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"Correlation Of Leptin And Adiponectin As A Promising Marker In Obese And Non Obese Women With Polycystic Ovary Syndrome Patients At A Tertiary Care Centre, Uttar Pradesh, India"

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common, complex and heterogeneous reproductive endocrinopathy of females throughout the world. Circulating leptin correlates strongly with obesity, which is frequently associated with polycystic ovarian syndrome (PCOS), Adiponectin is a circulating protein produced by adipocytes. Circulating levels of adiponectin are inversely related to adipocyte mass.

Aim and Objective: To Study the Association of Leptin and Adiponectin as a predictive marker in Obese And non Obese Women with Polycystic Ovary Syndrome Patients.

Material and Methods: This was a case control study carried out in the Department of Biochemistry with collaboration with the Obstetrics and gynaecology Department. The study comprised of 120 patients with PCOS and 120 controls without PCOS.Each group was analysed for the following parameters as TSH,Prolactin,FSH, LH,AMH, Total cholesterol,Systolic/diastolic(BP),BMI,Leptin, Adiponectin ,MDA(Malondialdehyde) and SOD(Superoxide dismutase).The validity of leptin toward the diagnosis of PCOS or leptin combined with these parameters was estimated by Descriptive and inferential statistical analysis at 5% level of significance.

Results: In the present study increased level of leptin among women with PCOS positively associated with FSH, LH, TSH, Total cholesterol, MDA in PCOS whereas Adiponectin was negatively correlated. However, there was no statistically significant correlation between the Adiponectin Insulin and the Body Mass index with respect to PCOS.

Conclusion: The relationships between leptin and adiponectin and insulin resistance and sensitivity, metabolic syndrome, and BMI in women with PCOS suggest that Leptin and Adiponectin potentially could serve as a marker for disease risk and provide opportunity for earlier intervention if knowledge is successfully translated from laboratory to clinical practice. However, further study of the relationship between adiponectin and PCOS is required before there can be direct application to clinical practice.

Keywords:PCOS, BMI,Thyroid stimulating hormone,Follicle stimulating hormone,Luteinizing hormone,Antimullerian hormone

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common, complex and heterogeneous reproductive endocrinopathy of females throughout the worldwith a worldwide prevalence rate of 5 to 20% [1,2]. Along with its classical reproductive and cutaneous manifestations, the metabolic problems are being increasingly recognized especially during later life [2]. The metabolic abnormalities in PCOS are thought to be related with adipose tissue dysfunction. Several adipocytokines secreted from hypertrophied adipocytes are found to be associated with insulin resistance, metabolic syndrome, and cardiovascular complications in PCOS [3]. The signs of PCOS include elevated luteinizing hormone (LH) and gonadotropin–releasing hormone (GnRH) levels, whereas follicular-stimulating hormone (FSH) levels are muted or unchanged. As a result of the increase in GnRH, stimulation of the ovarian the cells, in turn produce moreandrogens . Follicular arrest can be corrected by elevating endogenous FSH levels or by providing exogenous FSH [4]. According to the Rotterdam consensus, polycystic ovarian syndrome (PCOS) is defined by the presence of two of three of the following criteria: oligo-anovulation, hyperandrogenism and polycystic ovaries (≥ 12 follicles measuring 2-9 mm in diameter and/or an ovarian volume > 10 mL in at least one ovary).

Abdominal obesity is a feature of overweight, endocrine disorders which may influence women more prevalent to PCOS women than in normal reproductive age [5]. Leptin is a major adipokine that regulates weight balance and energy homeostasis. The ob gene product, called leptin, is a recently discovered hormone secreted by the adipose cells. Leptin, a product of OB gene, is produced in adipose tissues and has a long list of endocrine functions besides being responsible for causing obesity [6].

Leptin and adiponectin, adipocyte-secreted hormones, have important effects on the reproductive axis..These two are most familiar adipocytokines with opposite relation with obesity and insulin resistance. While adiponectin is usually reduced, leptin is elevated in patients with PCOS. Adiponectin may have anti-inflammatory and insulin sensitizing effects along with promotion of fatty acid oxidation. On the other hand, leptin usually regulates insulin signaling, appetite, reproductive as well as immune function. In comparison to adiponectin, its serum level usually depends on body mass index (BMI) [7].

