Frontiers in Health Informatics www.healthinformaticsjournal.com
ISSN-Online: 2676-7104
2024; Vol 13: Issue 4 Open Access

To Study The Correlation Of Leptin And Adiponectin As A Promising Biomarker In Obese And Non Obese Women With Polycystic Ovary Syndrome Patients.

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Cite this paper as: Dr. Nazia Nesar, Dr. Akanksha Singh, Dr. Ramis Khan, Dr. Shikha Verma (2024) To Study The Correlation Of Leptin And Adiponectin As A Promising Biomarker In Obese And Non Obese Women With Polycystic Ovary Syndrome Patients. *Frontiers in Health Informatics, 13* (4), 132-141

A B S T R A C T

Background: Polycystic ovary syndrome (PCOS) is an endocrine-gynecology disorder affecting many women of childbearing age. Although a part of the involved mechanism in PCOS occurrence is discovered, the exact etiology and pathophysiology are not comprehensively understood yet. Circulating leptin has a high correlation with obesity, which is usually linked to polycystic ovarian syndrome (PCOS). Adiponectin is a circulating protein produced by adipocytes. Circulating adiponectin levels are inversely proportional to adipocyte mass. Aim and Objective: Assessing the correlation 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 200 patients with PCOS and 200 controls without PCOS. Each group was analyzed for the following parameters as TSH, Prolactin, FSH, LH, AMH, Total cholesterol, Systolic/diastolic (BP), BMI, Leptin, Adiponectin, MDA(Malondialdehyde) and SOD (Superoxide dismutase). Results: In the present study it was observed that the maximum number of cases was recorded in the age group of 20-30 years of age for the PCOS as well as for the controls with 124 (62%) and 120 (60%) respectively. Oligomenorrhea in case of PCOS was 65% and in controls was 38.5% as there was increased cases of Oligomenorrhea in PCOS cases compared to the (control group). The increased level of leptin among women with PCOS was positively associated with FSH, LH, TSH, Total cholesterol, MDA in PCOS whereas Adiponectin was negatively correlated. 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.

Keywords: Polycystic ovarian syndrome, BMI, TSH, FH, Leptin, Adiponectin,

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a widespread, complex, and heterogeneous reproductive endocrinopathy that affects females worldwide, with a global prevalence rate ranging from 5 to 20% [1, 2]. Along with its traditional reproductive and cutaneous signs, metabolic issues are becoming more widely recognised, particularly in later age [2]. Metabolic abnormalities in PCOS are hypothesised to be associated with adipose tissue malfunction. Several adipocytokines released by hypertrophied adipocytes are linked to insulin resistance, metabolic syndrome, and cardiovascular problems in PCOS [3].PCOS is characterised by high levels of luteinizing hormone (LH) and

gonadotropin-releasing hormone (GnRH), while follicular-stimulating hormone (FSH) levels are reduced or stable. As a result of the increase in GnRH, the ovarian cells are stimulated, which produces more androgens. Follicular arrest can be addressed by increasing endogenous FSH levels or administering exogenous FSH [4].
The Rotterdam consensus defines polycystic ovarian syndrome (PCOS) as having two or more of the following criteria: oligoanovulation, 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 symptom of overweight endocrine diseases that may have a greater impact on PCOS women than on women of normal reproductive age [5]. Leptin is a key adipokine that controls weight and energy levels. The ob gene product, leptin, is a newly discovered hormone released by adipose cells. Leptin, a product of the OB gene, is generated in adipose tissues and serves a variety of endocrine roles in addition to promoting obesity [6].

Leptin and adiponectin, hormones released by adipocytes, have significant impacts on the reproductive axis.These two are the most well-known adipocytokines, and they have the opposite relationship with obesity and insulin resistance. While adiponectin is often low, leptin levels are high in PCOS individuals. Adiponectin may promote fatty acid oxidation while also acting as an anti-inflammatory and insulin sensitiser. Leptin, on the other hand, is known to influence insulin signalling, hunger, reproductive, and immunological function. In comparison to adiponectin, the serum level is normally determined by body mass index (BMI) [7].

Approximately 25% of PCOS patients have high prolactin levels. Furthermore, higher and lower levels of leptin are associated with infertility, but the mechanism of participation is unknown [8,9].
In addition to the correlation between leptin and obesity, PCOS patients may provide a suitable model for assessing the relationship between hyperinsulinemia, androgen excess, and leptin concentrations [8,10,11].

