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Evaluation of Some Hormones and Immunological Variables in Patients with Polycystic Ovary Syndrome: A Physiological Study

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Abstract— *Polycystic ovary syndrome (PCOS) is a common disease affecting women, causing psychological, reproductive and metabolic disturbances and consequently leading to complications such as obesity, diabetes, heart disease, and related changes in the concentrations of certain hormones and cytokines. The current study directed to measure the concentrations of the following parameters, including hormones (follicular stimulating hormone, luteinizing hormone, testosterone, resistin, copeptin, insulin) and cytokines (interferon-γ, and tumor necrosis factor-α) in the serum of affected women and compare them with the concentrations of the same parameters in the serum of healthy women (control group) in Tikrit governorate. Blood samples were collected from 80 individuals and divided into two groups: a group of affected patients and a control group, each comprising 40 individuals. The serum was then separated from the blood, and sandwich enzyme-linked fluorescence test was performed to measure the concentration of the parameters. A significant increase was found in every parameter's concentration in the serum of patients with PCOS compared with the healthy people at a probability level of $P \leq 0.001$.*

Keywords— *Resistin, copeptin, hormones, tumor necrosis factor.*

I. INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the prevalent illnesses that spread among women; it is problematic to provide healthiness maintenance for women affected with this disease. Patients visit a number of physicians for an extended period of time in order to diagnose the condition, but to no avail. The sickness remains unidentified, in addition to treating patients with medications without benefit. Definitely, the financial cost of PCOS was formerly assessed at roughly $3.7 billion once a year in 2020 when taking into account only the prices of preliminary detection as reproductive endocrine illness, without evaluation the prices of pregnancy-associated illnesses and long-standing sicknesses (1).It is documented as a frequent and complicated endocrine dysfunction that influences 5-20% of females of reproductive age with short- and long-standing impacts (2).

It is also recognized as the chief reason of ovulation disorder, which disturbs 3-13% of women, as this condition causes fluctuating degrees of metabolic, endocrine alterations and psychological syndromes and has a heightened risk of correlated healthy problems, including premature birth and gestational diabetes (3). It is one of the utmost prevalent causes of hormonal disorder in women. The definite reasons of its mechanism are not understood, but there are numerous factors that contribute to its occurrence; involving predominant hereditary factor, females are more vulnerable to suffer from this disease than others when one or more family members have previously had this illness. Additional factor is hormonal disturbance situation, most females who affected by PCOS have elevated level of insulin which lead to insulin resistance, the consequences are raising in production of testosterone hormone from ovaries, weight gain, acne, and hair thickness (4). Its management is problematic because it has strictly correlation with extreme androgen and low-quality inflammation (5).

It hinders numerous aspects of healthy living and comfort throughout life due to metabolic, psychological, and reproductive complications. It is most frequently lead to metabolic disorder, ovulatory defect, obesity, type 2 diabetes, and cardiovascular risk factors such as anxiety, ingestion illnesses, high blood pressure as well as and underwriting (6).

Resistin is one of the tinny polypeptide hormones which contain large amount of cysteine. It was described for the first time by the Steppan et al. group. It produced primarily from cells such as monocytes in peripheral blood as well as by mature white adipocytes. Its levels raise in kinds of obesity resulted by nutrition and genetic factors, and reduce with the utilization of anti-diabetic drugs such as: roseglitazone (7, 8). It is strictly associated with increase the weight or obesity and insulin resistance, as adipose tissue has significant relationship with controlling physiological processes such as glucose metabolism, immune responses, and reproduction and, all of which interfere with the synthesis of this fats (9). It is also firmly connected between obesity and PCOS, and it was lately observed in one research work that females with PCOS have elevated concentrations of resistin in the blood circulation (10).

The glycopeptide hormone copeptin, which has 39 amino acids, is made up of them. It is made up of copeptin, arginine, vasopressin, the first or second neurophysin, and a signal peptide. It is further steady under physiological situations than AVP itself. It has a significant correlation with the mechanism of water and salt balance in the body, therefore it regulates blood pressure, but it is rapidly removed from the body, and it rises in the situation of heart failure.

