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Assessment of Leptin and Prolactin in Women with Polycystic Ovarian Syndrome

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Authors' contributions

This work was carried out in collaboration between both authors. Author RGS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author BVR managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is one of the most frequent endocrine disorders among women at reproductive age and is characterized by infertility, hirsutism, obesity, insulin resistance, and menstrual irregularities. Leptin, an adipocyte derived hormone, serves as a link relaying metabolic signals to the neuronal networks in the brain to modulate hypothalamo-pituitary-ovarian axis. Circulating leptin correlates strongly with obesity, which is frequently associated with PCOS. PCOS is associated with hyperandrogenemia and relatively high estrogen levels, which could stimulate prolactin secretion.

Aims: 1. To assess serum leptin and prolactin in women with PCOS and to compare them with healthy women as controls. 2. To correlate the leptin, prolactin and body mass index (BMI) among a group of PCOS women and healthy women as controls.

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Methodology: The study was conducted at Kempegowda Institute of Medical Sciences & Hospital, Bangalore. A comparative study was conducted which includes 30 women who has diagnosed with PCOS and 30 healthy women with as controls. The age group for the study was 18 to 35 years. Fasting blood samples were drawn to measure serum leptin and prolactin. BMI was also calculated. Interpretation of data was done using SPSS version 13.
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 and prolactin were found elevated in the PCOS women compared to controls but they were not statistically significant. No significant correlation was found between leptin and prolactin.
Conclusion: Leptin levels were correlated with BMI both in PCOS women and in the healthy controls. Leptin may not have a direct role in the pathogenesis of PCOS, as the serum levels were not significantly higher in PCOS women and did not correlate with prolactin.

Keywords: Body mass index; leptin; polycystic ovarian syndrome; prolactin.

1. INTRODUCTION

Polycystic ovary syndrome (PCOS), also known as Stein–Leventhal syndrome, is one of the most frequent endocrine disorders among women at reproductive age and is characterized by infertility, hirsutism, obesity, insulin resistance, and menstrual irregularities. PCOS affects approximately 5%–10% of women in the reproductive age. One group of experts suggests that PCOS originates as an exaggerated adrenarche in obese girls. The combination of elevated levels of adrenal androgen and obesity leads to increased formation of extraglandular estrogen by the way of peripheral aromatization. This high amount of estrogen exerts a positive feedback on luteinizing hormone (LH) secretion and reverse in follicle-stimulating hormone (FSH) secretion resulting in a characteristic ratio of LH to FSH >2. The increased level of LH can lead to hyperplasia of ovarian stroma and theca cells causing increased androgen production that, in turn, provides more substrate for aromatization and the vicious cycle goes on [1]. Both PCOS and the metabolic syndrome share insulin resistance as a pathogenic feature [2]. The impact of obesity is usually considered to operate through the associated Insulin Resistance (IR). Dunaif and her colleagues have described a specific defect in transduction of the insulin signal (autophosphorylation of the serine rather than tyrosine residues of the intracellular component of the insulin receptor) creates IR which is considered to be a constitutive feature of fibroblasts of women with PCOS. Obesity itself, present in some 40% of women with PCOS, worsens IR and so causes further deterioration of ovarian function [3]. 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 [4].

Leptin, an adipocyte-derived hormone encoded by '*ob*' gene, has been proposed as the peripheral signal indicating the adequacy of nutritional status for reproductive functions. But contradictory reports are available pertaining to how leptin modulates or is being modulated by pituitary gonadotropin or sex steroids [5]. A positive relationship between leptin and BMI has been reported. Several studies suggested that leptin may be involved in the reproductive axis function at both central and peripheral levels. Leptin affects the hypothalamic secretion of GnRH and gonadotropin secretion [6]. Circulating leptin levels have been positively correlated with body fat independent of PCOS according to some studies. However, some studies have not shown significant differences in serum leptin levels in women with PCOS when compared with age and body mass index (BMI) matched controls. N. Jalilian et al concluded that an increased leptin level among women with PCOS was positively associated with BMI [7]. J. Chakrabarti concluded in his study that Hyperleptinemia was seen in PCOS patients. He has also shown in his study that positive correlation between serum leptin and BMI was present in PCOS patients [5].

Prolactin (Prl) is a hormone of pituitary origin and a single-chain polypeptide involved in several actions, such as lactation, luteal function, reproduction, appetite, suppression of fertility, homeostasis, osmotic balance, immunity, and coagulation. Prolactin has been reported as a potent lipogenic and diabetogenic factor, that affecting energy balance and fuel metabolism [8]. Prolactin is secreted not only from the pituitary gland but also from macrophages in the adipose

tissue in response to inflammation and high glucose concentrations. Low prolactin levels predicted adverse metabolic outcomes in some studies in healthy individuals and prolactin significantly increased following lifestyle intervention in obese children. These findings could suggest different associations between prolactin and metabolic risk factors when prolactin is within and outside the physiological range. Glintborg D has shown in his study that prolactin was decreased in PCOS patients [9]. While S. Zandi et al concluded that high level of prolactin was found in PCOS patients compared to controls but that was not statistically significant [10]. PCOS is associated with hyperandrogenemia and relatively high estrogen levels, which could stimulate prolactin secretion. On the other hand, depression and a decreased quality of life in PCOS could increase dopamine secretion and decrease prolactin levels.

