Circular Pentraxin-3 and Betatrophin as Novel Predictors and Promising Biomarkers in Polycystic Ovary Syndrome with or without Type 2 Diabetes Mellitus

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ABSTRACT
Background: Two recently discovered circulating proteins, pentraxin 3 (PTX3) and betatrophin, have a strong correlation with a number of illnesses, obesity, and the metabolic syndrome. Objective: This study was made to investigate whether pentraxin-3 (PTX3) and betatrophin levels are sensitive markers associated with PCOS in women with or without diabetes. Materials and methods: We conducted a case-control clinical study. Samples were collected from "infertility center" at Basra hospital for Obstetrics and children in Basra province-Iraq during the period from August 2023 till end of February 2024. Results: Levels of Ts, PRL, HOMAIR, PTX3, betatrophin, and MDA were elevated ($p < 0.01$), LH and insulin were increased ($p<0.05$) and ($p<0.01$), E2 and TAC decreased ($p<0.01$), while BMI and FSH levels showed non-significant changes ($p>0.05$) in PCOS women with or without diabetes (both 1ºPCOS and 2ºPCOS), respectively, as compared to the healthy control. Glucose was increased ($p<0.01$) in PCOS women with diabetes (both 1ºPCOS and 2ºPCOS), and AMH had increased ($p<0.05$) in PCOS women without diabetes. The area under the curve (AUC) indicate that PTX3 (AUC= 0.95, 0.90, 0.88, 0.85) and betatrophin (AUC= 0.89, 0.87, 0.86, 0.85) could potentially be used as greater predictive biomarkers in PCOS women (both 1ºPCOS and 2ºPCOS) with or without diabetes. Conclusion: Dysregulation of PTX3 and betatrophin may be associated with the metabolic consequences of PCOS. Therefore, we suggest that PTX3 and betatrophin may potentially serve as an independent predictor for the prognosis and development of PCOS in at-risk women, especially those with insulin resistance.

1. Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder associated with women infertility due to anovulation. PCOS is characterized by chronic anovulation and hyperandrogenism, either in the form of biochemical androgen excess or clinically as hirsutism, acne, and/or male pattern alopecia. Moreover, PCOS has been linked to obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, and heart disease (1). Although PCOS was described more than 50 years ago, the underlying cause of the disorder is still unclear. Recently, many studies have documented the presence of insulin resistance (IR) in both obese and lean PCOS patients, and some investigators consider IR to be an important risk factor for the development of metabolic syndrome in women with PCOS (2).

Accumulating evidence suggests that PCOS is a chronic inflammatory disease. The ovaries of women with PCOS exhibit inflammation and fibrosis; the peripheral blood of women with PCOS have reduced numbers of anti-inflammatory regulatory T cells and elevated serum levels of autoantibodies, and a recent study also indicated the pathogenic role of CD19+ B cells in the development of PCOS (3). Humoral innate immune molecule pentraxin 3 (PTX3), which belongs to the same superfamily of acute reactants as C-reactive protein (CRP), is a member of the long pentraxin family and has multifunctional properties for its capacity to interact with different types of ligands. In particular, PTX3 plays a non-redundant role in innate immunity by opsonizing selected pathogens and in female fertility. Recent research has demonstrated that PTX3 in circulation is associated with PCOS, but its role in PCOS is so far inconclusive. Unlike short pentraxin, PTX3 is produced at the local site of the inflammation, including follicle cells, and it is essential for the organization of the cumulus oophorus extracellular matrix and in vivo fertilization (4).

Betatrophin, also known as angiopoietin-like protein (ANGPTL8), is highly conserved in all mammalian species and is a newly identified circulating protein predominantly produced in the liver and adipose tissue. This protein regulates glucose homeostasis and lipid metabolism. It is induced as

a result of insulin resistance, therefore attracting increasing attention. Betatrophin was reported to promote pancreatic beta cell proliferation and improve metabolic control by increasing the beta cell division rate in insulin-resistant cells (5).

To date, a limited number of studies on Pentraxin-3 and Betatrophin in women with PCOS have been published. Hence, in the present study, an attempt was made to evaluate serum Pentraxin-3 and Betatrophin as a reliable noninvasive predictor of PCOS in women with or without Type 2 Diabetes Mellitus.