The current study was done to gain a better understanding of the interaction between leptin and adiponectin as a prognostic marker in individuals with polycystic ovarian syndrome who are obese or not fat.

MATERIAL AND METHODS

This was a case control study carried out in the Department of Biochemistry with collaboration with the Obstetrics and Gynaecology Department for 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 with PCOS who met the Rotterdam criteria, aged 20 to 40 years, and negative for serum Hepatitis B virus (HBV), Hepatitis C virus (HCV), and HIV were included in the study, as were women aged 20 to 40 years who were normal fertile and had no history of PCOS as controls.

Exclusion criteria:
Women with any other reproductive disease, women under the age of 20 or above the age of 40, and women having a history of acquired thrombophilia or tumours in any area of the body were all excluded from the study.Sample Processing:
5ml of venous blood was collected under aseptic conditions and transferred to serum separator tubes. The serum was isolated within an hour and stored at -200 degrees Celsius until analysis. Leptin and adiponectin levels were measured using the human sensitive leptin double-antibody sandwich enzyme-linked immunosorbent one-step procedure test (QAYEE-BIO Life Science) according to the manufacturer's instructions.
Each group was classified as normal- or hyper-fasting serum insulin (FSI), lean or overweight/obese (BMI), and systolic/diastolic (BP).
Statistical Methods: The Data was entered in the Excel sheet and a suitable statastics was carried out.

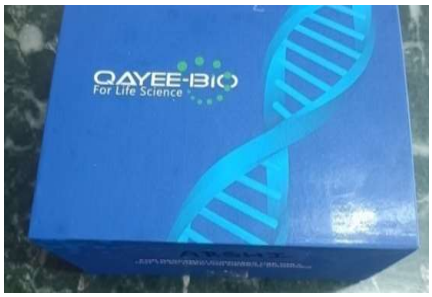


Figure 1: The Qayee Bio Kit

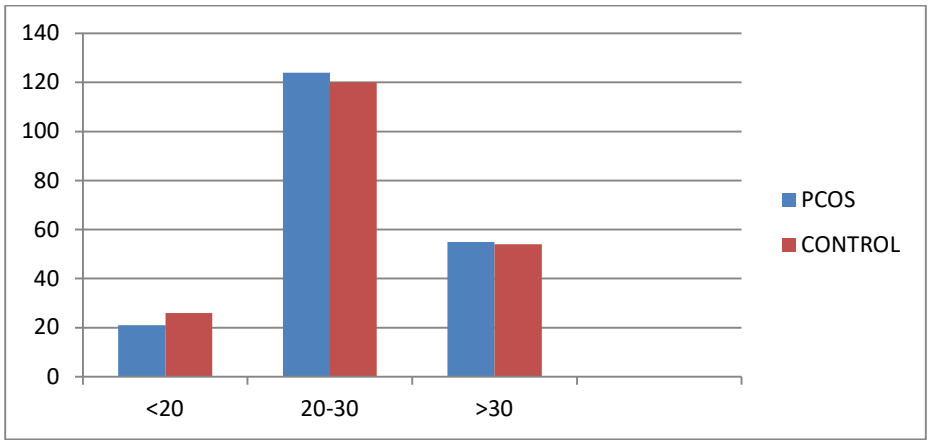

Figure 2: The Qayee Bio Kit Reagents

RESULTS

In the present study a total of 200 patients attending OPD of Obstetrics and the Gynecology Department and 200 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	21 (10.5%)	26 (13%)	47(11.7%)
20-30	124 (62%)	120(60%)	244 (61%)
>30	55 (27.5%)	54 (27%)	109 (27.2%)
Total	200(100%)	200(100%)	400(100%)