Insulin resistance and obesity are linked to copeptin levels in serum, and therefore it seems to have a significant

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association with the metabolic response and consequent evolution of atherosclerosis in persons suffers from PCOS and ovarian cysts. On the other hand, copeptin may also be a novel marker of insulin resistance (10, 11).

Cytokines are soluble molecules produced from various kinds of cells including immune cells. Their functions are evolution of angiogenesis with tumorigenesis, differentiation of immune cells, controlling immune response to diverse stimuli and inflammation events (12, 13). A network of pro-inflammatory cytokines are typically in counterbalance status because they are responsible for occurrence of inflammation (14).

Tumor necrosis factor-alpha (TNF-α) is a cytokine has multiple activities. It is produced by leukocytes, macrophages, fibroblasts, endothelial cells, pre-adipocytes and adipocytes (15). It contributes to controlling several cellular functions such as differentiation, reproduction, immune process, and energy pathways. It is also crucial in controlling the ovarian cycle, as it has significant relationship with the growth and progress of ovarian follicles (16, 17). Its concentration rises during various acute bacterial infections (18).

Interferon-gamma (IFN-γ) is a kind of cytokine with a 34 kDa molecular weight of. It was believed that it was released entirely from CD4+ T helper lymphocytes, CD8+ cytotoxic lymphocytes, and nature killer cells. Nonetheless, research has revealed that IFN-γ is also produced by other cells, including macrophages, dendritic cells, and B cells (19). Uncontrolled releasing of IFN-γ has been related with numerous illnesses, involving chronic autoimmune diseases such as inflammatory bowel disease and diabetes (20).

The present research aims at estimation the level of insulin, resistin, copeptin, and sex hormones accompanied by certain immune variables, in the serum of patients affected with PSOC in Tikrit governorate, based on the raise in the level of resistin, copeptin, and sex hormones.

II. Patients and Methods

The present cross-sectional study was conducted on eighty women who visited health centers in Tikrit city during the period from the beginning of the October until the end of December 2023.

It was dominated to the ethics committee of the Tikrit health direction and was accepted on the bases of the committee's assertion necessities. The objectives of the investigation were offered to all members, so they were subjected to the research after obtaining permission from them.

Eighty blood samples were obtained by taking one specimens from each woman (aged between 20-40 years) during the period of investigation, so that they were separated into two groups: Patients group involved 40 patient women affected with PCOS diagnosed according to Rotterdam criteria (21), i.e. the existence of at least two of the following three conditions: (1) biochemical or clinical hyperandrogenism; (2) oligomenorrhea (irregular menstrual cycles) or amenorrhea (absence of menses); (3) ultrasound results of polycystic ovaries in 1 or 2 ovaries. Moreover, a control group of 40 intact women was chosen from persons came to the clinic for examinations. Exclusion criteria for two groups were: pregnancy, adrenal hyperplasia, premature ovarian failure, Cushing's syndrome, thyroid dysfunction, use of oral contraceptive or antiandrogen for the last 3 months.

Afterward, the blood was drawn from individuals of both groups, and then the serum was separated from blood by centrifuge. Finally the biochemical parameters were evaluated, which comprised follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, resistin, copeptin, insulin, TNF-α, and IFN-γ.

A. Measurement the levels of resistin and copeptin hormones

To estimate the hormones resistin and copeptin, the sandwich enzyme-linked fluorescence assays (ELISA) technique (22) was employed, utilizing an evaluating kit appropriated for the hormones and manufactured from the Chinese company Sun Long Biotech.

B. Measurement the levels of sex hormones and insulin

Based on the steps illustrated in the minividas hormone testing device, the level of sex hormones and insulin was estimated, as the device is an automated testing scheme established on the fundamental of ELISA (22). The estimation kit appropriated for the hormones and manufactured from the French company Biomeerieux.

C. Measurement the levels of TNF-α and IFN-γ

A sandwich ELISA method (22) from the Chinese company (Melsin Medical) was utilized to estimate the level of inflammatory cytokines TNF-α and IFN-γ.

D. Statistical analysis

The mean and the value of the standard deviation (SD±) were assigned by utilizing the statistical program SPSS. The T-test at the probability level ($P \leq 0.001$) was applied to appoint the means for the patients group (PCOS affected people) compared to the control group (healthy people).

