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Polycystic ovary syndrome and inflammatory factors: Possible role of diet

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrinological disorder in women of reproductive age. Several studies have shown that inflammation factors have a crucial role in the function of the ovary as ovarian dysfunction can be caused by an imbalance of pro-inflammatory cytokines. Other studies have shown that PCOS patients have high levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), c-reactive protein (CRP(, interleukin-6) IL-6(, and interleukin-8 (IL-8). Inflammation can be caused by a variety of factors including diet, and diet-induced inflammation can contribute to insulin resistance and atherogenesis as well as ovulation problems in women with PCOS. It is possible to calculate the components of diet and inflammation caused by diet using many different indices. The Healthy Eating Index (HEI) and Dietary Inflammatory Index (DII) are relatively new indices. As HEI is the overall health index for diet and DII indicates the inflammatory index of the diet, it is possible that a person's diet can be generally healthy but has a high risk of inflammation, so these two indices should be considered together. Furthermore, dietary management of PCOS patients can reduce hyperinsulinemia, hyperandrogenism, and inflammation, which in turn helps to control and reduce disease complications such as infertility.

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1.Introduction

Infertility is a worldwide health issue that significantly impacts women of reproductive age (1). Infertility is a condition characterized by the absence of clinical pregnancy after 12 months of regular and unprotected intercourse or by impairment of a person's ability to reproduce, either individually or with a partner. According to the latest definition of the World Health Organization, infertility is a disease that causes disability as functional impairment (2). More than 186 million people worldwide suffer from infertility, the majority of whom are from developing countries (3). It has been reported that infertility in Iran has an increasing trend (4). Among the various diseases leading to infertility in women, the second most common cause is polycystic ovary syndrome (PCOS) (5). PCOS is one of the main health challenges worldwide, and is known as the most common endocrine disorder in women of reproductive age (6). This syndrome is a multifactorial disorder and is characterized by

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a combination of clinical (absence of ovulation and hyperandrogenism), biochemical (excessive concentration of androgen and luteinizing hormone), and morphological features of the ovary (polycystic ovary) (7). The presence of at last two of these disorders is the criterion for diagnosing this syndrome (8). According to the Rotterdam Criteria, its prevalence is reported to be around 10% worldwide (9). According to the same criteria, this syndrome affects 19.5% of Iranian women (6).

The most common symptoms in women with PCOS include ovulation disorders, menstrual disorders, infertility, oligomenorrhea, and some clinical manifestations of alopecia, acne, oily skin, and hirsutism (6). This syndrome is the most common cause of infertility without ovulation in about 75% of cases (7). Also, this syndrome is related to complications such as cardiovascular diseases, and endometrial cancer due to excess estrogen, psychological disorders, dyslipidemia, metabolic syndrome, type 2 diabetes, insulin resistance, and inflammation (8).

Although ovarian, neuroendocrine, and metabolic disorders play a key role in the pathophysiology of PCOS, the association of PCOS with hyperandrogenism, insulin resistance, and inflammation is not well-known (10).

2. Inflammation in PCOS

Several studies have shown that maintaining ovarian function requires a balance between inflammatory factors. Hence, an imbalance of pro-inflammatory cytokines can lead to ovarian dysfunction (11). Inflammatory markers are highly correlated with circulating androgens (12, 13).

Either the hyperandrogenemia-preactivated monocyte cell accounts for hyperglycemia-induced inflammation or glucose-stimulated inflammation may increase ovarian androgen production in PCOS patients. Data suggest that it is possible that both mechanisms may occur (14).

Furthermore, the genetic basis of chronic inflammation in PCOS women has not been strongly substantiated (15,16,17). In obese women with PCOS, unlike non-obese women, circulating androgens have a limited effect on lipolysis. On the other hand, in this population, subcutaneous adipose tissue is resistant to catecholamine, which prevents the effective induction of hormone-sensitive lipase activity (18). Several studies have shown elevated levels of pro-inflammatory cytokines such as TNF-α, CRP, IL-6, and IL-8 (19).

2.1 Tumor necrosis factor-alpha (TNF-α)

The inflammatory cytokine TNF-α stimulates and propagates follicular theca cells. It is also involved in regulating the normal activities of the ovaries during the follicular and lutein growth stages. TNF-α is present in macrophages, oocytes, granulosa cells, and theca cells (20). This cytokine inhibits the phosphorylation of the insulin receptor by tyrosine kinase, which is a contributor to obesity-related insulin resistance (21). Additionally, it decreases the activity of glucose transporter type 4 (GLUT-4), which affects glucose transport (22).

There is an association between this cytokine and insulin resistance in PCOS patients. Also, according to studies, TNF-α is related to hyperandrogenism (10). Research conducted on mice suggests that high testosterone levels in women with PCOS can increase TNF-α synthesis, which helps to increase androstenedione and decrease estradiol (23).

