ORIGINAL ARTICLE

Leptin Levels in Polycystic Ovarian Syndrome

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ABSTRACT

Objective: To determine the association of serum leptin levels with serum FSH, LH, blood glucose fasting and BMI in young unmarried females with Polycystic Ovarian Syndrome.

Study Design: Descriptive Cross Sectional Study.

Place and Duration of Study: The study was conducted from 15th March 2016 to 15th March 2017 in Gynea and Obs department of Benazir Bhutto Shaheed Hospital, Rawalpindi.

Materials and Methods: A sample of 77 young unmarried females of ages 15-30 years was recruited while obtaining their written consent and divided into four groups using Rotterdam Criteria. These were control (non PCOS) and study group (PCOS) with three subgroups based on their BMI (Lean, Overweight and Obese). Serum Leptin assay was measured using Sandwich-ELISA method. A pre-designed questionnaire was used to collect data from the patients. Data was analyzed in the Statistical Package of version 21.0, IBM SPSS.

Results: No association was found between leptin with FSH and LH in PCOS patients. However, body mass index (BMI) and blood sugar fasting were significantly correlated with leptin in PCOS subjects and controls. Correlation coefficient of leptin vs BSF is 0.488 with a p value of 0.000. Leptin was not significantly different between PCOS and non-PCOS with normal BMI 3637.9 ± 1259.1 vs 3263.4 ± 1461.8 respectively with P value 0.331. In a subgroup analysis of lean, overweight and obese PCOS patients, each category showed different mean serum leptin levels (3637.9 ± 1259.1 vs 4603.3 ± 1223.7 vs 4261.0 ± 1504.1 respectively) with p value 0.015.

Conclusion: Serum leptin has a positive association with BMI and blood glucose fasting in PCOS women. However, it has no relationship with serum FSH and LH in PCOS women. The increase in BMI and BSF is the reason of hyperleptinemia in PCOs.

Key Words: *Blood Sugar Fasting, Body Mass Index, Polycystic Ovarian Syndrome, Serum Leptin.*

Introduction

Polycystic Ovarian Syndrome (PCOS) is an endocrine disorder which has become cosmopolitan in nature. It is taking its toll in both clinical and public health sectors.[1] PCOS affects 1 in 15 women worldwide.[2] 5-10% of females are affected in reproductive age.[3] Prevalence of PCOS is 9.13% amongst South Asian adolescents.[4]

PCOS was first identified around 20th century by two Chicago Gynecologists - Dr. Irving Stein and Michael Leventhal.[5] Stein and Leventhal had found an association of polycystic ovaries with amenorrhea. It turned out to be a landmark study for the reproductive world.[6]

PCOS affects individuals in multiple ways including reproductive repercussions (subfertility, hyperandrogenism and hirsuitism), metabolic derangements (raised insulin, DM and CVD) and psychological health issues (anxiety, depression and deteriorated quality of life).[7]

Leptin is a Greek word stemming from leptos. Leptos means thin. It is a satiety hormone. It is secreted by fat cells and inhibits hunger to regulate energy balance. Leptin consists of 167 amino acid peptide that is secreted in a pulsatile manner. The key role of leptin is monitoring energy homeostasis. This is accomplished by impacting on feeding behavior and energy expenditure.[8]

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Leptin receptors (LepRs) are expressed in two different neurons in arcuate nucleus of hypothalamus. These either repress or arouse feeding. The mutual orchestrated functioning of both kind of neurons help regulate energy balance. Both types are sensitive to leptin and insulin as they have LepRs.[9] Leptin plays an important role in homeostasis by participating in reproductive axis with excitatory effects at hypothalamus and suppressive actions at ovaries.[10]

Our study was planned to estimate the serum leptin level in PCOS among young unmarried females reporting at our hospital. The study was conducted on young girls to find if an early detection of PCOS along with certain parameters can help in alleviation of symptoms. The gap in study is still the controversial relation between leptin and other parameters. The study aims to determine the correlation of serum leptin levels with serum FSH, LH, Blood Glucose fasting and BMI in young females with Polycystic Ovarian Syndrome.

Materials and Methods

This descriptive cross sectional study was conducted in department of Gyne and Obs. Benazir Bhutto Shaheed Hospital, Rawalpindi from 15th March 2016 to 15th March 2017. The target population was all unmarried women who were between 15-30 years of age. We collected responses of 77 cases based on consecutive sampling. Women with adrenal or hypothalamic aberrations, Cushing's syndrome, hypo-or hyperthyroidism, hyperprolactinemia were excluded from the study. Those patients were also excluded from our population who were on a prescription affecting their hormones for at least 3 months prior to study. The females taking any drugs (oral contraceptive pills, insulin sensitizers, steroids, androgenic drug use) or suffering from any medical diseases (diabetes mellitus, thyroid dysfunction, congenital adrenal hyperplasia, Cushing's syndrome) were sidelined from research. Written consent from patients was taken individually.