Approximately 25% of patients with PCOS have elevated prolactin levels.Additionally, higher and lower levels of leptin are also related with infertility but the mechanism of involvement is still undiscovered [8,9].

In addition to the correlation between leptin and obesity, PCOS patients may provide a valid model for evaluating the link between hyperinsulinemia and androgen excess with leptin concentrations [8,10].

In order to better understand the relationship between leptin and adiponectin as a predictive marker in patients with polycystic ovarian syndrome who are obese or non-obese, the current study was conducted.

MATERIAL AND METHODS

This was a case control study carried out in the Department of Biochemistry with collaboration with the Obstetrics and Gynaecology Departmentfor the period of 1 year i.e, August 2022 to August 2022. The Ethical clearance was duly obtained from the Institutional Ethical Committee.

Inclusion criteria:
Women diagnosed of PCOS who are covered or fulfilling the Rotterdam criteria , aged between 20 to 40 years, negative for serum Hepatitis B virus (HBV), Hepatitis C virus (HCV) and HIV were included in the study and women aged from 20 to 40 years, normal fertile women without a history of PCOS were inclusion for the controls.

Exclusion criteria:
Women with any other reproductive disorder, women aged below 20 or above 40-years,women with known history of acquired thrombophilia or tumors in any part of the body were excluded from the study.

Sample Processing:
5ml of venous blood sample was collected under aseptic precautions and transferred in the serum separator tubes. The serum was separated within an hour and stored at -20^0 C until analysis. Leptin and Adiponectin levels were assayed by human sensitive leptin double-antibody sandwich enzyme-linked immunosorbent onestep process assay (QAYEE-BIO Life Science) according to the manufactures's guidelines.
Each group was stratified as either normal- or hyper-fasting seruminsulin (FSI), lean or overweight/obese (BMI) and systolic / diastolic (BP).

Statistical Methods: Descriptive statistics were used to represent the baseline variables, number, and percentage for the categorical variables and mean and standard deviation for the continuous variables.

Student t test (two tailed, independent) has been used to find the significant study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven`s test for homogeneity of variance has been performed to assess the homogeneity of variance.

Chi-square/ Fisher Exact test has been used to find the significant study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test was used when cell samples are very small.

Figure 1: The Qayee Bio Kit**Figure 2:** The Qayee Bio Kit Reagents

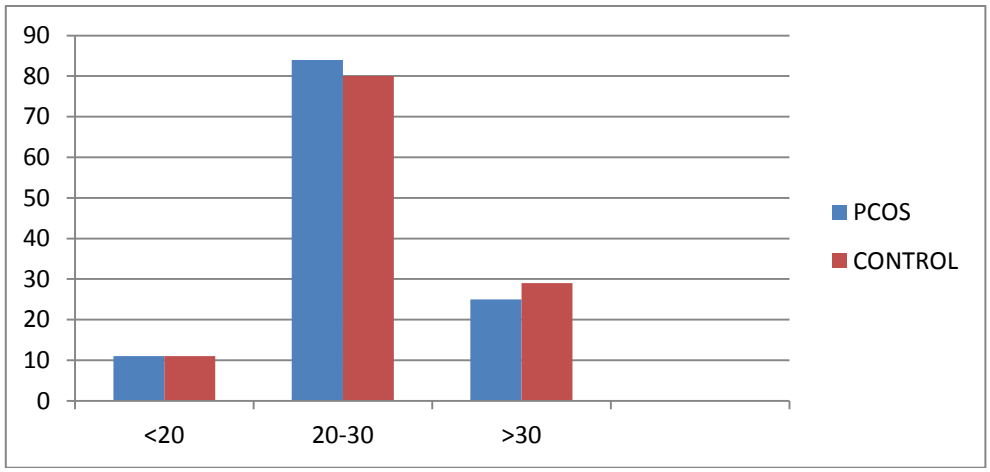
RESULTS

In the present study a total of 120 patients attending OPD of Obstetrics and the Gynecology Department and 120 controls recruited from the tertiary care centre, were studied.Each group was analysed for the following parameters as TSH, Prolactin, FSH, LH, AMH, Total cholesterol, systolic / diastolic (BP), BMI, Leptin, Adiponectin , MDA and SOD.