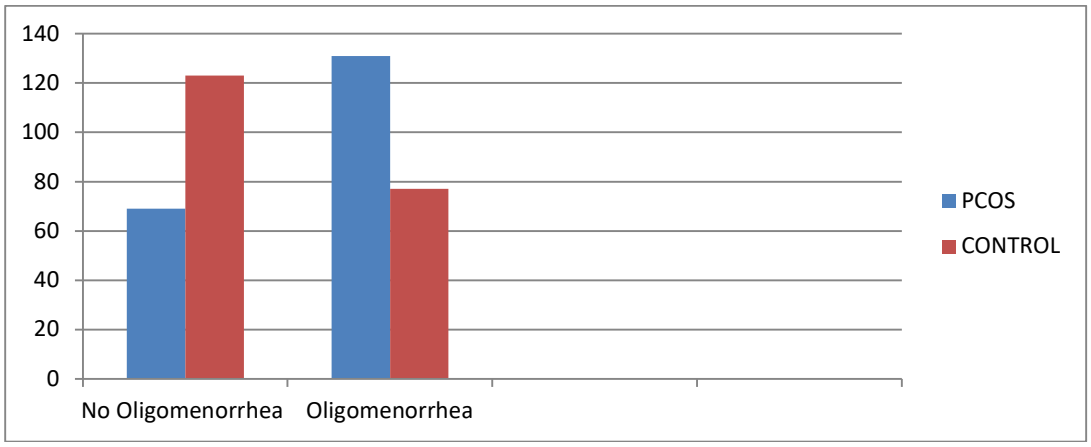


Graph No. 1: The graphical Representation of the Age in years- Frequency distribution in two groups of patients studied

TableNo. 2: Oligomenorrhea- Frequency distribution in two groups of patients studied

Oligomenorrhea	PCOS	CONTROL	Total
No Oligomenorrhea	69 (34.5%)	123 (61.5%)	192 (48%)
Oligomenorrhea	131 (65.5%)	77(38.5%)	208 (52%)

Total	200(100%)	200(100%)	400(100%)



Graph No. 2: Graphical representation of the Oligomenorrhea - Frequency distribution in two groups of patients studied.

Table No. 3: Diabetics/Hypertension - Frequency distribution in two groups of patients studied

Variables	PCOS	CONTROL	Total	P Value
DIABETES				
0	200 (100%)	200(100%)	400(100%)	1.000
1	0(0%)	0(0%)	0(0%)	
HYPERTENSION				
0	180 (90%)	191 (95.5%)	371 (92.7%)	1.000
1	20 (10%)	9 (4.5%)	29 (7.2%)	
Total	200 (10%)	200(100%)	400(100%)	

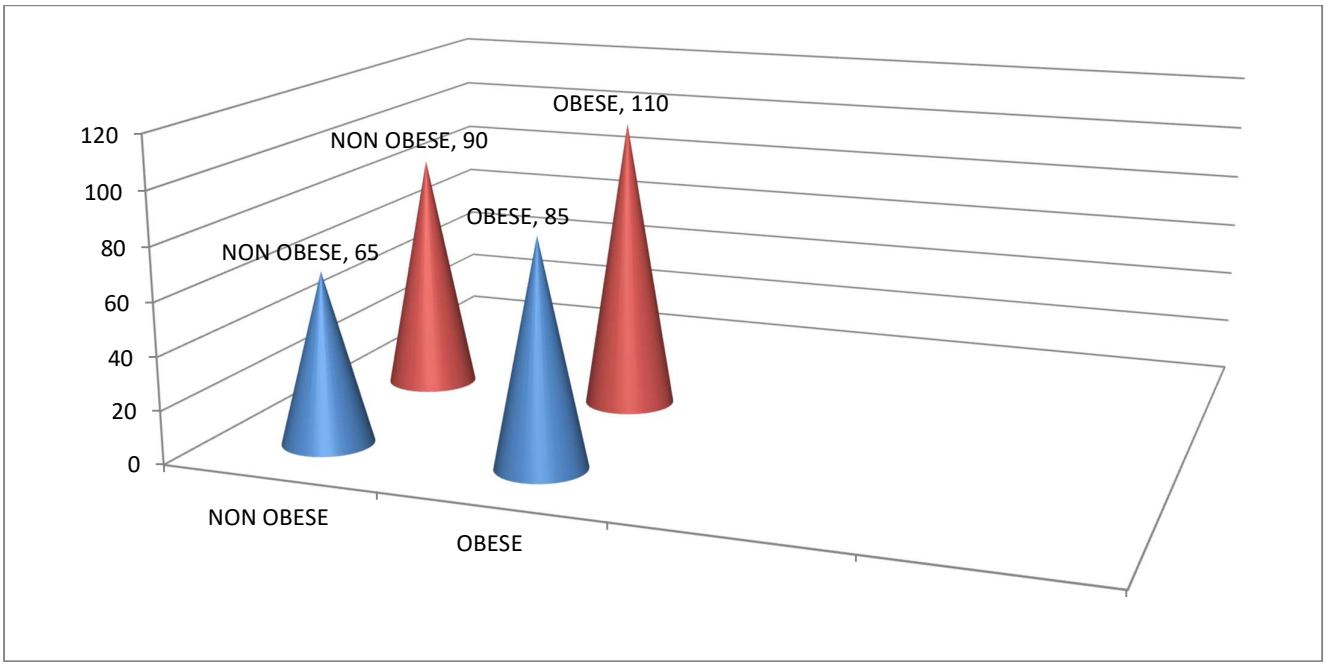
No Significant; Chi-Square Test/Fisher Exact Test