2. Materials and methods

2.1. Study population

The present study is a case-control study. Samples were collected from "infertility center" at Basra hospital for Obstetrics and children in Basra province-Iraq during the period from August 2023 till end of February 2024. In addition, patient samples were obtained from private clinics in Obstetrics and Infertility medicine. In this clinical study, 123 volunteers of married females of Basra governorate (Souther of Iraq) with an age range of 35–45 years were divided into three groups, including 61 PCOS women with type2 DM (31 primary and 30 secondary), 62 PCOS women without type2 DM (30 primary and 32 secondary) and 33 normal ovulatory women (apparently healthy controls) who participated in the study. The diagnosis of PCOS was confirmed using the Rotterdam ESHRE/ASRAM criteria (2004), including at least two of the following: irregular periods or no periods, caused by lack of ovulation oligo- or anovulation, clinical or biochemical signs of hyperandrogenism (acne, hirsutism), and polycystic ovaries on ultrasound on the 12th day of the menstrual cycle (6). All the participants were of Basra province (Souther of Iraq). The sample populations are married women who live together with her husband and have not used any contraceptive method for a period of one year, but they are still childless. The control group was apparently healthy females; not suffering from type-2 diabetes nor having any family history of type-2 diabetes mellitus; having regular menstrual cycles (28–33 days), not using oral contraceptives for at least the preceding 3 months and had no clinical signs of hyperandrogenemia or any sign of PCOS symptoms. Patients, who were pregnant females, Females presenting endometriosis, uterine fibroid, breast cancer, T1DM, epilepsy, or migraine, and those with hormone-dependent cancer. Furthermore, hyperthyroidism, hypothyroidism, mental disease, and serious disease with dysfunction of the heart, liver, and kidney, as well as those using estrogen replacement therapy. were excluded from the study.

2.2. Serum samples collection

The blood of volunteer women (10 ml) was routinely obtained in the morning following an overnight fast on days 2-3 of a natural menstrual cycle. Blood was allowed to clot for 30 minutes at 25 ºC and centrifuged at 402×g for 10 min at room temperature; then serum was separated and immediately used in the detection of variables in this study, and others were stored in deep freezing at (-70 ºC) until using.

2.3. Methods of Biochemical Estimation

The control and PCOS patients' blood samples were analyzed for biochemical parameters by standard procedures as follows: Body mass index was calculated as the following formula [BMI (kg/m^2) = Wt in kg / Ht in m^2] (7). Serum glucose was estimated by kit (Abnova-KA0831/Taiwan), serum betatrophin level was determined using the (Elabscience, USA, Cat. No. E-EL-H2206) kit and PTX3 level was determined using the (Elabscience, USA, Cat. No. E-EL-H6081) kit which was a solid phase ELISA based on the sandwich principle. Anti-Mullerian hormone was estimated by kit (E-EL-H0317/USA), Insulin was estimated by kit (Abnova-KA0921/Taiwan), Follicle stimulating hormone was estimated by kit (Abnova-KA0213/Taiwan), Luteinizing hormone was estimated by kit (Abnova-KA0214/Taiwan), Prolactin was estimated by kit (Abnova- KA0217/Taiwan), Testosterone was estimated by kit (Abnova- KA0236/Taiwan), and Estradiol was estimated by kit (Abnova-KA0234/Taiwan). Insulin resistance (IR) was determined by the homeostasis model assessment

[HOMA-IR=insulin (μIU/mL) × glucose (mg/dL)/405] (8).

2.4. Statistical analysis

Statistical analysis was performed using SPSS software version 26 (IBM Corporation, Armonk, NY, USA). The data were distributed normally and the comparison between groups was analyzed using the analysis of variance followed by Dunnett's t-test to find the statistical significance. The receiver operating characteristics (ROC) curve, which is formed by graphing sensitivity (y-axis) against 1-specificity (x-axis) and calculating the area under the ROC curve (AUC), was used to calculate the sensitivities and specificities, as well as the 95% confidence interval. A $p<0.05$ was considered statistically significant, $p<0.01$ highly significant, and an AUC value near 0 (or 1) implies a strong diagnostic value, the values of one group were mainly greater (or lower) than the values of the comparison group in this circumstance.

