOS population had higher leptin levels. This observation is because leptin is predominantly synthesized by adipocytes, and higher BMI is observed in the PCOS group than in control women [8]. Tayfun Alper et al observed in their study that serum leptin levels and BMI were significantly high in PCOS women. Although leptin production mainly occurs in adipose tissue, when the difference in body fat mass between PCOS and controls was corrected for, the difference in the leptin levels remained significant. This finding suggested that there might be other reasons for the increase in the serum leptin concentration in PCOS cases [9]. Study done by Javed Mohiti-Ardekani et al showed a significant high total and free leptin in PCOS women as compared to controls and total leptin levels correlated significantly with BMI in both PCOS women and controls [10]. In contrast, Laughlin G.A. et al found that leptin levels in PCOS did not differ from those of normal cycling women with similar BMI or adiposity [11]. Rouru J et al also found in their study that serum leptin concentrations were not significantly different in PCOS and control subjects [12].

The Hyprthalamic arcuate nucleus is well established as a major target for the central action of leptin to regulate energy homeostasis in response to fasting or fed state. This region of the brain contains a high concentration of leptin receptors expressed in several populations of neurons, including neuropeptide Y (NPY)-, agouti-related protein (AgRP)-, and POMC (Pro-opiomelanocortin) containing neurons, that are involved in the regulation of appetite, reproductive function, autonomic regulation, and thermogenesis. AgRP and NPY may mediate the inhibitory effect of fasting on pro-TRH gene expression and contribute to the reduction in thyroid hormone levels in fasting animals [13]. The hypothalamic peptide, thyrotropin-releasing hormone (TRH), is essential for the normal production of thyroid-stimulating hormone in the pituitary and thyroid hormones in the thyroid gland. Within the paraventricular hypothalamic nucleus (PVH), TRH is regulated at the transcriptional level by thyroid hormone (T_3), such that in hyperthyroid states TRH expression is reduced and in hypothyroid states its expression is increased. Recently, it has become clear that TRH is also regulated by nutritional states. To conserve energy during periods of food deprivation, rodents dramatically reduce their thyroid hormone levels, which in turn allow reductions in their metabolic rate. This adaptation to starvation is accomplished through a reduction in the expression of TRH in the PVH, indicating that a central process contributes to the regulation of this physiological adaptation [14]. Since leptin and thyroid hormones have similar effects on thermogenesis and energy metabolism, the possibility has been raised that they could both exert their effects through the same pathways, i.e. regulation of sympathetic nervous system activity, mainly adrenergic upregulation. Leptin seems to influence the feedback regulation of the hypothalamic TRH secreting neurons by thyroid hormone [7]. The arcuate POMC and NPY/AgRP neuron as well as some direct actions of leptin stimulate the TRH neuron to enable the full elaboration of thyroid hormone to permit energy expenditure by modulating the basal metabolic rate [15]. After crossing the blood brain barrier leptin can act either directly on the TRH neuron or via an indirect pathway by increasing the production of α-Melanocyte

Stimulating Hormone (α-MSH) in the POMC neuron in the arcuate nucleus. Leptin, through the phosphorylation of Stat3, can directly activate the TRH promoter as can α-MSH through the activation of cAMP response element binding protein (CREB) [14]. Leptin has a selective, central action modulating the hypothalamic-pituitary-thyroid axis by regulating proTRH gene expression in the PVH without peripheral effects in thyroid-binding proteins. In the human leptin receptor mutation, a hypothalamic hypothyroidism was seen, with reduced secretion of thyrotrophin, low levels of free thyroxin, normal basal TSH levels but a sustained TSH response to a TRH stimulation test [7]. Human studies show no conclusive evidence on relation between thyroid hormone and leptin levels [16]. In present study, higher mean T_3, T_4, TSH were recorded in cases compared to controls but differences between cases and controls were not statistically significant ($P \geq 0.05$). No significant correlation could be found between leptin and TSH in cases ($\rho = -0.139$, $p = 0.465$) or controls ($\rho = -0.058$, $p = 0.762$). This finding was consistent with study done by Mani Ravishankar Ram et al [17].

Our study implicates the utility of BMI, serum leptin and TSH in PCOS subjects for evaluating risk of thyroid dysfunction which would be helpful for an early medical intervention.

Conclusion

There was a significant positive correlation between BMI and leptin in PCOS subjects and controls which suggests that leptin is secreted from adipocytes into circulation. We could not find significant correlation among BMI and TSH and similarly between TSH and leptin in PCOS cases and controls. Because our study consisted of a limited number of PCOS subjects and controls from a single population, further studies with larger number of PCOS subjects will be beneficial in elucidating the relationship between leptin, TSH and BMI in polycystic ovarian syndrome subjects for evaluating risk of thyroid dysfunction.

Table 1: Mean distribution of biochemical parameters in PCOS cases and controls. Values are expressed as means ±SD.

Parameters	Cases with PCOS (n=30)	Controls (n = 30)	P value
Age (years)	23.37 ± 4.09	23.73 ± 3.81	0.744
BMI ((kg/m2)	24.00 ± 4.41	22.51 ± 2.31	0.126
Serum Leptin	10.61 ± 12.52	9.01 ± 4.87	0.813
T3	118.31 ± 14.11	113.06 ± 20.14	0.245
T4	8.80 ± 2.95	8.11 ± 1.47	0.728
TSH	2.76 ± 1.14	2.53 ± 1.54	0.311

Table 2: Correlation between various parameters

Parameters	Cases		Controls	
	ρ value	P value	ρ value	P value
Leptin and BMI	0.683	< 0.001*	0.485	0.007*
Leptin and TSH	-0.139	0.465	-0.058	0.762
BMI and TSH	0.244	0.193	-0.094	0.621

*denotes significant difference

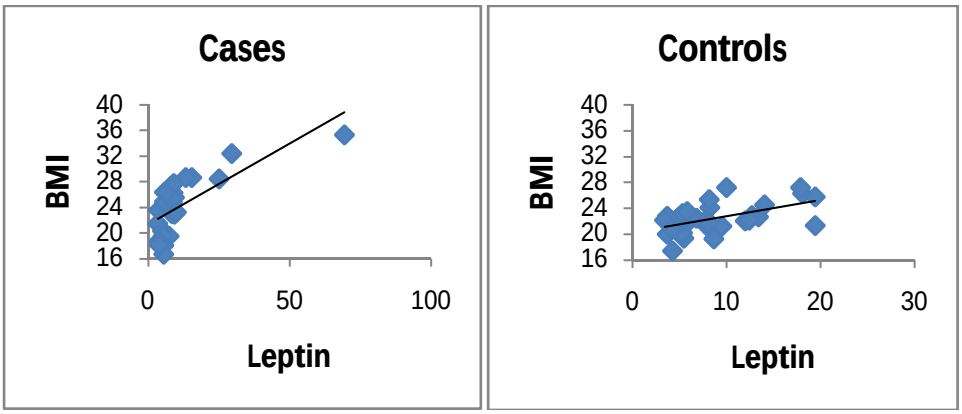

Figure 1: Correlation scatter plot of leptin vs. BMI in cases and controls

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