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Assessment of Monocyte Chemoattractant Protein-1 and Fertility Hormones in Iraqi Women with Polycystic Ovarian Syndrome

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Abstract

Polycystic ovarian syndrome (PCOS) is a well-known endocrinopathy and one of the most frequent endocrine-reproductive-metabolic syndromes in women, which can result in reduced fertility. While the actual cause is unknown, PCOS is regarded as a complicated genetic characteristic with a great degree of variability. Moreover, hormones and immune cells, including both innate and acquired immune cells, are thought to interact in PCOS. Chronic low-grade inflammation raises the risk of autoimmune disease. The study's purpose is to investigate the chemokine monocyte chemoattractant protein-1 (MCP-1) and fertility hormones in samples of women patients with polycystic ovary syndrome (PCOS) in the City of Medicine. Sixty PCOS women comprise 30 healthy control women; their average age was 20–40 years, and their weight ranged from 60 to 100 kg. The results showed an increase in the level of MCP1 in PCOS patients, but this increase was not significant ($P<0.05$), which was not influenced by BMI or fertility hormones. As well as elevated fertility hormones, this study, when compared to controls as well as patients with PCOS, showed a significant increase in the level of testosterone (14.63 ±2.30 nmol/L) while in control women (0.627 ±0.04), LH hormone in patients and control group (6.54 ±0.51 mIU/mL), and 2.93 ±0.18, respectively. Prolactin hormone was increased in PCOS patients (16.27 ±1.25 ng/mL) when compared to the control group \ (12.85 ±0.62). There was no significant difference in FSH hormone in women with PCOS (5.27 ±0.28 mIU/mL) compared with the control group (5.59 ±0.18).

Keywords: PCOS, MCP-1, Testosterone, Prolactin, LH, FSH.

1. Introduction

Polycystic ovarian syndrome (PCOS) is a hormonal condition that is linked with a number of metabolic disorders, including impaired insulin resistance and glucose metabolism. PCOS is also linked to an increased chance of developing type 2 diabetes, dyslipidemia, and cardiovascular disorders such as hypertension and atherosclerosis [1]. PCOS clinical signs include clinical or biochemical hyperandrogenism, polycystic ovaries on ultrasonography, ovulatory dysfunction,

and obesity [2]. PCOS affects 6%–10% of reproductive-age women and is the most common cause of infertility [3]. There is evidence that PCOS is also a proinflammatory condition, with chronic low-grade inflammation and elevated levels of many inflammatory cytokines linked to insulin resistance (IR). Diabetes mellitus and obesity have also been linked to the condition [4].

The monocyte chemoattractant protein-1 (MCP-1) is a secretory chemokine encoded by the CCL2 gene on chromosome 17. It has 76 amino acids and is a member of the C-C chemokine family [1]. It has been found that macrophages and monocytes are the primary producers. However, MCP-1 can be secreted by non-immune cells such as fibroblasts, endothelial, epithelial, and smooth muscle cells [1]. It has an important role in T-lymphocyte differentiation and monocyte chemotaxis, with a critical role in the pathogenesis of numerous diseases [5]. The receptor of MCP-1, chemokine receptor 2 (CCR2), is expressed on a variety of ovarian cell types and serves critical regulatory roles in a variety of ovarian functions such as folliculogenesis, luteolysis, and ovulation [6]. In human reproduction, it has a crucial role in immunological detection, pregnancy maintenance, parturition, and acceptance of the fetal allograft [7]. Several studies have discovered a correlation between PCOS as a cause of infertility and elevated levels of proinflammatory cytokines and chemokines such as MCP-1 [8]. The levels of MCP-1, on the other hand, are elevated in obesity and abnormally increased, eventually resulting in the recruitment of tissue monocytes and, as a result, contributing to the adipose tissue's chronic low-grade condition [9]. Obesity can have a negative impact on fertility. Obesity at a young age causes the development of menstrual abnormalities in women. and in women, a BMI greater than 30 kg/m2 may also raise the chance of miscarriage and affect the results of assisted reproduction operations and pregnancy [10].