The Diabetes and Hypertension was found to have no statistical significant between PCOS and the (control) group without PCOS [Table No. 3].

Table No. 4: BMI - Frequency distribution in two groups of patients studied

BMI (kg/m2)	PCOS	CONTROL	Total
Non obese	65 (32.5%)	90(45%)	155 (38.7%)
Obese	135(67.5%)	110 (55%)	245 (61.2%)
Total	200(100%)	200(100%)	400(100%)

P=0.17, Not Significant, Chi-Square Test



Graph No. 3: 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. 5: Study/Outcome variables –Comparison in two groups studied

Variables	PCOS	CONTROL	P Value
TSH	4.8±3.33	2.85±1.93	0.046
PROLACTIN	17.65±6.50	15.26±3.39	0.532
LH	6.94±2.57	7.45±4.64	0.042*
FSH	8.92±3.84	6.8±1.01	<0.06**
AMH	7.39±4.25	6.94±2.70	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. 6: Study/Outcome variables- Comparison in two groups studied

Variables	PCOS	CONTROL	P Value
TOTALCHOLESTEROL(MGDL)	218.72±8.32	184.26±24.8	0.037
SYSTOLIC BP	128.21±7.81	103.73±6.33	0.59

DIASTOLIC BP	93.68±3.72	89.29±5.72	0.764
BMI (KGM2)	29.04±4.33	24.32±3.46	0.064+
LEPTIN	16.69±6.92	14.23±6.0	<0.001**
MDA	4.9±1.21	3.27±2.83	0.01**
SOD	112.76±50.59	91.60±43.64	0.682
ADIPONECTIN	10.68±3.3	12.05±5.4	0.07+

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 (218.72±8.32) as compared to controls ((184.26±24.8) with p=0.037 [Table 6].

DISCUSSION

Polycystic ovarian syndrome (PCOS) is a heterogeneous endocrine disorder with the underline indication of ovarian cysts, anovulation, and endocrine variation affecting the women. According to the World Health Organization (WHO) estimation revealed over 116 million women (3.4%) are affected by PCOS worldwide [12].
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 , the exact etiology and pathology have not been comprehensively well-known [14].
Obesity is defined medically as a condition of excessive accumulation of adipose tissue, of sufficient extent to produce adverse health consequences [15]. However, in the last years adipose tissue has been shown to behave as a highly active endocrine organ, based on its ability to secrete a wide variety of biologically active adipokines, such as leptin, adiponectin, tumor necrosis factor-α (TNF-α), or interleukin-6 (IL-6), which are known to be involved in different physiological processes. It is well recognized that adipokines play an important role in the pathophysiological link between dysfunctional adipose tissue and cardiometabolic alterations. Leptin is primarily produced by adipose tissue in proportion to the amount of body fat stores being involved in the regulation of food intake, energy homeostasis and other physiological processes. Adiponectin is also secreted almost exclusively by adipocytes, and decreases in obese patients. This adipokine protects against insulin resistance and excessive hepatic lipid accumulation with anti-inflammatory effects. Both leptin and adiponectin have been related to cardiometabolic risk factors [16,17].
In the present study the maximum number of cases was recorded in the age group of 20-30 years of age for the PCOS as well as for the controls with 124 (62%) and 120 (60%) respectively. 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 Baiget al.,[19] which also correlates to the present study where the maximum number affected was in the age group of 20-30 years of age.
Women with PCOS have greater anti-Müllerian hormone (AMH) levels than controls [20], and AMH levels are closely linked with antral follicle count on ultrasound and can be used as a proxy for follicle number [21]. Forslund et al. [22] found that women with PCOS had menopause four years later than age-matched controls. S-follicle-stimulating hormone (S-FSH) levels and the proportion of women with S-FSH levels greater than 50 IU/L were also lower in PCOS women. There was no difference in parity or nulliparity between PCOS and control groups [23].
Despite the fact that leptin inhibits appetite, obese individuals have higher serum leptin levels and may be leptin resistant, which is comparable to the insulin resistance that is frequently observed in obesity. Serum leptin levels are also influenced by steroids, fat distribution, and gender. Additionally, subcutaneous and visceral adipose tissue express leptin differently [24,25] .
It was observed that Oligomenorrhea in case of PCOS was 65% and in controls was 38.5% as there was increased cases of Oligomenorrhea in PCOS cases compared to the (control group). 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 a polypeptide hormone produced mostly by adipocytes and is thought to regulate proper body weight.