3. Results and Discussion

The general demographic characteristics of all women volunteers participated in this work were presented in Table 1.

Table 1. The main demographic and clinical characteristics of the study population.

Characteristics		**Control**	**PCOS Patients Women**			
			with Type2 DM		**without Type2 DM**	
			Primary (1ºPCOS)	**Secondary (2ºPCOS)**	**Primary (1ºPCOS)**	**Secondary (2ºPCOS)**
Total (No.)		33	123			
			31	30	30	32
Smoking habit	Negative	33	29	30	27	31
	Positive	0	2	0	3	1
Drinking Alcohol	Negative	33	31	30	30	32
	Positive	0	0	0	0	0
Food Habits	Vegetarian	14	10	9	7	10
	Non-Vegetarian	19	21	21	23	22
Demographic area	Urban	27	28	27	26	27
	Rural	6	2	3	4	5
Education	Learned	25	27	24	21	29
	Illiterate	8	4	6	9	3
Employment	Employed	31	27	25	23	24
	Not Employed	2	4	5	7	8

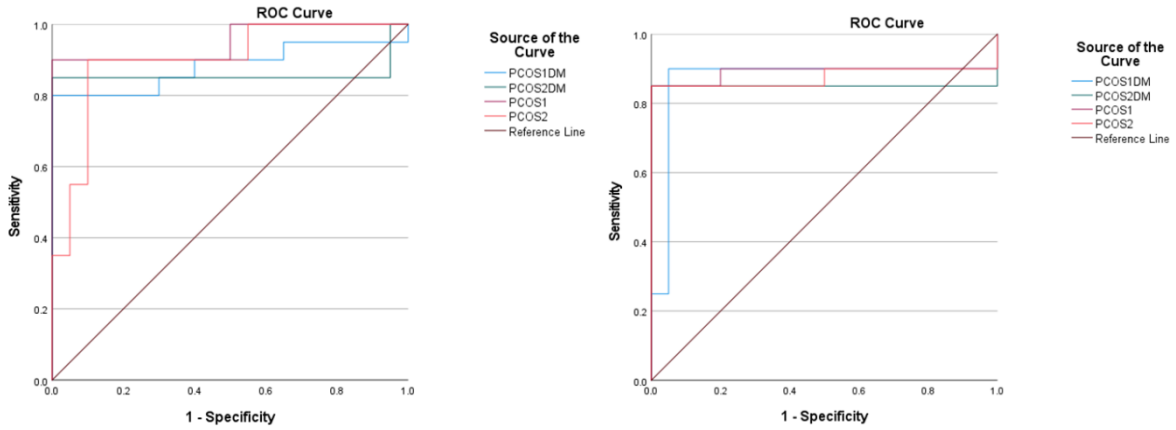
Table 2 clearly showed that significant ($p < 0.01$) increases were seen in the levels of Ts, PRL, HOMAIR, PTX3, Betatrophin, and MDA in PCOS women with or without diabetes (both 1ºPCOS and 2ºPCOS), respectively, as compared to the healthy control. Levels of serum LH and insulin were significantly ($p<0.05$) and ($p<0.01$) increased in PCOS women with or without diabetes (both 1ºPCOS and 2ºPCOS), respectively, as compared to the healthy control. On the other hand, levels of serum E2 and TAC were significantly ($p<0.01$) decreased in PCOS women with or without diabetes (both 1ºPCOS and 2ºPCOS), respectively, as compared to the healthy control. Also, level of glucose was increased ($p<0.01$) significantly in PCOS women with diabetes (both 1ºPCOS and 2ºPCOS). Furthermore, data obtained in study (table 2) indicated that PCOS women without diabetes had significantly increased ($p<0.05$) level of AMH, while BMI, and FSH levels showed non-significant changes ($p>0.05$), in PCOS women with or without diabetes (both 1ºPCOS and 2ºPCOS), respectively.

Table 2. Levels of PTX3, betatrophin and some endocrinological hormones in PCOS women with or

without diabetes and healthy control.