Testosterone is an important yet enigmatic female hormone. It serves as an androgen directly as well as being an essential precursor for oestradiol production [11]. In women, testosterone has physiological effects on both reproductive and nonreproductive tissues. Testosterone levels are significantly related to sexual function in women [12]. The androstenedione and dehydroepiandrosterone (DHEA), which are pre-androgens, are synthesized primarily in the adrenal, gonad, and peripheral tissues, whereas testosterone synthesis occurs mostly in the ovaries as well as adipose tissue and other peripheral tissues. Also, increased serum testosterone levels are linked to insulin resistance, obesity, particularly abdominal obesity, and increased glucose tolerance tests. As a result of increased androgen and insulin resistance in PCOS patients, testosterone production in the ovaries rises.

Luteinizing Hormone (LH) is a gonadotropin that is secreted from the anterior pituitary gland as a result of high-frequency gonadotropin-releasing hormone (GnRH) release. LH promotes ovulation, prepares for fertilized oocyte uterine implantation, and stimulates ovarian progesterone production via theca and luteinized granulosa cells [13]. In women with PCOS, a change in GnRH secretion has been seen, leading to an increase in luteinizing hormone (LH) secretion with normal follicle-stimulating hormone (FSH) secretion [14]. As a result of high LH levels, ovulation does not occur in polycystic ovarian disease patients [15]. The ovary is the primary androgen source in PCOS, and adrenal hyperandrogenism may be caused by a combination of factors such as altered cortisol metabolism, hyperinsulinemia, and increased ovarian steroid production. [16]. The prolactin hormone (PRH) is primarily synthesized and produced by lactotroph cells of the anterior pituitary gland. It induces the proliferation and differentiation of mammary cells, which is necessary for lactation. The prolactin receptor (PRL R) is widely expressed; however, there is

tissue-specific variation in expression patterns. There are several functions of prolactin, both physiological (lactation, reproduction, metabolism, growth, behavior, and electrolyte transport) and pathological (carcinogenesis and immunity) [17]. PRL serum levels have been observed to be variable and inconsistent in PCOS. As a result, some studies have found that anovulatory women with PCOS have greater serum levels of PRL than controls [18], while others have discovered evidence of dysregulation [19], or PRL levels comparable to controls [20]. Follicle stimulating hormone (FSH) is a hormone secreted by the anterior pituitary gland in response to hypothalamic gonadotropin-releasing hormone (GnRH). [21], is involved in sexual development and reproduction,specifically in women, and is involved in follicular development and Estrogen production [22]. A disruption in the gonadotropin-releasing hormone (GnRH) secretion pattern causes a relative increase in LH to FSH release. In non-PCOS women, the ratio of LH to FSH is typically between 1 and 2. This ratio is reversed in women with polycystic ovarian disorder, and it can reach as high as 2 or 3 [23]. Continuous use of GnRH lowers the anterior pituitary's secretion of FSH and LH, which suppresses ovulation and estrogen formation in women. FSH production is reduced by negative feedback from estrogen levels [24].

2. Materials and Methods

The study was an investigation of a sample of PCOS patients in infertility consultations in Baghdad, Medical City. Sixty PCOS women comprise 30 non-PCOS women. The average age of patients and control groups was 20–40 years. The study was approved by the University of Baghdad, College of Sciences, Ethics Approval No. (Ref.: CSEC/1022/0120) on October 5, 2022. Written consent was obtained before participating in this study from all subjects, and all parameters were assessed from samples of blood (serum) from patients and control groups. The blood sample was pulled from PCOS and non-PCOS individuals at the early follicular phase. The diagnosis of PCOS was based on the 2003 Rotterdam criteria and the 2006 Androgen Excess and PCOS Society [25] by doctors in infertility consultation in Baghdad Medical City during the period from October 2022 to January 2023. Laboratory tests included fertility hormones (testosterone, LH, prolactin, and FSH) and chemokines (MCP 1). Five ml of venous blood was collected from study subjects, and serum was kept at -20 °C until used. The body mass index (BMI) of the studied subjects was calculated using the following equation: weight (kg) divided by height (m2) squared.