Out of 77 samples, 63 were diagnosed cases of PCOS and remaining 14 were non-PCOS. The subjects were divided into two groups namely control and study group. Control group (group I) without PCOS comprised of 14 subjects with lean weight. Study group with PCOS was divided into three subgroups. Subgroup II of 15 subjects with lean weight, subgroup III of 30 subjects with overweight and subgroup IV of 18 subjects with obese.

These subgroups were divided by BMI categories. BMI was calculated by dividing weight by height in square meter (kg/m^2). Classification of PCOs and non-PCOs is according to World Health Organization. PCOS comprise of two of three features: 1) oligo- and/or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, and 3) polycystic ovaries on ultrasonography. This classification is according to World Health Organization.[11] These criteria include exclusion of androgen excess or related disorders before diagnosing it as PCOS.[12]

After an overnight fast, blood samples were taken to be centrifuged at 25,000 revolutions per second for 8 minutes for sera separation which were stored at -20°C for further analysis at Biochemistry Research Laboratory IIMC. All samples were examined for blood glucose fasting (BGF), luteinizing hormone (LH), follicle stimulating hormone (FSH) and serum leptin level. Statistical analysis was done in SPSS version 21.0. We used Kolmogrov Smirnov test to test the normality of quantitative variables, Mann-Whitney U test for comparison of leptin level in PCOs and non-PCOs. Kruskal Wallis test for comparing leptin levels against 3 BMI groups in PCOs. Spearman rho correlation was used to determine correlation between leptin and BGF. P value <0.05 will be considered as significant.

Results

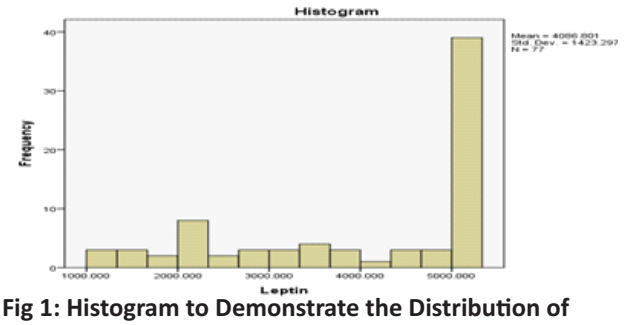

Fig 1: Histogram to Demonstrate the Distribution of Leptin Levels Among Various Groups

A total of 77 patients were included in the study which are distributed in further 4 sub-groups with respect of BMI, Lean (Non-PCOS), Lean (PCOS), over weight (PCOS) and obese (PCOS) with numbers 14 (18.18%), 15 (19.48%), 30 (38.96%) and 18 (23.37%) respectively. Overall age was 26.77±3.81 whereas the age with respect of subgroups I (Lean and Non-

PCOS), II (Lean and PCOS), III (Overweight and PCOS), and IV (obese and PCOS) was 26.79±3.47, 25.6±4.64, 27.27±3.78 and 26.89±3.46. Kolmogrov-Smirnov test shows that the leptin level does not follow normal distribution with p value 0.000. (Fig 1). Hence we use non-parametric tests to test the leptin level within groups.

Table I: Comparison of Leptin Level in Study and Control Group with Normal Weight

Groups	N	Mean ± SD	P value
Control group	14	3263.46 ± 1461.83	0.331
Study group	15	3637.97 ±1259.18	

There was no significant difference in average leptin level between control group (non-PCOS) and study group (PCOS) with p value 0.331 by Mann-Whitney U test (Table 1).

Table II: Serum Leptin Levels in Different BMI Categories of PCOS Women

Study Group	N	Mean ± SD	P value
Subgroup II (Lean weight)	15	3263.46 ±1461.83	0.015
Subgroup III (Overweight)	30	4603.37 ± 1223.73	
Subgroup IV (Obese)	18	4261.05 ± 1504.13	

The Kruskal-Wallis test shows that there was significant difference of average leptin level between subgroups II, III and IV with p value 0.015 (Table 2). The above table shows that the average leptin level changed in different BMI categories. Here we applied Kruskal-Wallis (Non Parametric ANOVA) test to test the hypothesis that "average leptin level of different BMI categories is equal" against the alternative that it is not. The P value 0.015 shows that average leptin level is different in different BMI categories. The difference in mean leptin levels in lean, overweight and obese patients was highly significant. Thus, in PCOs, leptin level is significantly changed in different BMI groups. There is considerable elevation in leptin levels in the PCOS women as compared to controls.