According to some studies, increased levels of TNF-α have been seen in women with PCOS compared to healthy women (24). In the study of Gao et al., the elevated level of TNF-α in patients with PCOS, without taking into account the body mass index (BMI), can increase the production of androgens and contribute to insulin resistance (25).

2.2 Interleukin-6 (IL-6)

IL-6 is another pro-inflammatory cytokine that plays a major role in acute and chronic inflammation. Moreover, it is involved in regulating the synthesis of CRP in the liver (26). An endocrine cytokine, IL-6, is produced by adipose tissue cells and is involved in several metabolic processes, including those related to glucose and lipid metabolism (27). IL-6 cytokine levels are associated with insulin resistance (10). Recent studies have shown the correlation of serum IL-6 with insulin action (28).

An in vitro study of rats found that IL-6 inhibited glucose-stimulated insulin release from the pancreatic islets of Langerhans cells. The cytokine also exerts its effect on insulin resistance by stimulating the production of an adrenocorticotropin-releasing hormone (ACTH) and growth hormone in the brain (28).

In addition, obesity is associated with a high level of cytokine IL-6 (10). The findings of Hotamislighil's study indicate that IL-6 secretion is correlated with adipocyte size. Therefore, following weight gain and high BMI, IL-6 levels are elevated (29). In addition, obesity increases insulin resistance and increases the risk of PCOS. Studies show that IL-6 levels are associated with IR and androgen production as well (30). In a recently conducted study, increased levels of IL-6 were found to be associated with ovarian dysfunction (10).

2.3 C-reactive protein (CRP)

An acute-phase protein, CRP, is produced by

the liver as a response to IL-6 and TNF-α (31). As a marker of low-grade chronic inflammation, CRP can activate the complement system (32). The presence of high levels of this cytokine is associated with insulin resistance, visceral fat accumulation, metabolic syndrome, and type 2 diabetes (31).

CRP and body weight increase in obese women with PCOS (14). Testosterone as an androgenic hormone is known to stimulate catecholamine-induced hormone-sensitive lipase activation, which limits adipose tissue expansion (33). Androgen suppression of lipolysis is reduced and may explain progressive weight gain in obese women with PCOS taking GnRH agonists. On the other hand, circulating free fatty acids are reduced in obese women with PCOS during GnRH agonist administration and its subsequent effect on the CRP level (34).

On the other hand, there is an inverse relationship between adiponectin and CRP (35). Adiponectin has insulin-sensitizing, anti-atherogenic, and anti-inflammatory properties (35).

Based on some studies, an increase in CRP, IL-6, and TNF-α and a decrease in adiponectin have been reported in obese and non-obese women with PCOS (31). In women with PCOS, an increase in inflammation may affect folliculogenesis and ovulation, resulting in infertility (36).

3.The role of diet-induced inflammation in PCOS

Several pro-inflammatory cytokines are produced by tissue mononuclear cells (MNCs) and macrophages in response to inflammation (37). During glycolysis, circulating MNCs utilize glucose for mitochondrial respiration. In the process of generating nicotinamide adenine dinucleotide phosphate (NADPH), some glucose is diverted toward the hexose monophosphate shunt (38).

P47phox, a cytosolic component, is translocated to the membrane to activate membrane-bound NADPH oxidase (37). By oxidizing NADPH, superoxide is produced, which is a reactive oxygen species that induces oxidative stress (37).

In turn, this dissociation activates the nuclear factor kappa B (NF-kB) transcription factor, which in turn activates inhibitory protein. When NF-kB is activated, it translocates to the nucleus and promotes the transcription of TNF-α and IL-6 genes (37). As a result of the mentioned mechanism, glucose consumption in PCOS results in an inflammatory response that leads to increased oxidative stress. Consequently, diet-induced inflammation causes insulin resistance and atherogenesis in women with PCOS, followed by ovulation disorders (37).

To prevent or reduce the complications of PCOS, it seems necessary to investigate the various types of diets and their association with the increase of inflammatory markers. There have been numerous studies conducted on dietary indicators concerning inflammation, and a few are outlined below.

In the study of Lin et al. in 2019, based on the latest international guidelines, nutritional behaviors, and physical activity were examined in women with PCOS. The study involved eighty participants with PCOS and forty-four participants in the control group. According to the study, carbohydrate, fat, and protein intakes were within an acceptable range for women with PCOS. However, the intakes of vitamin D, B9, fiber, and sodium were insufficient when compared to the recommended levels.

The physical activity of these patients followed the standards of the United States. Dietary intake, diet quality, and physical activity levels did not differ between the groups. Therefore, diet and physical activity levels are comparable between women with and without PCOS (39).

