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Correlation between levels of Cytokines and Different parameters in PCOS patients

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common causes of infertility that cause a massive health and economic costs around the world, it is identified as hyperandrogenism, chronic anovulation and metabolic disorder also chronic inflammation maybe one of the pathogenesis mechanisms in PCOS. due to the increased infertility rates and miscarriage cases in PCOS women and because of the great number of women infected by PCOS in Iraq and in city Basrah in particular, the current study has been designed to evaluate the correlation between proinflammatory cytokines with different biochemical and hormonal parameters in PCOS patients . This study was done in basrah city since 2018, serum samples were collected from 150 women (75 PCOS patients and 75 healthy women)), blood samples were collected from private gynecological clinic and Basra hospital for Maternity and Children ,relatives and friends, and the required data were collected by using the questionnaire. Then the concentrations of the study parameters were measured by using ELIZA and spectrophotometer methods, the procedure of kits followed accurately as demonstrated in the leaflet with the kit. The results showed a significant positive correlation were obtained between serum IL-18 with cortisol, and a significant positive correlation between serum IL-18 with insulin and TNF-α showed a significantly negative correlation with T4. In conclusion proinflammatory cytokines abnormalities may correlate with the levels of metabolic hormone parameters in PCOS patients.

Keywords

polycystic ovary syndrome, PCOS, TNF-α, IL-18.

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1. Introduction

PCOS, also known as Stein–Leventhal Syndrome or Hyperandrogenic Anovulation Syndrome, is one of the most common endocrine disorder in reproductive age women around the world, It is identified as hyperandrogenism and chronic anovulation. It was reported in several studies that the factors which are responsible for PCOS include (androgen excess, insulin excess, low grade inflammation and heredity). The exact cause is a mystery till date although many numbers of hypotheses and theories have been developed since the PCOS discover but many arguments still continues due to lack of clinical evidences [1,2,3]. Many studies suggest several factors which are involved in the PCOS development: Genetic factors such as genetic variations (mutations and polymorphisms), genes differential regulation, environmental factors such as adrenal dysfunction, drinking alcohol and plastic-packaged food [4]..However, the happening of PCOS varies across different populations, even when they are exposed to the same environmental factors, suggesting that heredity could influence the PCOS pathogenesis [5]. Also the chronic inflammation may be involved in the PCOS etiology unclear [6]. The proinflammatory cytokines have many appearances as a molecules with major roles in inflammatory responses Cytokines are essential components of a complete system of inflammatory and endocrine interactions [7]. Proinflammatory cytokines are essential for immunity foundation and fighting infections ,One of these cytokines is IL-18 which is secreted by inflammasomes under response to threats and is deleterious in sterile inflammation [8]. TNF- α is produced by several cell types such as monocytes and macrophages and plays a key role in the systemic inflammatory diseases pathogenesis like rheumatoid arthritis, autoimmune diseases and graft versus host disease [9,10,11,12]. The current study aims to determine the relationship between proinflammatory cytokines and the extent of their influence in some vital parameters in PCOS patients.

2. Methods

The present study included (75) PCOS patient group and (75) healthy women as control, the blood collection was performed during the luteal phase of the menstrual cycle. 10 ml of venues blood samples were collected in Gel/clot activator tubes and serum was separated by using centrifuge, 3500 rpm for 10minutes, the serum divided in to eppendorf tubes and kept frozen at -20 C° with avoiding multiple freezing. The analysis includes the using of ELIZA for measuring (estradiol, progesterone, prolactin, testosterone, LH, FSH, TSH, T3, T4,insulin ,cortisol), spectrophotometer kits for measuring (TG, VLDL-C, LDL-C and HDL-C), the procedure of kits followed as established in the kits leaflet. The statistical analysis are performed by using SPSS version 20 with $P<0.05$, $P\leq0.01$at a significant.

3. Results

Correlation of proinflammatory cytokines with reproductive hormones:

As shown in table(1), TNF-α and IL-18 did not correlate with any of the reproductive hormones. Not significant negative correlation were obtained between serum TNF-α with estradiol, testosterone, progesterone hormones , while had a non-significant positive correlation with prolactin, LH and FSH. Not significant negative correlation were obtained between serum IL-18 with estradiol, prolactin, progesterone, while had a non-significant positive correlation with testosterone, LH and FSH.

Table 1 - Correlation of TNF-α and IL-18 with the reproductive hormones.