Table No. 1: Age in years- Frequency distribution in two groups of patients studied

Age in Years	PCOS	CONTROL	Total
<20	11(9.1%)	11(9.1%)	22(9.1%)
20-30	84(70%)	80(66.6%)	164 (68.3%)
>30	25(20.8%)	29(24.1%)	54(22.5%)
Total	120(100%)	120(100%)	240(100%)
Mean ± SD	27.81±2.37	32.31±4.61	30.06±3.32

Samples are age matched with P=0.129, student t test



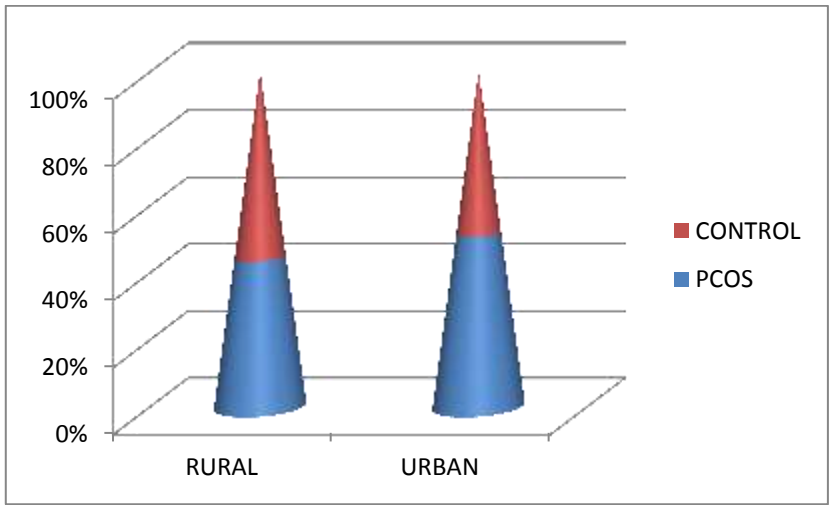
Graph No. 1: The graphical Representation of the Age in years- Frequency distribution in two groups of patients studied

In the present study it was observed that there was no statistically significant difference between the mean age of the two groups with PCOS cases and other without PCOS as controls listed above in [Table 1].

Table No. 2: Residence- Frequency distribution in two groups of patients studied

Residence	PCOS	CONTROL	Total
Rural	31(25.8%)	38(31.6%)	69(28.7%)
Urban	89(74%)	82(68.3%)	171(71.2%)
Total	120(100%)	120(100%)	240(100%)

P=0.04, Significant, Chi-Square Test



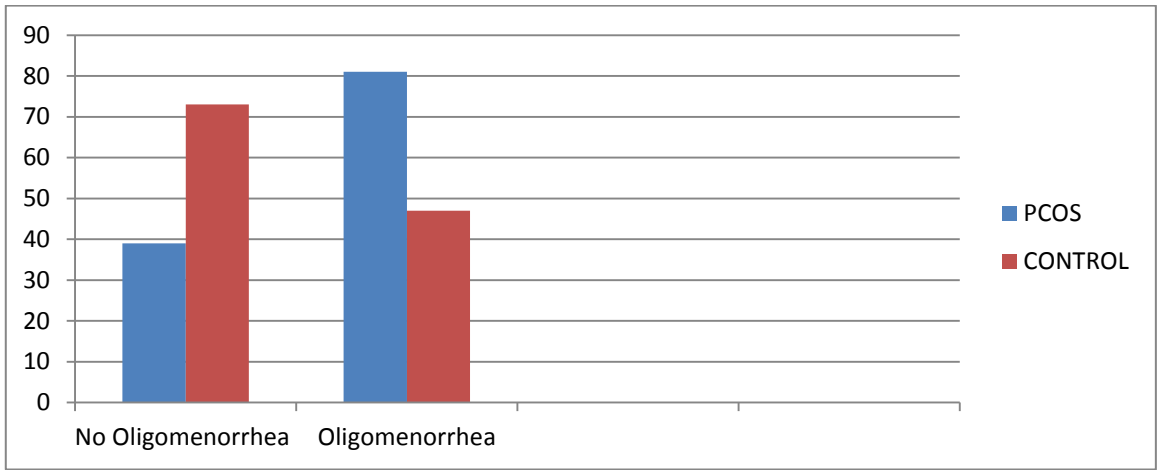
Graph No. 2: The graphical representation of the Residence- Frequency distribution in two groups of patients studied

From the above [TableNo.2] it was clear that there was statistically significant difference between the residence of both the groups one with PCOS and the other as controls (without PCOS).