2.1. Measurement of parameters

The chemokine (MCP 1) value was measured by ELISA technique according to the kit procedure (cat no. ELK5252, to company ELK Biotechnology) of Chinese origin. Hormones (testosterone, LH, prolactin, and FSH) were measured by an American Abbott Architect plus i1000SR device based on ECLIA technology using a special kit for each parameter. Also, BMI was measured according to the equation of weight divided by height squared.

2.3. Statistical Analysis

The Statistical Analysis System-SAS (2018) program was used to detect the effect of different factors on study parameters.

3. Results

According to the current study, there is no significant difference between BMI and MCP1 (Correlation coefficient-r 0.06), no correlation was found between waist-hip ratio (WHR), and

there is also no significant difference between fertility hormones (Testosterone, LH, Prolactin and FSH) and MCP1, whose correlation coefficients were (0.02, 0.04, 0.07, and 0.01, respectively) (**Table 1**). The monocyte chemoattractant protein-1 (MCP-1) increased in PCOS patients (154.53 ± 14.92) but was not significant when compared to the control (123.5 ± 11.91).

In our current study, testosterone results indicated a significant (P<0.05) increase in the PCO group (14.63 ±2.30 nmol/L) compared to the control (0.627 ±0.04 nmol/L). LH levels showed a significant (P<0.05) increase in the PCOS group compared to the control (6.54 ±0.51 mIU/mL) and (2.93 ±0.18 mIU/mL), respectively. Prolactin Hormone was increased in PCOS patients (16.27 ±1.25 ng/mL) when compared to the control group (12.85 ±0.62). The level of FSH showed no significant difference between PCOS and the control (5.27 ±0.28 mIU/ml) and (5.59 ±0.18 mIU/ml), respectively (**Table 2**).

Table 1. Correlation coefficient between MCP-1 and others parameters.

Parameters	**Correlation coefficient-r MCP 1**
Age	-0.009 NS
BMI	0.06 NS
Waist hips Ratio	0.09 NS
Duration of pco	-0.03 NS
Duration of treatment	0.10 NS
Number of children	0.15 NS
FSH	0.04 NS
LH	0.02 NS
Prolactin	0.07 NS
Testosterone	0.01 NS
* (P≤0.05), ** (P≤0.01), NS: Non-Significant.	

Table 2. Comparison between PCOS and non PCOS groups in MCP 1 and Hormones levels

Group	**Mean ± SE**				
	FSH (mIU/ mL)	**LH (mIU/ mL)**	**Prolactin (ng/mL)**	**Testosterone (nmol/ L)**	**MCP 1 (pg/mL)**
patients	5.27 ±0.28	6.54 ±0.51	16.27 ±1.25	14.63 ±2.30	154.53 ±14.92
control	5.59 ±0.18	2.93 ±0.18	12.85 ±0.62	0.627 ±0.04	123.5 ±11.91
T-test	0.819 NS	1.441 **	3.562 NS	6.334 **	44.445 NS
P-value	0.434	0.0011	0.0602	0.0011	0.0642
** (P≤0.01), NS: Non-Significant.					

4. Discussion

Polycystic ovarian syndrome is a frequent reproductive condition that can lead to infertility and has serious social, medical, and economic consequences for individuals. Its reasons are still unclear. Several studies have been published in order to investigate the levels of MCP-1 in PCOS women. According to some studies, circulating MCP-1 levels in PCOS patients are much higher than in non-PCOS individuals [26]. However, other investigations have found no significant differences in levels of MCP-1 between non-PCOS and PCOS women [27, 28].