Variables	PCOS Patients Women				Control (mean±SD)
	with Type2 DM (mean±SD)		without Type2 DM (mean±SD)		
	Primary (1ºPCOS)	Secondary (2ºPCOS)	Primary (1ºPCOS)	Secondary (2ºPCOS)	
BMI	28.84±0.25	28.98±0.69	28.66±1.53	29.95±1.98	28.26±2.51
LH (mU/mL)	9.22±0.22*	8.79±0.53*	15.68±1.33**	15.82±1.2**	6.68±1.33
FSH (mU/mL)	6.42±1.34	6.62±1.32	7.18±1.21	7.27±1.35	8.09±1.33
LH\FSH ratio	1.43±0.16*	1.32±0.40*	2.18±1.09**	2.17±0.88**	0.82±1.00
E2 (pmol/l)	78.45±1.62**	74.29±0.43**	87.25±1.54**	85.12±0.51**	102.43±0.35
Ts (nmol\l)	1.56±1.34**	1.42±1.24**	1.78±0.23**	1.73±1.42**	0.58±1.3
E2\Ts ratio	50.28±1.20**	52.31±0.34**	49.01±6.69**	49.20±0.29**	176.6±0.26
PRL (ng/mL)	19.38±5.85**	19.96±6.79**	16.23±1.53**	16.93±1.41**	10.66±2.45
Glucose (mg\dl)	157.41±1.5**	160.12±1.37**	102.37±2.33	104.21±2.13	96.21±1.5
Insulin (mU/L)	15.21±2.14*	15.86±1.32*	23.02±2.45**	22.98±2.56**	10.42±2.64
HOMAIR±SD	5.91±1.56**	6.27±1.67**	5.26±2.01**	5.47±1.32**	1.92±1.25
PTX3 (pg/mL)	91.64±2.12**	96.35±1.56**	78.69±1.23**	78.98±1.52**	30.21±2.54
Betatrophin (pg/mL)	872.31±2.15**	895.12±1.67**	788.65±1.28**	790.11.±1.52**	678.21±1.62
TAC (U/mL)	1.88±0.59**	1.64±0.21**	2.06±1.2**	2.13±1.34**	6.39±2.5
MDA (nmol/mL)	17.22±1.24**	18.18±1.02**	14.26±1.80**	14.71±1.67**	7.89±1.34
AMH (mg/mL)	12.84±1.90	13.99±1.24	17.94±2.11*	18.09±1.94*	10.42±1.30

Data are presented as mean±standard deviation (SD); $p>0.05$: p-value not significant, $*p<0.05$: p-value significant; $**p<0.01$: p-value highly significant, indicating the level of significance in comparison with the corresponding control value.vThe area under the curve (AUC) results obtained indicate that PTX3 and betatrophin could potentially be used as greater predictive biomarkers in PCOS women (both 1ºPCOS and 2ºPCOS) with or without diabetes (PTX3: AUC= 0.95, 0.90, 0.88, 0.85; Betatrophin: AUC= 0.89, 0.87, 0.86, 0.85, respectively), as illustrated in Figure 1.



(A) Pentraxin-3 **(B) Betatrophin**

Figure 1. Receiver operating characteristic curve (ROC) for PTX3 and betatrophin levels in PCOS women (both 1ºPCOS and 2ºPCOS) with or without diabetes.

A failed pregnancy or Infertility and the inability to conceive after 12 months or more of unprotected sexual activity are the actual expressions of infertility. As a result, it can be assessed at first following a year of infertility (9). Urban populations differ significantly from those in rural locations in several critical ways, including pollution, environment, social and psychological aspects, genetics, food considerations, and other areas where population density is higher. Conversely, the demands and strains of labor have an impact on women's psychological health. Additionally, tension elements related to family life, like raising children and marital relationships, exacerbate the issue of oxidant/antioxidant status (10).