III. Results

Table (1) below clarified the mean ± standard deviation of the hormonal and immune parameters found in blood specimens collected from women of both patient and control groups:

TABLE I. Serum parameters' levels in studied groups.

Parameters	Mean ± SD		P-Value
	PCOS n=40	Control n=40	
LH (μIU/ml)	16.01±2.12	7.23±1.72	P ≤ 0.001
FSH (μIU/ml)	8.96±1.29	5.06±2.14	P ≤ 0.001
Testosterone (μIU/ml)	1.09±0.64	0.46±0.09	P ≤ 0.001
Insulin (μU/ml)	35.47±3.18	15.72±2.13	P ≤ 0.001
Resistin (ng/dl)	3.51±1.45	1.53±0.83	P ≤ 0.001
Copeptin (ng/ml)	6.31±0.58	3.26±0.37	P ≤ 0.001
(pg/mL) -γIFN	258.79±32.07	164.34±12.85	P ≤ 0.001
(ng/ml) TNF-α	98.11±4.51	60.81±4.93	P ≤ 0.001

The results of the present research displayed a prominent elevation in the FSH level in the serum of women suffered from PCOS compared with the healthiness individuals, at the

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$P \leq 0.001$ probability levels, as in the figure 1.

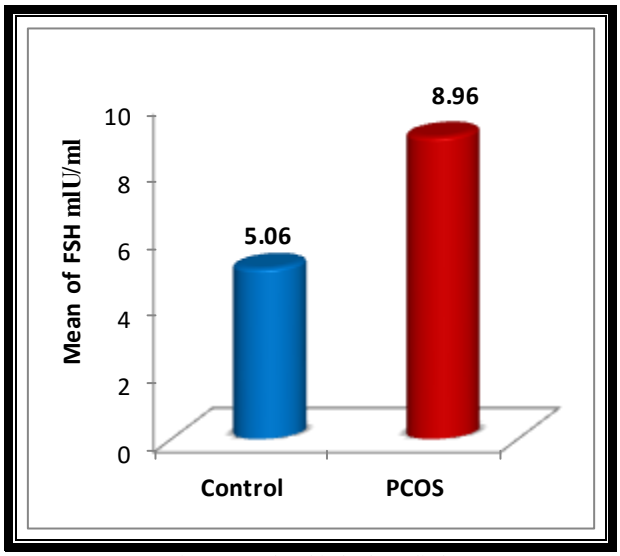

Fig. 1. FSH level in both studied groups.

Figure 2 presented the disparities in the serum levels of the LH in both examined groups. The quantity of testosterone in patient group showed a significant rising ($P \leq 0.001$).

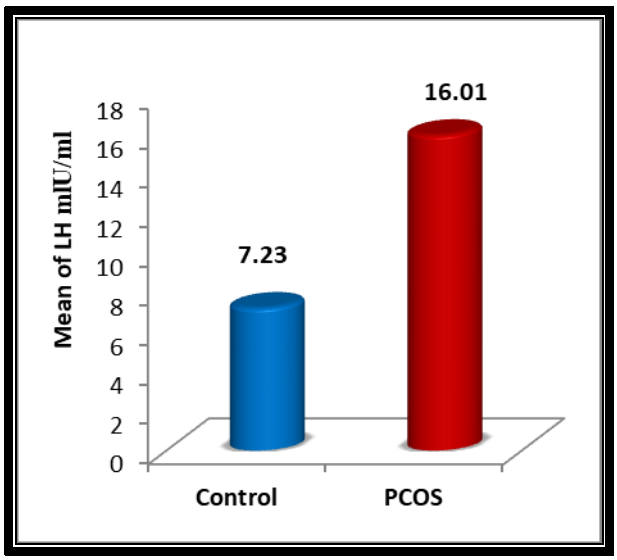

Fig. 2. LH level in both studied groups.

A comprehensive investigation in the both group exhibited that PCOS people had increased levels of testosterone hormone than control group at the $P \leq 0.001$probability level. The complete findings are revealed in figure 3.

The comparison between insulin levels in women with and without PCOS is demonstrated in figure 4. The PCOS group had statistically significantly elevated insulin levels than the healthy subjects ($P \leq 0.001$).