On the basis of above findings, the present study was designed to assess serum leptin and serum prolactin in women with PCOS and to compare them with healthy women as controls and to correlate the leptin, prolactin and BMI among a group of PCOS women and healthy women as controls.

2. MATERIALS AND METHODS

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. Informed consent was obtained from all the participants. The case control study was done which includes 30 PCOS women as cases and 30 healthy women as controls.

2.1 Inclusion Criteria

30 PCOS women in the age group of 18 to 35 years as cases and 30 voluntary age and BMI matched healthy women with normal menstrual cycle as controls.

2.2 Exclusion Criteria

Patients with diabetes mellitus, hypertension, dyslipidemia, renal and liver failure and other endocrine disorders and patients receiving hormonal / non-hormonal treatment for PCOS.

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 prolactin was measured in all participants from morning blood samples collected after 12 hours of fasting by electrochemiluminescence immunoassay (Elecsys 2010 analyzer, Roche Diagnostics). Serum leptin was measured by Sandwich ELISA method (Diagnostic Biochem Canada Inc. Cat. No. CAN-L-4260; Version:8.1; August 2009). Body mass index (BMI) was calculated as the ratio of weight (Kg) to height squared (m2).

2.3 Statistics Analysis

The Statistical Package for Social Sciences (SPSS) software version 13.0 was used for statistical analysis. Data were expressed as mean ± standard deviation (SD) following analyzes using the Mann-Whitney test, which was performed for comparison between control and patient groups. Correlation analysis between BMI, serum leptin and serum prolactin were done using Spearman's rank order correlation coefficients. Interpretation of results was done according to P value. A P value < 0.05 was considered statistically significant.

3. RESULTS

Results on continuous measurements are presented as Mean ± SD. The basic characteristics and mean distribution of biochemical parameters in the cases and controls are depicted in Table 1. There was no significant difference in age between the two groups. Slightly higher mean was recorded in BMI, leptin and prolactin in cases than in controls but difference in mean between the two groups was not statistically significant ($P>0.05$). Correlation of leptin with testosterone and BMI is depicted in Table 2. Significant positive correlation between leptin levels and BMI in cases and controls ($\rho= 0.683$, $p < 0.001$; $\rho= 0.485$, $p = 0.007$ respectively) was found in our study, which is shown in Fig. 1. No significant correlation could be found between leptin and prolactin in cases ($\rho= 0.014$, $p = 0.943$) or controls ($\rho= 0.105$, $p = 0.580$). Also there was no significant correlation found between BMI and prolactin in cases ($\rho= - 0.117$, $p = 0.537$) or controls ($\rho= -0.075$, $p = 0.694$).

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
Serum Prolactin	14.08 ± 6.87	10.78 ± 6.72	0.065

PCOS – Polycystic ovarian syndrome, BMI – Body mass index
**p < 0.05 - significant, **p< 0.001 - highly significant, #p ≥ 0.05 - not significant*

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	< 0.05*
Leptin and Prolactin	0.014	0.943	0.105	0.580
BMI and Prolactin	-0.117	0.537	-0.075	0.694

BMI – Body mass index
**p < 0.05 - significant, **p< 0.001 - highly significant, #p ≥ 0.05 - not significant*

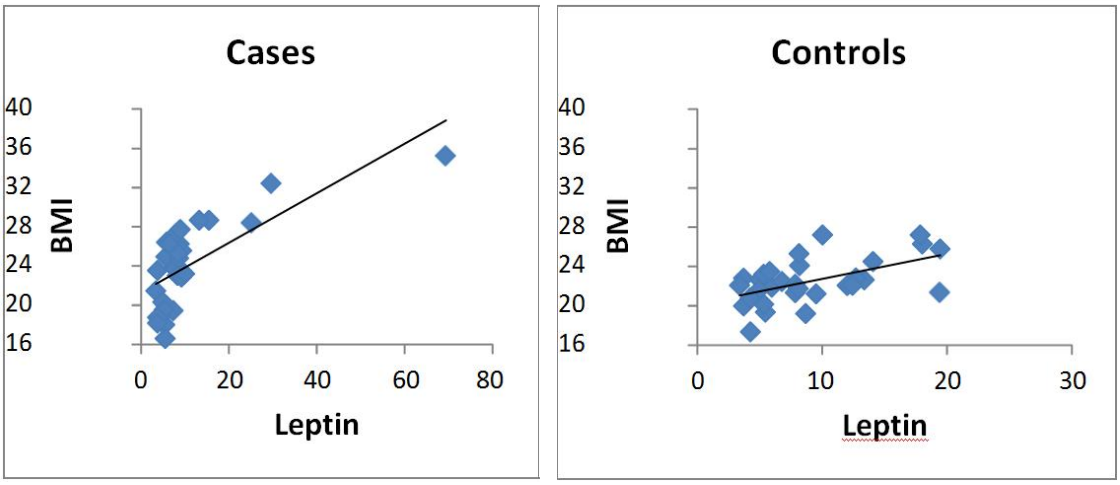

Fig. 1. Correlation scatter plot of leptin vs. body mass index (BMI) in cases and controls