Although the relationship between PTX3 and PCOS with or without type 2 diabetes is still unknown, numerous studies have looked into serum PTX3 levels in PCOS to date. These investigations revealed that the serum PTX3 level in women with PCOS was either greater (11; 12), lower (13; 14), or about the same (15) as in women without PCOS. Ovarian follicular cells have inherent immunological capacities that affect their endocrine function, and they generate PTX3 in response to local inflammatory stimuli, unlike the primarily liver-produced short pentraxin CRP (16). According to certain earlier research, PCOS women's granulosa cells expressed more PTX3 than did non-PCOS women's (17). As such, measuring the PTX3 level in the ovarian milieu is crucial. Unexpectedly, elevated PTX3 production was linked to increasing levels of inflammation, insulin resistance, and overweight in PCOS patients with and without diabetes. Regardless of dietary state, some findings have demonstrated a clear correlation between the levels of circulating PTX3 and the effects of hyperandrogenism and insulin resistance on the function of hormonal stromal adipose tissue in PCOS (18). The second possible explanation is that hepatocytes in the obese liver produce more PTX3. The correlation that our study revealed between PTX3 levels and insulin levels, HOMA-IR values, and betatrophin levels supports this theory. The characteristics of PCOS women include elevated insulin resistance, hyperinsulinemia, increased risk of glucose intolerance, diabetes, particularly type 2, and a higher frequency of anomalies related to lipids. Although the mechanisms behind PCOS in women are not fully known, insulin resistance may be a key factor in the pathogenesis of PCOS. Moreover, hyperinsulinemia has previously been shown to exist in PCOS-affected women, regardless of obesity (19). Circulating PTX3 levels have been linked in the past to the metabolic syndrome's components, such as elevated body mass index, waist-to-hip ratio, serum triglyceride levels, systolic blood pressure, and reduced levels of high-density lipoprotein cholesterol, as well as the degree of insulin resistance in overweight and obese individuals. However, because the accumulation of Tg in the liver or ectopic fat causes hypertriglyceridemia and hyperinsulinemia, which in turn triggers PTX3 synthesis and secretion in the liver or ectopic fat and serves as an indicator of infertility, it has been suggested that impaired metabolism of free fatty acids may play a significant role in regulating PTX3 levels (11). Furthermore, markedly increased PTX3 levels may impair insulin-stimulated glucose

uptake in muscle, promote hepatic gluconeogenesis via stimulating phosphoenolpyruvate carboxykinase, and enhance hepatic glucose synthesis in PCOS women with and without diabetes (12).

Our findings in this study showed that both PCOS with or without diabetes women (both 1ºPCOS and 2ºPCOS) had considerably higher levels of betatrophin as compared to parently healthy control. Some previous reports indicated that betatrophin is a unique and strong activator of β-cell replication, improving glucose tolerance by speeding up β-cell division. Evidence suggests that insulin and a high-fat diet can promote betatrophin production, which, rather than improving glucose metabolism, leads to elevated serum triglyceride levels and insulin resistance. Nonetheless, several studies have shown that PCOS patients with T2DM have higher levels of betatrophin, suggesting that betatrophin may be a useful biomarker for T2DM diagnosis (20). According to this research, betatrophin may have a part in the etiology of T2DM and insulin resistance, particularly in women with PCOS. Insulin resistance may be the cause of the noticeably elevated blood betatrophin levels in PCOS patients-both those with and without diabetes-in both primary and secondary PCOS cases. According to certain reports, the relationship between IR and betatrophin in female PCOS patients appears to be independent of body mass and is likely due to insulin-stimulated hepatic betatrophin synthesis (21).

So, recurrent miscarriages and the discovery of polycystic ovaries may be related, and one of the key mechanisms explaining this link could be significantly higher levels of betatrophin. In female patients with PCOS, hyperandrogenism is a characteristic that may impair pore growth and inhibit ovulation. This condition could be caused by an imbalance in plasminogen levels, which can cause the interstitium (theca) to enlarge and set off a series of events that in turn continue to produce testosterone in men. Thus, the reason for ovarian dysfunction in PCOS-affected women may be attributed to markedly increased levels of betatrophin, which would ultimately lead to disrupted and disordered endothelium, metabolic, and reproductive processes (22; 23). Additionally, therapeutic approaches targeted at inhibiting betatrophin and lowering insulin resistance may be crucial to reestablishing proteolytic balance in many damaged tissues, such as the ovary, enabling proper ovulation; PCOS treatment can also enhance a patient's fertility and prevent complications that lead to a variety of cardiovascular diseases, menstrual irregularities, and infertility in PCOS patients). Moreover, betatrophin production and expression may be enhanced by inflammatory cytokines released by macrophages in an IR environment (24; 25).