A study conducted by Panje Shahin et al. in 2020 examined the relationship between diet and PCOS. One hundred and eight patients with PCOS and one hundred and eight patients as part of the control group participated in this case-control study. People were asked to complete the 168-item Food Frequency Questionnaire (FFQ) questionnaire to assess their usual diet and the relationship between different diets and PCOS. According to the study results, the consumption of food with a high glycemic index and high-fat food has an increasing effect on PCOS, while moderate adherence to anti-inflammatory diets has a decreasing effect (40).

In 2021, Wang et al. investigated dietary intake, eating behavior, physical activity level, and quality of life among infertile and obese women with PCOS (n=171) and those without PCOS (n=321). There were no differences in QOL scores (physical and mental) between women with PCOS and those without. Also, there were no differences between infertile women with PCOS and obesity and infertile women without PCOS and obesity in terms of their eating habits and quality of life (41).

In a study conducted by Mizgir et al. in 2021, the relationship between the intake of specific nutrients, inflammation, and oxidative stress was examined in girls with PCOS. Fifty-nine subjects with PCOS (14-18 years old) were divided into two groups: overweight and obese (22 subjects) and normal weight (37 subjects). The nutritional status of the subjects was assessed through the analysis of their food records for three days. The indicators studied included total antioxidant capacity, malondialdehyde (MDA), CRP, TNF-α, interleukin-1 (IL-1), and IL6. According to this study, a decrease in vegetable protein consumption and low carbohydrates in the diet correlated with an increase in inflammation and oxidative stress in overweight and obese individuals.

Moreover, it was indicated that cholesterol intake may increase inflammation in lean PCOS girls. Similarly, reducing fiber intake and protein intake may increase inflammation. This study did not consider environmental factors such as smoking and stress, which may have an impact on inflammation and oxidative stress. Also, substances such as flavones and trans fatty acids were not considered when calculating the nutritional value of foods (42).

An important component of treatment for PCOS is a healthy lifestyle intervention, including a healthy diet, which is one of the most important methods of treating this disease (43). The Dietary Inflammatory Index (DII) and Healthy Eating Index (HEI) are new indexes for the evaluation of quality of diet (7).

DII is designed to assess the inflammatory potential of a diet by evaluating the anti-inflammatory and inflammatory properties of a variety of food components. It consists of macronutrients, vitamins, minerals, flavonoids, alcohol, and other specific food compounds. For determining the level of inflammation caused by diet, this index can be very useful (44). According to the studies conducted to date, people with metabolic and inflammatory disorders also have higher DII values (42).

Besides the DII index, the HEI is also useful for evaluating dietary patterns (45). Based on the 1995 Food Pyramid and Dietary Guidelines, this index was designed to determine the overall quality of diets and to determine their compatibility (45). Until now, only two articles have examined the relationship between these two indicators and PCOS.

Hosseini et al. investigated the relationship between HEI and PCOS in 2017. A total of 297 women were included in this case-control study. Statistical regression analysis of the results of this study revealed that people with higher HEI index scores had a 50% lower prevalence of PCOS. Despite controlling various variables, the remaining confounders were not removed because they were unknown or unmeasurable (7).

In 2021, Zirk Sharkesh et al. investigated the relationship between DII and PCOS. In this case-control study, 291 non-PCOS patients were compared with 203 patients with PCOS (case group). To calculate DII, thirty-six macronutrients and micronutrients were extracted from the FFQ.

PCOS patients had higher weights, BMIs, waist circumferences, and less physical activity than healthy individuals. Compared to the control group, PCOS subjects consumed more carbohydrates, cholesterol, and refined grains, but fewer unsaturated fatty acids, fiber, vitamin B12, vitamin D, and dairy products. According to this study, a high DII score is associated with a greater likelihood of developing PCOS (46).

In previous studies, the HEI and DII were examined separately. However, it has been argued that it is more practical to examine and compare them simultaneously instead of examining them separately. The reason is that the HEI indicators represent the health indices for the entire diet and not inflammation indices while the DII only measures inflammation indices, and a healthy diet may have a high risk of inflammation, so the two indices should be measured at the same time.

Conclusion

PCOS is one of the most common disorders affecting women of reproductive age. It is widely accepted that inflammation and an increase in inflammatory factors are key factors in disease pathophysiology. There is a direct link between inflammation, excessive androgen production, and ovarian dysfunction. Additionally, obesity and insulin resistance can increase PCOS's inflammatory burden, resulting in a long-term inflammatory response. In some studies, dietary-induced inflammation has been identified as a key factor in the development of PCOS.

So, these patients should be simultaneously evaluated using the HEI and DII indices. Recent studies have shown that PCOS patients with higher dietary DII and lower HEI scores produce more pro-inflammatory cytokines. It is possible to control and reduce the complications of PCOS through dietary management. Adherence to a healthy diet with lower inflammation risk will result in reduced levels of insulin, androgens, inflammation, and other complications of PCOS.

Conflict of interest

No Conflicts of Interest.

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