Figure 5 illustrated the level of resistin in the PCOS group, and compares the level to this hormone in the healthy persons. An SPSS indicated significant rise in the hormone level among the PCOS group ($P \leq 0.001$).

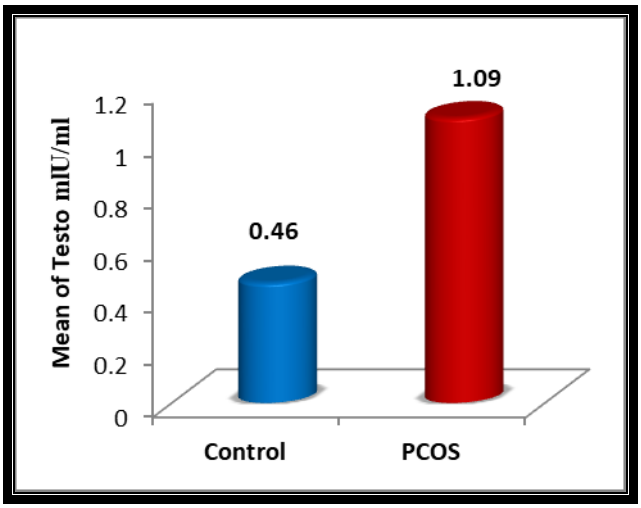

Fig. 3. Testosterone level in both studied groups.

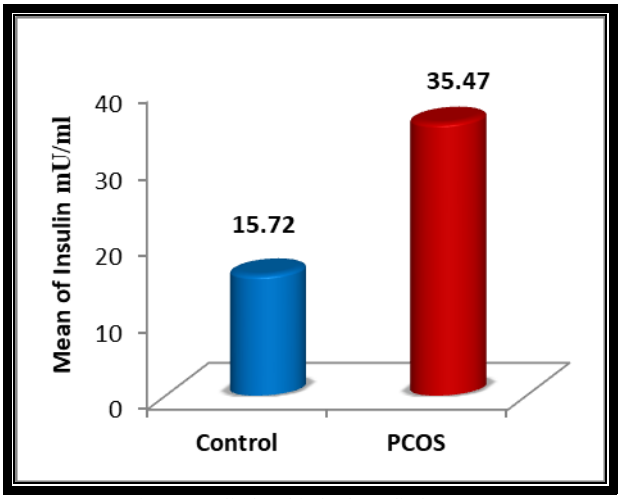

Fig. 4. Insulin level in both studied groups.

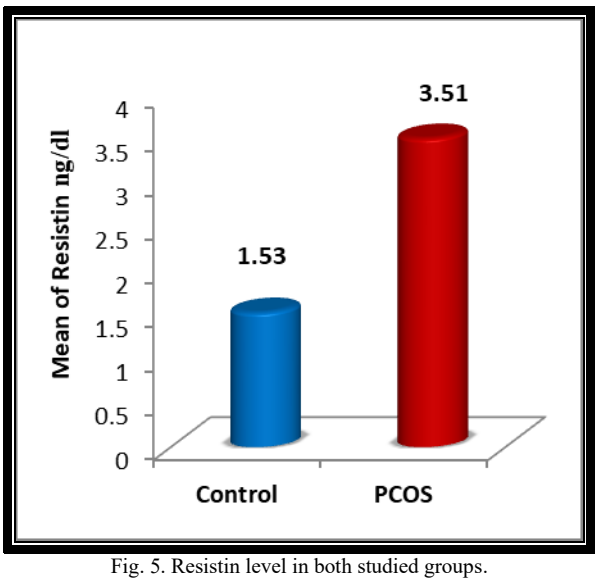

Fig. 5. Resistin level in both studied groups.

The correlation between PCOS and copeptin is displayed in figure 6. According to our findings, PCOS patients had a

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significant association with a high copeptin level; the variations were statistically significant (P ≤ 0.001).