In our current study, MCP-1 in women with PCOS (154.53 ± 14.92) was higher than in women without PCOS (123.5 ± 11.91), but did not reach the degree of probability (0.05). MCP1, regarded as a chemotactic cytokine, regulates the placement of leukocytes and monocytes in tissues during inflammation and infection response [29]. The interaction of MCP-1 with its receptor CCR2 is critical in inflammation and inflammation-related diseases, and MCP-1-CCR2 binding contributes to the innate immune response by attracting monocytes to the sites of inflammation. [5]. MCP-1 may be involved in ovulation, follicular growth, and the formation and regression of the corpus luteum. The authors hypothesized that increased levels of MCP-1 may have an effect on follicular cell function and oocyte quality by causing an intracellular proinflammatory state via MCP-1 receptor activation or an influx of monocytes into the ovary [8]. It has been linked to the development of a variety of disease disorders, both directly and indirectly, including the Corona virus, cancer, neuroinflammatory disorders, cardiovascular diseases, rheumatoid arthritis, insulin resistance, and respiratory tract infection [30].

In the present study, we conducted analysis based on patients' BMI (<25 and ≥25). The results of the study showed no significant relationship between MCP1 and either the non-obese or obese groups. The small size of the included studies is a limitation of this study, which will influence the analysis results. Also, there were no significant associations between MCP1 and fertility hormones; the lack of significant associations between these hormones and MCP1 may indicate that changes in these hormones alone are insufficient to generate any corresponding changes in chemoattractant cytokine activity.

Luteinizing Hormone (LH) was higher in patients' group (6.54 ±0.51 mIU/ml) than control group (2.93 ±0.18 mIU/ml). The results of the current study were similar to many previous studies which reported that increased levels of LH hormone are mostly due to GnRH dysfunction. Disruptions in the hypothalamic-pituitary-ovarian or adrenal axis have been implicated in the etiology of polycystic ovarian syndrome. Anomalies in the gonadotrophin-releasing hormone (GnRH) secretion mechanism cause a relative increase in LH to FSH release [23].

LH is responsible for ovulation (releasing eggs from the ovary). The aberrant release of ovarian androstenedione appears to be an inherent feature of PCOS theca/granulose cells. Chronic LH stimulation in PCOS causes the theca compartment to secrete androgens continuously [31].

Prolactin Hormone showed no significant increase in the PCOS group compared to non-PCOS individuals. High blood PRL levels above the normal range can directly block the production and release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, as well as limit GnRH secretion to the portal vein [32].

[33] were proposed that the stimulatory effects of recombinant human follicle-stimulating hormone (r-Hfsh) increased the capacity for estradiol (E2) generation in women with PCOS, which may lead to an increase in PRL. Since Dopamine inhibits the secretion of pituitary prolactin, excessive luteinizing hormone (LH) and prolactin (PRL) production in PCOS women may be connected to low dopamine (DA) hypothalamic tone. The reduced dopamine levels result in hyperprolactinemia [34].

Testosterone levels in the current research were elevated significantly (P<0.05) in the PCOS group compared to the control group, and this rise may be due to obesity, particularly abdominal obesity, and insulin resistance, which are linked to elevated blood testosterone levels. As a result

of increased androgen and insulin resistance in PCOS patients, testosterone production in the ovaries rises [35]. Also, this increase mostly results from the inherent alteration of ovarian theca cells, characterized by a disruption in the expression and/or activity of essential steroidogenic enzymes [36].

5. Conclusions

In the current study, we concluded that MCP1 increases in patients with PCOS, but this increase is not significant. It was not influenced by BMI, waist-hip ratio, or fertility hormones, as well as elevated fertility hormones, as shown in this study.

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Conflict of Interest

There are no conflicts of interest.

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Ethical Clearance

The study was approved by the University of Baghdad, College of Sciences, Ethics Approval No. (Ref.: CSEC/1022/0120) on October 5, 2022.

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