Correlation	Estradiol	Prolactin	Testosterone	Progesterone	LH	FSH
TNF-α	-0.073	0.071	-0.120	-0.180	0.116	0.165
IL-18	-0.159	-0.085	0.035	-0.007	0.810	0.030
*Significant at the (P≤0.05) **significant at the (P≤0.01) (-): negative correlation						

Correlation between proinflammatory cytokines and metabolic hormones:

As shown in the table(2),a significant positive correlation were obtained between IL-18 with cortisol, and a significant positive correlation between serum IL-18 with insulin. However, IL-18 did not correlate with other parameters and recorded a non-significant positive correlation with TSH and a non-significant positive correlation with T3 and T4. While serum TNF-α showed a significantly negative correlation with T4, while showed a non- significant positive correlation with TSH, T3 and insulin, also a non-significant positive correlation with cortisol.

Table 2 - Correlation of TNF-α and IL-18 with the metabolic hormones.

Correlation	**TSH**	**T3**	**T4**	**Insulin**	**Cortisol**
TNF-α	**0.029**	**0.018**	**-0.344****	**0.254**	**0.250**
IL-18	**0.150**	**-0.180**	**-0.245**	**0.254***	**0.258***
***Significant at the (P≤0.05)** ****significant at the (P≤0.01)** **(-): negative correlation**					

Correlation between proinflammatory cytokines and lipid Profile:

All parameters of lipid profile which including cholesterol ,TG ,HDL-C , LDL-C and VLDL-C did not correlate with TNF-α and IL-18, table(3). Where a non-significant negative correlation were obtained between serum TNF-α and IL-18 with HDL-C, while TNF-α and IL-18 had a non-significant positive correlation with cholesterol ,TG, LDL-C and VLDL.

Table 3 - Correlation of TNF-α and IL-18 with the lipid profile.

Correlation	Cholesterol	TG	HDL-C	LDL-C	VLDL-C
TNF-α	0.079	0.123	-0.111	0.079	0.098
IL-18	0.013	0.153	-0.067	0.008	0.113
*Significant at the (P≤0.05) **significant at the (P≤0.01) (-): negative correlation					

4. Discussion

Our results showed that there is a significant possitive correlation were obtained between IL-18 and cortisol , and a significant positive correlation between IL-18 and insulin. While TNF-α showed a significantly negative correlation with T4 only. Cortisol increases neuronal atrophy via early reactive oxygen species stimulation. Cortisol also initially increases IL-18 and was found that IL-18 gene expression can be changed during stress and consequently could be used as an indicator of stress [13,14].. The biological significance of positive correlations between high levels of cortisol and IL-8 in present unclear, it may possibly suggest that some immunopathogenic mechanisms may be operating [15]. Cortisol involves in the genes regulation of proinflammatory via signal transduction by cortisol

receptor. These receptor signaling can play a double role in the immune response regulation. Glucocorticoids cause quick movement of amino acids and fats from their cellular stores, making them available for energy and synthesis of other compounds, needed by body tissues. Damaged tissues that are depleted of proteins can use these amino acids to form new proteins that are essential to the cells lives [16, 17]. Raised IL-18 in plasma found in many conditions sharing insulin resistance as a common feature [18]. Chronic inflammatory are related with the high levels of a number of cytokines like IL-18, which appears to be directly involved with insulin resistance and metabolic syndrome and it is an vital marker of cardiovascular disease [19]. PCOS and obesity induce an increase levels of serum IL-18, which are also related with several indexes of global and visceral adiposity and with insulin resistance. Serum IL-18 levels are increased by PCOS and obesity independently and the alternation in the production of proinflammatory leads to increased infiltration of immune cell and stimulation of a macrophage phenotype exchange in visceral adipose tissue in patients with Insulin resistance [20,21].The increased level of IL-18 found in obese women correlated with insulin resistance [22]. Inflammatory cytokines like IL-18 operate via paracrine and autocrine mechanisms to induce insulin resistance in the adipose tissue of PCOS women and L-18 might be involved in the insulin resistance pathogenesis, explaining the increase in PCOS patients who are insulin resistant [23,24]. In conclusion there is a significant correlation between proinflammatory cytokines and some of metabolic hormones in PCOS patients and it is better to manner other researches to observe the effect of other immunological parameters on other parameters in PCOS patients.

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