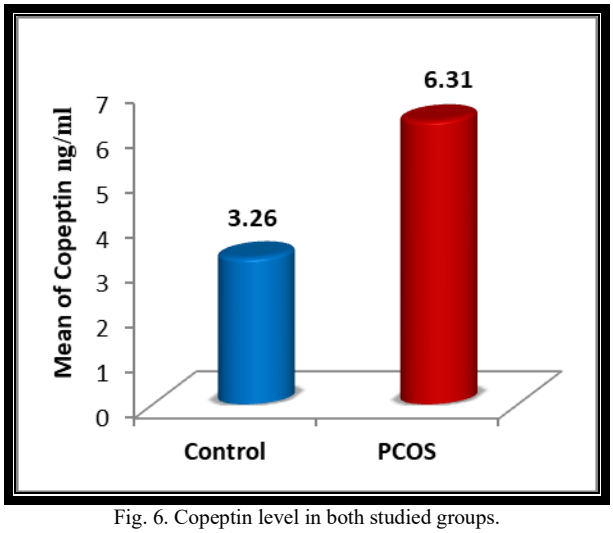

Fig. 6. Copeptin level in both studied groups.

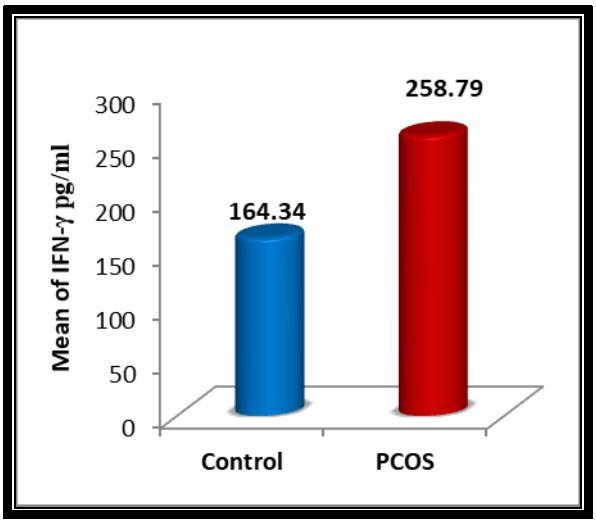

Fig. 7. IFN-γ level in both studied groups.

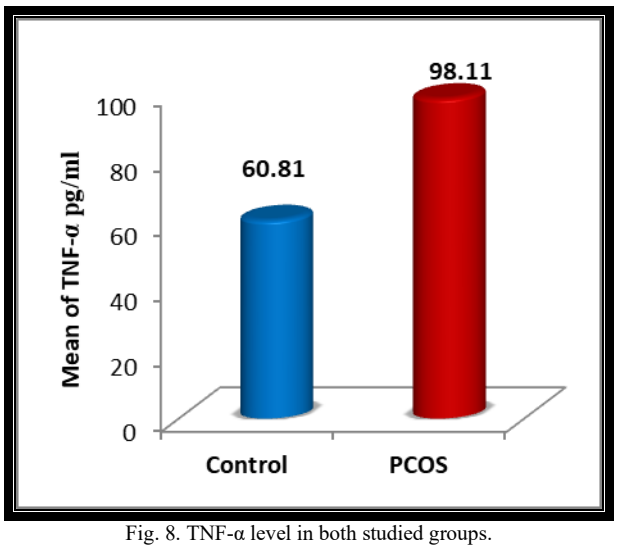

Fig. 8. TNF-α level in both studied groups.

Serum levels of IFN-γ were significantly (P ≤ 0.001) high in women with PCOS compared to control individuals. The results of difference are demonstrated in figure 7.

As revealed in figure 8, there was a significant difference in serum TNF-α level between the PCOS and control females, theTNF-α was significantly increased in patients had PCOS (P ≤ 0.001).