TableNo. 3: Oligomenorrhea- Frequency distribution in two groups of patients studied

Oligomenorrhea	PCOS	CONTROL	Total
No Oligomenorrhea	39(32.5%)	73(60.89%)	112(46.6%)
Oligomenorrhea	81(67.5%)	47(40%)	128(53.3%)
Total	120(100%)	120(100%)	240(100%)

P≤0.003**, Highly Significant, Chi-Square Test



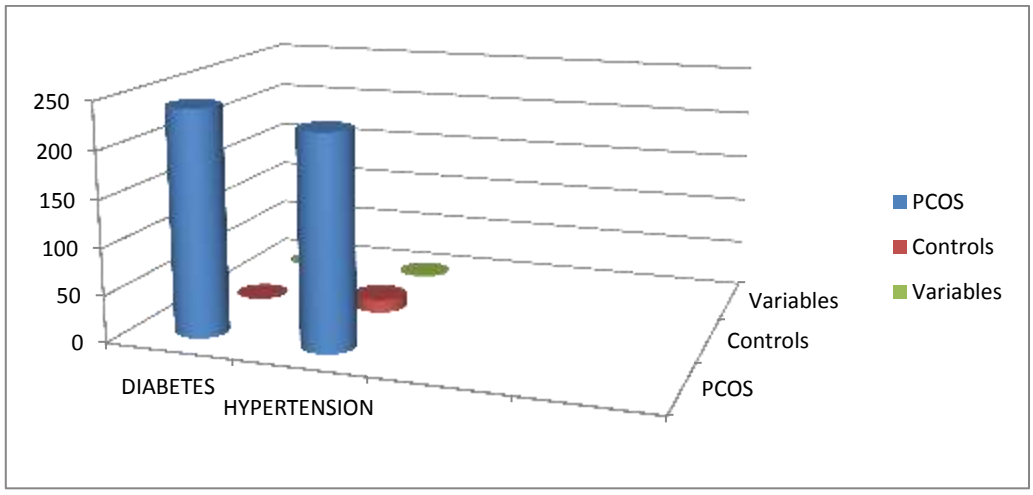
Graph No. 3: Graphical representation of the Oligomenorrhea - Frequency distribution in two groups of patients studied

From the above Table No. 3 observed for Oligomenorrheathat there was a Statistically significant difference between PCOS and the control group as there was increased cases of Oligomenorrhea in PCOS cases compared to the (control group) without PCOS .

Table No. 4: Diabetics/Hypertension - Frequency distribution in two groups of patients studied

Variables	PCOS	CONTROL	Total	P Value
DIABETES				
• 0	120(100%)	120(100%)	240(100%)	1.000
• 1	0(0%)	0(0%)	0(0%)	
HYPERTENSION				
• 0	110(91.6%)	116 (96.6%)	226 (94.1%)	1.000
• 1	10 (8.3%)	4(3.3%)	14 (5.8%)	
Total	120 (10%)	120(100%)	240(100%)	