Several studies have found a high relationship between circulating leptin and obesity, as well as PCOS, a common cause of anovulatory infertility in women[28].

In the current study there was a elevation of serum leptin in women with PCOS. This finding was in comparable with the study by Mohiti Ardekani and Taarof, which showed elevated level of serum leptin in women with PCOS[29].

In the present study for PCOS leptin observed was 16.69 and for controls 14.23±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 statistically significant 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 statistical significant in serum leptin levels of PCOS women with insulin and BMI matched controls [19,20].

Nasrin Jalilian et al., in 2016 studies 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].

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 reduces glucose mediated insulin secretion through its receptorsin the hypothalamus and also reduces its action at the cellular 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 was 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 was a significant positive relationship between leptin and LH.but in contrast with the study by Sir Petermann et al., [32]where no correlation between leptin secretion pulses and LH were 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 218. 72±72 compared to controls184.26±24.8 with p= 0.037. In the present study Adiponectin observed for PCOS was 10.68±3.3 and in controls 12.05±5.4 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 Chenet 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 confirmed that obese women have adiponectin levels significantly lower than normal-weight healthy controls [34,35]. Lastly, adiponectin levels were inversely correlated with BMI both in PCOS and healthy women. A study indicated that normal-weight PCOS patients had greater insulin levels and worse insulin sensitivity (measured by HOMA) compared to controls. However, serum adiponectin concentrations did not change between the two groups. As a result, the high level of insulin resistance in women with PCOS has no effect on (or is unlikely to affect) adiponectin levels [36], despite the fact that adiponectin levels are commonly recognised to be lower in an insulin resistant condition [37]. The discovery that adiponectin can boost glucose utilisation while decreasing hepatic glucose synthesis [38,39] strengthened the relationship between adiponectin and insulin sensitivity. As a result, the current study found a negative correlation between adiponectin and PCOS patients. With the prospect of using these indicators as treatment targets for PCOS. There appears to be a favourable link between insulin resistance and leptin, but a negative relationship with adiponectin in PCOS patients [40].

Obesity is currently the most widespread metabolic disturbance in the world, increasing the risk of cardiometabolic changes such as type 2 diabetes, hypertension, and dyslipidaemia. Obesity and metabolic syndrome (MS) are characterised by an increase in circulating leptin concentrations and a reduction in blood levels of adiponectin.

As a result, the adiponectin/leptin ratio has been implicated as a cause of adipose tissue malfunction. This new biomarker correlates with insulin resistance better than adiponectin or leptin alone, or even HOMA, and decreases with an increasing number of metabolic risk factors, making it a potential prognostic sign for MS. Furthermore, the

adiponectin/leptin ratio has a negative correlation with markers of low-grade chronic inflammation [41].
PCOS is a highly prevalent heterogeneous syndrome of clinical and/or biochemical androgen excess, ovulatory dysfunction and polycystic ovaries (PCO). Despite it being one of the most common reproductive health problems of women, its effective treatment remains a significant challenge to medical profession. The gold standard for improving insulin sensitivity in obese PCOS women should be weight loss, diet, and exercise. It is recommended as the first line of treatment in obese women.

CONCLUSION

In the present study women with PCOS had higher levels of leptin, which was positively associated with FSH, LH, and TSH, while adiponectic was negatively associated with PCOS. In PCOS patients, high serum leptin is substantially related with total cholesterol and MDA levels. There was no significant association between leptin and BMI, diabetes, hypertension, prolactin, AMH, or SOD.
Leptin and adiponectin levels can be used to predict the probability of developing PCOS in women without evident symptoms.
Adiponectin and leptin may play a significant role in the mechanism of neuroendocrine disorders in PCOS, which is characterized by an increased LH/FSH ratio.

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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