Insulin resistance is a type of biological misunderstanding in which the body's cell membrane insulin hormone receptors are inappropriately not responding to insulin. As a result, blood glucose cannot enter cells, leading to a hypoglycemic response. Because of this, the pancreas must produce large amounts of insulin in an attempt to get glucose from the bloodstream into the cells; thus, the insulin hormone's ability to regulate and signal is compromised, which alters blood glucose levels and may lead to insulin resistance (26). It is necessary to first understand how insulin works because the processes underlying markedly elevated insulin resistance in PCOS women with or without diabetes seem too complicated. The cell surface receptor for the insulin hormone, which resembles the insulin-like growth factor-1 (IGF-1) receptor structurally, may attach to the hormone itself. Insulin-responsive glucose transporter 4 (GLUT4) is translocated from intracellular vesicles to the cell surface in tissues in response to insulin hormone, which stimulates the tissue cells to ingest glucose (27). It's possible that phosphatidylinositol 3-kinase (PI3-K) sharing and mediation are necessary for this route to occur. Conversely, the MAPK-ERK pathway supports cell growth and differentiation because it can activate a series of enzymes, such as Raf, MAPK, MAPK-ERK1/2 of the non-classical models, and serine/threonine (28).

Oxidizing radicals can cause the abundant supplies of polyunsaturated fatty acids (PUFA) to readily target the membranes of cells. Lipid peroxidation is the process in question, and one of the process's key byproducts is malondialdehyde (MDA). It is one of the most often utilized indicators to evaluate oxidant status since it correlates with the level of lipid peroxidation. Insulin resistance, hyperandrogenism, dyslipidemia, and obesity or overweight associated with PCOS likely raise MDA

levels while lowering those of antioxidant enzymes (29). Accordingly, an excess of reactive oxygen species (ROS) and an imbalance between oxidants and antioxidants are referred to as oxidative stress. It is believed that persistent hyperinsulinemia brought on by relative insulin resistance causes aberrant ovarian androgen metabolism, poor follicle development, and altered gonadotrophin response. Insulin resistance has been associated with oxidative stress and reactive oxygen species generation (30). Oxidative stress decreases insulin production from the pancreatic β cells and hinders glucose absorption in muscle and adipose tissue. Furthermore, the vascular endothelium is unable to secrete nitric oxide (NO) due to hyperinsulinemia in PCOS patients. Endothelial dysfunction results from this decrease in membrane fluid, which raises intracellular calcium levels. Endothelial dysfunction is one of the early signs and symptoms of diabetes mellitus. PCOS causes an increase in ROS generation, and several PCOS characteristics, such as abdominal adiposity, insulin resistance, obesity, and androgen excess, may help these individuals' oxidative stress levels (31).

The increased level of oxidative stress in PCOS women with or without diabetes may be due to the excess ROS in the follicle, which may overcome the follicular fluid antioxidant defense and directly damage oocytes. It is known scientifically that the follicular fluid microenvironment contains leukocytes, macrophages, and cytokines, all of which are known sources of reactive oxygen species (ROS). ROS within the follicular fluid plays a role in modulating oocyte maturation, folliculogenesis, ovarian steroidogenesis, and luteolysis. When the peritoneal cavity microenvironment is exposed to severe oxidative stress, the DNA of oocytes may be damaged, leading to defective fertilization (32). Even when fertilization is achieved, oxidative stress-induced apoptosis may result in embryo fragmentation, implantation failure, abortion, impaired placentation, and congenital abnormalities. Excess ROS may hinder the endometrium, which normally functions to support the embryo and its development. Oxidative stress may induce luteal regression and insufficient luteal hormonal support for the continuation of a pregnancy (33).

According to the current study, PCOS women with type 2 diabetes had significantly ($P<0.05$) lower serum LH levels than PCOS women without diabetes. In contrast to healthy controls, PCOS patients' LH levels were significantly higher. Furthermore, although not a defining feature of PCOS women overall, our research indicates that high LH/FSH ratios are frequently seen in PCOS women, both with and without diabetes. Individuals with obesity and hyperinsulinemia comprise the majority of PCOS women with normal gonadotrophin ratios (3). The conventional wisdom, which dates back to Stien Leventhal's time, holds that overweight or obesity has a significant role in the pathophysiology of PCOS with or without diabetes. However, it is unclear why not all PCOS-affected women are overweight or obese, nor do all of them exhibit the disease's hormonal and biochemical abnormalities. Because disease criteria vary so much, we were motivated to consider quantifying relationships between disease manifestations and provide an answer to the following query: "Is there a link between a higher BMI and a higher incidence of menstrual disturbance, hirsute behavior, or both?" (5). Moreover, the main explanation for the persistence of the anovulatory state in PCOS participants could be the aberrant LH/FSH ratio. Therefore, pulsatile release of gonadotropin-releasing hormone (GnRH) or an environment with high estrogen levels may be the cause of elevated LH and unchanged or normal FSH (6; 9).