No Significant; Chi-Square Test/Fisher Exact Test



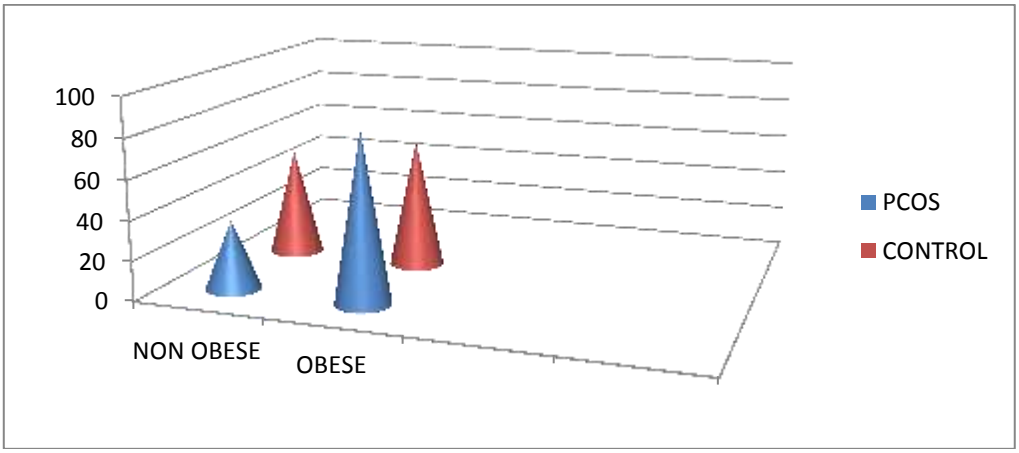
Graph No. 4: The graphical Representation of Diabetes/ Hypertension- Frequency distribution in two groups of patients studied

The Diabetes and Hypertension was found to have no statistical significant between PCOS and the (control) group without PCOS [Table No. 5].

Table No. 5: BMI - Frequency distribution in two groups of patients studied

BMI (kg/m2)	PCOS	CONTROL	Total
Non obese	35(29.1%)	55(45.8%)	90(37.5%)
Obese	85(70.8%)	65(54.1%)	150(62.5%)
Total	120(100%)	120(100%)	240(100%)

P=0.16, Not Significant, Chi-Square Test



Graph No. 5: The graphical representation of BMI- Frequency distribution in two groups of patients studied

In the present study the PCOS was not statistical significant to the BMI for both the groups of PCOS and the other (control) group without PCOS.

Table No. 6: Study/Outcome variables –Comparison in two groups studied

Variables	PCOS	CONTROL	Total	P Value
TSH	4.9±3.43	2.83±1.92	3.89±2.09	0.037
PROLACTIN	18.35±6.50	15.37±3.38	16.84±4.83	0.521
LH	6.92±2.59	7.35±4.61	7.13±3.61	0.041*
FSH	8.90±3.82	6.7±1.02	7.8±2.08	<0.06**
AMH	7.38±4.26	6.93±2.70	7.15±3.65	0.09+

In the present study the TSH, LH and FSH was found to be statistical significant, in which our statistical analysis demonstrated that LH: FSH ratio is statistically significantly.

Table No. 7: Study/Outcome variables- Comparison in two groups studied

Variables	PCOS	CONTROL	Total	P Value
TOTALCHOLESTEROL(MGDL)	217.63±8.31	183.26±24.7	200.4±6.3	0.036
SYSTOLIC BP	126.23±7.60	102.73±6.31	114.5±7.1	0.59
DIASTOLIC BP	92.67±3.71	88.29±5.61	90.5±4.61	0.723
BMI (KGM2)	28.03±4.32	24.32±2.46	26.175±3.46	0.063+
LEPTIN	15.69±6.90	13.23±6.0	14.46±6.5	<0.001**
MDA	4.9±1.20	3.27±2.82	4.08±20.8	0.01**
SOD	110.76±50.58	91.60±43.62	101.18±47.60	0.682
ADIPONECTIN	10.67±3.2	12.05±5.3	11.36±4.23	0.06+

In the present study it was observed that Total Cholesterol, Leptin and MDA was found to be statistical significant. The higher level of serum leptin in women with PCOS compared to controls with P <0.001. Similarly, PCOS women had statistically significant raised total cholesterol level (217.634±8.31) as compared to controls ((183.26±24.7) with p=0.036 [Table 7].