IV. Discussion

The PCOS is not definitely understood, but utmost information and reports reveal an excess of LH at the expense of FSH, androgen excess, insulin resistance, as well as hyperinsulinemia (23). Other concepts and descriptions indicate the correlation between theca cells in the ovary, which they are accelerated by LH and hyperandrogenism. Hyperinsulinemia and insulin resistance cause the aggregation of the hormone in the blood, leading to a raise in the releasing of androgens from the ovary, which consecutively causes destroy to the immature follicles and absence of ovulation. Extreme insulin precisely causes a decline in the level of sex hormones (SHBG) binding globuline, and this cause a raise in free sex hormones in the blood serum, particularly testicular lipotropic hormone, which causes problems and clinical signs represented by reduces of vascular system, hyperinsulinism, central obesity, and anxiety disorder glucose metabolism (24). The findings of the present investigation displayed a prominent raise in the levels of LH and FSH in the patients group in comparison with group that include control persons, which is in parallel with the findings of Dewailly et al. (25), Esmaeilinezhad et al. (26), and Genazzani et al. (27), and the reason for the elevation is due to the raise in pulse frequency produced by gonadal-stimulating hormones (GnRH) in women with PCOS, which leads to an elevation in LH production in correlation with the releasing of follicle-stimulating hormone (28). The reason for the heightened in the level of LH hormones may be FSH expresses a disorder in the ovary (a decline or raise in the reproductive gland) and may also result due to an disturbance in the nutrition or psychological pressures (29).

The reason for the raising FSH hormone may also be due to hormone promotion the eggs when its level raises overhead the standard level and thus leads to failure in ovarian action through its correlation with negative feedback of estrogen, as the pituitary gland produces elevated amounts of this hormone in women suffered from PCOS (30). The reason for the heightened may also be due to a decline in ovarian reserve or initial incapability, and as a result, the woman becomes increasingly less fertile (31). Furthermore, to the mentioned overhead, there are numerous reasons for elevated FSH, involving autoimmune diseases such as thyroid disorder, adrenergic gland dysfunction, chromosomal disorder, irregular contraceptive utilize, as well as destruction resulting from pelvic surgical operation, inflammatory pelvic illnesses and miscarriage (32, 33).

Regarding with testosterone hormone, its level exhibited important elevation in the group of PCOS patients in comparison with control group. The findings of the present study similar to the results of both AL-Akabi et al. (34) and

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Valdimarsdottir et al. (35), as the reason for the raise is due to extreme releasing of androgen by the ovaries, which is associated with reduced efficacy of egg development and embarrassment of their maturation, which leads to a diminish in the level of estrogen and progesterone secretion in women with PCOS (36).

Patients with PCOS have extreme androgenism in ovarian cells; this condition impedes the controlling of negative feedback of the estradiol and progesterone hormones, which stimulate the secretion of luteinizing hormone. Thus, extreme production of luteinizing hormone occur due to elevated secretion of GnRH from the hypothalamus, and raises the construction of testosterone in the theca cell in the ovary, and heightens its level in the blood. This is concordant with the present findings that revealed a high level of the LH hormone in women affected with PCOS (37).

Concerning with insulin hormone, it presented a significant raise in the serum of persons have PCOS in comparison with the normal persons. The same findings was specified by Tarkun et al. (38) and Goodarzi et al. (39), as the reason for the heighten is that resistant insulin may be a main and significant factor in the evolution of PCOS, and when it happens, the body attempts to recompense by secreting extra insulin and releasing it into the blood, leading to hyperinsulinemia in the body (40), which activates the ovaries to raise the secretion of the androgen hormone, which causes the consequence of signs related to PCOS. Increased testosterone also disturbs the secretion and growth of follicles and inhibits the normal ovulation mechanism. Insulin resistance may lead to increase in weight, and thus lead to aggravation of the signs (41). The interpretation of this situation is that obesity is correlated with the fat existing in the body, which leads to the secretion of extra insulin. Overall, utmost females with PCOS have a convinced degree of insulin resistance, abnormal concentrations of blood fats and weight gain (42). Insulin resistance and hyperinsulinemia are considered metabolic defects distinguishing of utmost women with PCOS, as hyperinsulinemia represents an image for hyperproduction of insulin itself, and hyperinsulinemia diminishes the globulin that links sex hormones in the liver, which causes circulating androgens staying free in high concentrations, which is one of the properties of PCOS. The cellular process of insulin resistance in PCOS remains unclear; it may be due to lack or feeble attachment of insulin to its receptors in blood cells and lessened lipolysis in adipocytes (43, 44). In the respect of resistin hormone, there was a prominent raise in the serum of patients suffer from PCOS in comparison with the persons of control group; the finding are in the line with the findings of both Vassault et al. (45) and Baldani et al. (46), as the reason for the elevation is due to production of resistin from blood cells and adipose tissue, which suppresses glucose tolerance and insulin sensitivity. The supreme significant cause of insulin resistance is fat cells because they decrease the number of insulin receptors, and since they release the hormone resistin, insulin resistance happens. Therefore, the weight loss leads to decline insulin resistance and boost blood sugar estimation (47). Due to the predominance of elevated concentrations of resistin in women commonly and patients have PCOS especially; it is proposed that resistin contributes directly or indirectly in stimulating ovarian hyperandrogenism in PCOS, as there is a variance in the level of resistin between the sexes in humans represented by increased resistin concentrations in females if compared with males (48). There is a significant adjacent correlation between obesity and PCOS, and it was lately pointed out in one investigation that women with PCOS have high concentrations of resistin in the blood circulation (49).