Some scientific reports that because CYP19 mediates the conversion of androgens to estrogens, the E2/T ratio may serve as a direct biomarker of aromatase activity, offering the most information on the activity of aromatase enzymes. Theca cells may produce more androgens in the polycystic ovary than in the normal ovary due to increased androgen synthesis. On the other hand, the polycystic ovary's granulosa cells have reduced aromatase activity, which causes an imbalance in the production of androgen and estrogen (7; 24). In the present study, PCOS with low estradiol levels may lead to more serious hyperandrogenism with relatively decreased levels of E2/T. Some previous reports indicated that lower levels of estradiol may result from decreased RNA expression of granulosa cell aromatase and its activity. Nevertheless, higher levels of testosterone in PCOS patients may inhibit aromatase activity. Thus, the androgen can dose-dependently directly affect aromatase activity, or

indirectly regulate other factors such as E2 and LH. Some reports suggest that early exposure of women to androgen may induce sex-specific organizational changes in aromatase expression in the preoptic area (28). One potential explanation for PCOS's arrested follicular growth could be decreased aromatase activity. According to a study, women with PCOS have lower amounts of estradiol, aromatase mRNA, and aromatase activity in their follicles. One or more endogenous inhibitors of aromatase activity are present in PCOS follicular fluid. A competitive inhibitor of aromatase activity, 5α-androstane-3, 17-dione, is a 5α-reduced androgen that is noticeably higher in PCOS follicular fluid. Furthermore, compared to control follicles, PCOS follicles have significantly higher 5α-reductase activity, which causes PCOS-affected women to produce more 5α-androstane-3,17-dione. All things considered, enhanced 5α-reductase activity and decreased aromatase activity may be the cause of women with PCOS producing more androgen and less estradiol (9; 30).

In the current study, prolactin levels were considerably greater in PCOS women with or without diabetes than in the control group. This could result in amenorrhea and anovulation, as well as suppression of the hypothalamic-pituitary-gonadal axis and resistance of the ovary to gonadotropin activity. Prolactin can suppress granulosa cell aromatase activity and prevent folliculogenesis in the ovary, which results in hypoestrogenism and ovulation. Therefore, by preventing the pulsatile release of GnRH and thereby interfering with ovulation, an elevated level of PRL may negatively impact fertility potential (32). On the other hand, a significant increase in basal prolactin levels or an enhanced reserve of prolactin in the pituitary gland may be the cause of PCOS, as evidenced by significantly elevated levels of PRL and Ts in patients with or without type 2 diabetes. Therefore, one of PCOS's characteristics is PRL variability in secretion. Furthermore, excessively high serum levels of PRL have been shown in certain studies to be associated with an increased risk of dysmetabolism, obesity, and overweight, all of which can result in poor glucose tolerance, impaired insulin sensitivity, or increasing insulin resistance (33).

5. Conclusion

From this study, it can be concluded that increased oxidative stress, may be a sensitive marker for beta cell malfunction and insulin resistance, a part of the pathophysiology of PCOS, and be exacerbated by being overweight or obese and having hormonal abnormalities. and as a result, these metrics might be recommended as diagnostic indicators for high-risk group screening and early diagnosis. Also, it may be possible to prevent PCOS-related problems like diabetes by incorporating betatrophin and PTX3 screening into routine check-ups for people with PCOS. Further studies are warranted to confirm this association.

Conflict of interest

The authors declared no conflicts of interest. No funding was received for this study.

Informed consent

The study received an ethical approval from Basrah University (9/57/4963), and an informed consent was obtained from each participant after explanation of the procedures in full detail. The informed consent and ethical guidelines were followed, based on the deceleration of Helsinki for year 2000.

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Conflict of Interest

All authors declare that they have no conflict of interest.

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