DISCUSSION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder that impacts many women of the reproductive age worldwide [11]. This syndrome is often associated with enlarged and dysfunctional ovaries, excess androgen levels, resistance to insulin, etc. [12]. It is estimated that approximately 1 in 10 women face PCOS before menopause and struggle with its complications [13]. Although the high ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) and increased frequency of gonadotropin-releasing hormone (GnRH) is known as the underlying causes of PCOS [4], the exact etiology and pathology have not been comprehensively well-known [14,15]. Evidence suggests the role of different external and internal factors, including insulin resistance (IR), hyperandrogenism (HA), environmental factors, genetic, and epigenetics. In addition, it is worth mentioning that PCOS increases the risk of further complications like cardiovascular diseases [15,16], type 2 diabetes mellitus [15,16], metabolic syndrome [16], depression, and anxiety [17].

In the present study the maximum number of cases was recorded in the age group of 20-30 years of age with the mean age of 27.81±2.37 for the PCOS for the controls 32.31±4.61 and the minimum in the age group below 20 years of age. This finding was in support with the study performed by the Yuanyuan Peng et al.,[18]where, the mean age for the controls was 31.00 (29.00-33.00and PCOS group was 32.00 (30.00-33.00). There was another study performed by Mukhtiar Baig*et al.*,[19]which also correlates to the present studywhere the maximum number affected was in the age group of 20-30 years of age.

Women with PCOS have higher anti-Müllerian hormone (AMH) levels as compared with the controls,[20] and the AMH levels are highly correlated with antral follicle count on ultrasound and can be used as a surrogate for follicle number [21] Forslund *et al*.,[22] demonstrated that women with PCOS reached menopause 4 years later than their age-matched controls. S-follicle-stimulating hormone (S-FSH) levels and the proportion of women with S-FSH >50 IU/L were also lower in women with PCOS. Neither parity nor nulliparity differed between PCOS and controls [23].

In the current study there was a statistically significant difference between the residenceof both the groups one with PCOS and the other as controls (without PCOS).This study was in contrast with another study where there was no statistical significant in the residence or life style[24][25]. It was also observed that for Oligomenorrhea there was a statistically significant difference between PCOS and the control group as there was increased cases of Oligomenorrhea in PCOS cases compared to the (control group) without PCOS . In the current study the diabetes and hypertension was found to have no statistically significant difference between PCOS and the (control) group without PCOS. This study was parallel to the study conducted by Nomair A [26]in Taif where there was no statistically significant difference between the insulin levels and hypertension with obese and non obese cases.

Oligomenorrhea was associated with decreased risk of most invasive histologic subtypes of malignancy. Fewer ovulatory cycles or more anovulatory cycles among women with long and irregular menstrual cycles is a possible explanation for the observed decreased risks [27].

Leptin is mainly produced by the adipocytes and considered as a polypeptide hormone for the regulation of normal body weight. Several studies have observed a strong association of circulating leptin with obesity, which has also been associated with PCOS, a major form of anovulatory infertility in women[28]. In the current study there was a elevation of serum leptin in women with PCOS. This finding iscomparable with the study of Mohiti Ardekani and Taarof,which showed elevated level of serum leptin in 27 Iranianwomen with PCOS[29].

In the present study for PCOS leptin observed was 13.23±6.0 and for controls 14.46±6.5 with P value of <0.001.Our results indicate that serum leptin is significantly higher in PCOS women compared with controls. This result also supports the findings of other studies which showed elevation of serum leptin in women with PCOS [30,31].

In the present study, the possibility of a relationship between leptin and BMI in women with PCOS was investigated where it was observed that PCOS was not statisticallysignificant to the BMI for both the groups of PCOS and the other (control) group without PCOS.However, there are many studies reported that have no statisticalsignificant in serum leptin levels of PCOS women with insulin and BMI‐ matched controls [19,20].

Baig *et al*. in their study revealed , compared to controls, PCOS women had higher serum leptin levels but it was not statistically significant[21].

This study was also in support by Nasrin Jalilian *et al.*, in 2016 where the correlation between serum leptin and other variable study among PCOS patients were analyzed, the Pearson correlation analysis revealed only a positive correlation between leptin and BMI and also LH level. However, there was no significant correlation between leptin and insulin, FBS and FSH [24].

By preserving energy balance through a reduction in food intake and an increase in energy expenditure, leptin appears to be directly linked to obesity [16]. However, in our investigation, there was no statistically significant difference between PCOS sufferers' serum leptin levels and controls with similar BMIs. Numerous further research performed by different authors where Leptin seems to be related with BMI and controls. This study was in support with the study by Nasrin Jalilian [13] where, serum leptin level is significantly correlatedwith BMI in PCOS women and this resultscorrelates with other studies [22,23].