Table III: Correlation of Leptin and other Variables in PCOS Group

Correlation with Leptin	Follicle Stimulating Hormone	Luteinizing Hormone	Blood Sugar Fasting
Correlation coefficient	-0.113	-0.053	.488
P value	0.327	.65	.000

Spearman rho correlation was calculated between Leptin, FSH, LH and BSF (Table 3). Leptin level significantly correlated with BSF with high correlation coefficient 0.488. There was no significant correlation between leptin and follicle stimulating hormone as well as luteinizing hormone.

Discussion

In the current study, the possible relation between leptin, BMI, BSF, FSH and LH in females with PCOS is investigated. Our findings suggest that PCOS women show a considerable elevation in leptin levels as compared to controls. Also that leptin is significantly correlated with BMI and blood sugar fasting. There is no correlation between FSH and LH.

Our study highlights that increased BMI is associated with increased leptin levels. These findings are similar to those observed by Baig et al. in which serum leptin is considerably correlated with BMI.[7] Chakrabarti confirmed that positive relation exists between serum leptin and BMI.[13] Serum leptin concentration was found to be related with BMI by a study conducted by Erturk.[14] Leptin levels were found significantly raised in patients with PCOS than in controls in study underwent by Zheng.[15]

The major action of leptin on nutrition is visible through the hypothalamic-pituitary gonadal axis. (Christian et al.,2008)[16] In our study, serum leptin level is significantly related with BMI in PCOS women. This result is corroborated with other studies as given above. This finding is expected as greater the fat depots, increased the BMI and more fat would lead to higher secretion of leptin.

Leptin has been shown to be raised with increasing BMI in many other studies. Our study is comparable with the study of Olszanecka-Glinianowicz et al. (2013) who reported considerably raised serum leptin level in PCOS subjects with changing BMIs.[7] Jacobs and Conway reported higher serum leptin levels in women with higher BMIs among PCOS.[17] Shore et al. found hyperleptinemia among adolescent girls with PCOS.[18] Leptin controls reproductive physiology and pathophysiology by two ways. One is by changing perceptibility of adenohypophysis to GnRH and second, by modulating the follicles and corpus luteum in ovaries to form steroid hormones. Hence, serum leptin has definitely a role to play in the pathogenesis of PCOS with raised BMI categories. Thus, leptin is assumed

to be a bridge between body's metabolic gauge and axis of reproduction.[19]

Leptin shows no correlation with FSH and LH whereas blood sugar fasting has a significant correlation with leptin. Sir-Petermann *et al*. had conducted a study with no relation found between leptin and LH.[20] Baig et al. narrated same observation for FSH and LH.[7] Studies by Legro and colleagues revealed that women with PCOS had hyperglycaemia. Vast proportion of them had glucose intolerance, a few had impaired glucose tolerance and little number had type II diabetes.[21] Susanne Hahn et al. found that leptin correlated with blood glucose, insulin resistance and other metabolic parameters in PCOS patients. Similarly, same study found no significant correlation with gonadotropins (FSH, LH).[22] Baig et al. found strong correlation between leptin and BSF.[7] These effects were due to raised blood sugar levels and ensuing insulin resistance. Leptin decreases glucose-mediated insulin secretion by leptin receptors in hypothalamus and therefore attenuates its action at level of cells.[20]

Leptin plays an important role in PCOS of higher BMI categories. Obesity leads to leptin resistance which opposes insulin action.[23] It is seen that females with PCOS and obesity show greater tendency of being hyperglycaemic and hyperinsulinemic. The role of leptin in PCOS-related obesity is that it changes the sensitivity and secretion of end organ tissues to insulin.[24,25] Simultaneously, obesity encourages increased levels of insulin like growth factors by way of insulin resistance leading to increased blood sugar.[26]

Conclusion

Body mass index influences serum leptin levels as well as blood sugar fasting. Leptin levels fluctuate with changing amount of fat tissue. There is no difference in average leptin levels between PCOS and non PCOS however, leptin level variates with changing BMI categories. Obesity leads to leptin resistance which opposes insulin action. Obesity adds fuel to fire by augmenting effects of leptin on metabolism and reproductive health. Leptin plays a role in obesity, emergence of PCOS and worsening of biochemical as well as metabolic profiles. Adiposity and glucose appear to be main determinant of leptin levels.

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