An association between resistin and androgen creation has been recognized in rats, where the elevation of testosterone production was detected when a dose of resistin was administered (50).

According to the results of current research work, it was noted that copeptin hormone significantly elevated in group involved individuals have PCOS in comparison with control group; the findings of both Karbek et al. (51) and Sarhat and Abbas (52) are in concordance with our findings, as women with PCOS considered an typical biological perfect that illuminates the correlation between hormonal design and cardiovascular risk outline includes a range of cardiovascular conditions, such as high blood pressure, insulin resistance, obesity, autonomic dysfunction, compromised cardiopulmonary function, and chronic low-grade inflammation. Women with PCOS have been reported to have a higher prevalence of cardiovascular disorders (53).

The increased level of testosterone in women suffer from insulin resistance means the lower efficiency of released insulin in response to heightened sugar, so the pancreas acts to produce higher quantities of insulin, leading to an elevation in the insulin percentage, which rises the risk of diabetes, and excessive levels of testosterone cause insulin resistance, high cholesterol and hypertension. Subsequently, the risk of heart disease rises, and this is the reason for the high level of copeptin in women with PCOS compared to those who do not have it (54). The association between copeptin and patients with PCOS is remain unclear. Thus, a research was achieved to explore the link between copeptin and the evolution of atherosclerosis in PCOS patients (55). In individuals with PCOS, higher serum copeptin levels may provide valuable prognostic information (56).

Furthermore, inflammatory cytokines including IFN-γ and TNF-α were demonstrated a significant raise in the patients' serum in comparison with healthy individuals' serum. This finding is in agreement with the finding of Wang et al. (57) for the level of IFN-γ. As for TNF-α, the findings comparable with the findings of both Shorakae et al. (58) and AL-Musawy et al. (59), and the reason for this is that inflammatory cytokines participate numerous biological functions such as the controlling of inflammatory processes, regulation of cell differentiation and tissue regeneration, and has relationship with follicle growth, ovulation, steroid genesis, atresia, and autolysis (60,61).

A raise in the level of TNF-α causes disorder in hormonal controlling, which has negative impacts on women’s fertility, through extreme presentation of sex steroid hormone receptors in the uterus and heightened aromatase action (62). The reason for the elevation in IFN-γ and TNF-α can be associated with

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inflammatory factors, as PCOS is described by the existence of low-grade chronic inflammation (63). The increased level of inflammatory cytokines in women with PCOS is a marker of immune dysfunction in females, as extra androgenism, which is an indication of this illness, has an effect on frequent formulas in the genes that encode TNF.

Adipose tissue also has relationship with the beginning of inflammation in PCOS, and inflammatory indicators are strictly positively associated with androgens, so that the raise in adipose tissue in females with PCOS is likely the reason for the increased level of proinflammatory cytokines is due to (64). Adipose tissue is a significant organ in androgen metabolism through the stimulation or inhibition of androgen enzymes, as elevated presentation of the chief androgen-activating enzyme type 1-androgen in subcutaneous adipose tissue in women with PCOS causes increased levels of testosterone and dihydrotestosterone (65).

V. CONCLUSION

It is concluded that suffering from PCOS leads to an elevation in the concentrations of FSH hormone, LH hormone, testosterone, resistin, copeptin, insulin, IFN-γ, and TNF-α and that the reason for the raise in the level of each parameter differs from the other; and this explains the multiple causes of the disease. Therefore, there is a need to conduct additional studies to clarify the reasons for the increase in the levels of these parameters or to show the relationship of these parameters together with the occurrence of PCOS.

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