In the present study Total cholesterol, Leptin and MDA were found to be statistically significant but it was also observed that blood Pressure and superoxide dismutase were not statisticaly significant in PCOS patients. Moreover, in our study, no association was found between leptinlevel and insulin level which was parallel to the study by Nasrin Jalilian [13].Leptin reducesglucose‐mediated insulin secretion through its receptorsin the hypothalamus and also reduces its action at thecellular level[24].

In the present study the TSH, LH and FSH was found to be statistically significant, in which our statistical analysis demonstrated that LH: FSH ratio is statistically significantly higher in the women with PCOS as compared to controls, but AMH and Prolactindoes not show any correlation with the PCOS patients. This study was in support with the study by Mohiti‐Ardekani and Taarof [29]where there is a significant positive relationshipbetween leptin and LH.but in contrast with the study by Sir‐Petermann *et al.,* [32]where no correlation between leptin secretion pulses and LHwere observed.

The Total Cholesterol, Leptin and MDA was found to be statistical significant. The higher level of serum leptin in women with PCOS as compared to controls with P value being significant. Similarly, PCOS women had statistically significant raised total cholesterol level as 217.63±8.31compared to controls183.26±24.7 with p= 0.036
In the present study Adiponectin observed for PCOS was 10.67±3.2 and in controls 11.36±4.23 with P value of 0.06. In the present study it was also observed that Adiponectin was negatively correlated with insulin resistance, body mass index (BMI), and total testosterone, triglyceride, and

low-density lipoprotein (LDL) levels. The present study was in support with the study performed by the other author Chin-I Chen*et al*.,[33] where the Adiponectin was negatively correlated with insulin resistance, body mass index (BMI), and total testosterone, triglyceride, and low-density lipoprotein (LDL) levels; conversely, leptin reversed the aforementioned reaction and was negatively correlated with adiponectin levels. The adiponectin to leptin ratios were significantly lower in PCOS women than in those without PCOS. Compared to women with non-PCOS, overweight/obese women with PCOS had lower serum adiponectin levels than women without PCOS, which was not the case for lean women.

There was another study by Yang WS et al., and Berg AH *et al*., that confirmedthat obese women have adiponectin levels significantlylower than normal-weight healthy controls [34,35]. Lastly, adiponectin levels were inversely correlated with BMI both in PCOS and healthy women.

In an study it was found that the insulin levels were higher and insulin sensitivity, as assessed by HOMA, lower in normal-weight PCOS group than in controls; serum adiponectin concentrations did not differ between the two groups. Therefore, the high degree of insulin resistance in women with PCOS does not influence (is unlikely to modify) adiponectin levels [36] despite the evidence that adiponectin levels have been widely recognized to be decreased in an insulin resistant state [37]. The link between adiponectin and insulin sensitivity was further enforced by the observation that this adipocytokine is able to stimulate glucose utilization and reduce the hepatic glucose production [38,39].
Therefore, in the present study the adiponectin was negatively correlated with the PCOS patients.

With the possibility of considering these indicators as therapeutic targets for PCOS. it appears to be a positive relationship between insulin resistance and leptin and a negative relationship with adiponectin in PCOS patients [40].

CONCLUSION

The results of the present study indicated an increased leptinlevel among women with PCOS that positively associatedwith FSH, LH and TSH, whereas adiponectic was negatively correlated with the PCOS. Substantially elevated serum leptin is significantly associated Total cholesterol, MDA in PCOS patients. However, there was no significantcorrelation between leptin with BMI ,diabetes, hypertension, Prolactin ,AMH and SOD.

The levels of leptin and adiponectin can be considered effective biomarkers in the early diagnosis of PCOS, and can be used to predict the risk of developing PCOS in women without obvious symptoms.

DECLARATIONS

Conflicts of interest: There is no any conflict of interest associated with this study

Consent to participate: We have consent to participate.

Consent for publication: We have consent for the publication of this paper.

Authors' contributions: All the authors equally contributed the work.

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