4. DISCUSSION

Polycystic ovary syndrome (PCOS) is a multisystem, endocrinological, reproductive and metabolic disorder characterized by oligo-/anovulation, hyperandrogenism and polycystic ovaries [11]. Ovary is an ever-changing tissue and dynamic multicompartmental organ, which is under the chief regulatory control of hypothalamic, pituitary principles. Leptin has emerged as a peripheral signal and a potential regulator of many reproductive functions including gametogenic and steroidogenic potential of ovary. It is considered as a possible link between nutrition and reproduction [12]. Leptin seems to be directly associated with obesity by preserving homeostasis of energy with reduced food intake and increased energy spending [7].

This study was aimed to assess the relationship of leptin with BMI among a group of PCOS women compared to healthy women as controls. 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. These findings were consistent with study done by Olszanecka-Glinianowicz et al. [13] which recognized considerably higher serum leptin level in PCOS subjects compared to age and BMI matched control group. Furthermore, they observed that the serum leptin level was significantly higher in obese PCOS patients compared to lean PCOS and obese non-PCOS patients. The results of the study done by Ramanand S J et al. [14] showed that the percentage of women showing higher leptin levels was more in the PCOS group as compared to the control group. The mean leptin level in the PCOS group was significantly higher in the PCOS group as compared to the control group. Tayfun Al-per et al. [15] 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 cases and controls was corrected for, the difference in the leptin levels remained significant.

The secretion of prolactin is stimulated by thyrotropin-releasing hormone (TRH), estrogen, epidermal growth factor, vasoactive intestinal peptide (VIP) and dopamine receptor antagonists. Hyperprolactinemia is a state of prolactin excess characterized by symptoms of menstrual irregularities, galactorrhea and rarely hirsutism in females. It may occur secondary to medications, hypothyroidism, renal dysfunction and sellar or parasellar masses [16]. In present study, higher mean prolactin was recorded in PCOS women compared to controls but differences between cases and controls were not statistically significant (P≥0.05). This finding is consistent with the study done by H Fakhoury [17]. In the literature, there are various studies which document elevated levels of prolactin in patients with PCOS [18,19,20]. Study done by Amar kumar has also shown mild increase in prolactin levels in PCOS patients [21]. There is no causative relationship between PCOS and hyperprolactinemia, and the reason behind this hyperprolactinemia could be hypothyroidism [22]. While Hernandz et al. [23] concluded that a hypothalamic deficiency of dopamine (DA) could explain the mild elevation in prolactin level frequently present in women with PCOS. In a study done by Shibli-Rahhal and Schlechte were concluded that the association between prolactin, weight gain and obesity suggests that prolactin may play a role in the modulation of body weight and composition, and they added it remains unclear whether weight gain is associated with hyperprolactinemia due to stimulation of lipogenesis or due to disruption of central nervous system (CNS) dopaminergic tone [24]. In our study, there was no significant correlation found between BMI and prolactin in cases (ρ= - 0.117, p = 0.537) or controls (ρ= - 0.075, p = 0.694). This finding is consistent with the study done by Kate E. Therkelsen, et al. [25].

The correlation between prolactin and leptin levels is not clear. Though some case–control studies have documented higher levels of leptin in patients with hyperprolactinemia compared to matched controls with positive correlation between leptin and prolactin, with some studies showing a significant decline in leptin levels in men with prolactinomas, after dopamine agonist treatment [26]. Leptin is one of the various factors modulating prolactin secretion and the administration restores lactation in the leptin-deficient ob/ ob mice. Infusion of leptin raises serum prolactin concentration in fasted rats to levels present in normal fed animals. Furthermore, a direct effect on prolactin secretion by leptin on the pituitary in vitro has also been demonstrated [27]. In our study, no significant correlation could be found between leptin and prolactin in cases (ρ= 0.014, p = 0.943) or controls (ρ= 0.105, p = 0.580). This study is not biased.

5. CONCLUSION

Our findings showed that leptin levels were correlated with BMI both in women with PCOS and in the healthy controls. Leptin levels were found to be correlated with the amount of fat tissue not only in women with PCOS but also in healthy women. Leptin may not have a direct role in the pathogenesis of PCOS, as the serum levels were not significantly higher in women with PCOS. There was no significant correlation found between leptin and prolactin. Also we didn't find any significant correlation between BMI and prolactin. Because our study consisted of a limited number of PCOS cases and controls from a single population, further studies with larger number of PCOS cases will be beneficial in elucidating the relationship between leptin, prolactin and BMI in polycystic ovarian syndrome patients.

ETHICAL APPROVAL

As per international standard or university standard written ethical permission has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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