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Review

The Role of Dietary Supplements and Lifestyle Changes in Reducing Polycystic Ovary Syndrome Complications

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous disease characterized by metabolic and endocrine disorders, especially in women of reproductive age, and the criteria of "oligo-ovulation or anovulation", "clinical or biochemical findings of hyperandrogenism" and "polycystic ovaries" are used for diagnosis. PCOS is associated with inflammatory diseases such as obesity, Type 2 DM, cardiovascular disease and insulin resistance. Studies have shown that monounsaturated fatty acids (omega 9), polyunsaturated fatty acids omega 3, vitamin D, vitamin E, curcumin, cinnamon, fennel and flaxseed supplements, high-protein diets and exercise can reduce the complications of PCOS and can be effective in the treatment of PCOS. In this review, nutritional supplements and lifestyle changes that can be made in the reduction or treatment of PCOS complications will be examined with scientific reality.

Keywords: *PCOS, unsaturated dietary fats, exercise*

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Introduction

Polycystic Ovary Syndrome (PCOS), which is a heterogeneous disorder characterized by metabolic and endocrine disorders and which is particularly prevalent in women of reproductive age, was initially defined by Stein and Leventhal back in 1935 to describe women with obesity, infertility, and multiple cystic ovaries (Stein and Leventhal, 1935). In order to diagnose PCOS, three different references are made use of. Initially, as per the meeting reports of the National Institutes of Health (NIH) in 1990, it was argued that both biochemical and clinical hyperandrogenism (acnes) and chronic anovulation (menstrual irregularity) were needed in order to diagnose PCOS (Zawadzki and Dunaif, 1992). As per the second criterion, however, at least two of the features of oligo-anovulation, clinical or biochemical findings of hyperandrogenism, and polycystic ovaries during an ultrasonography examination need to be present in order to diagnose PCOS (Rotterdam, 2004). As to the third criterion, on the other hand, the Androgen Excess and PCOS (AE-PCOS) Society reports that clinical or biochemical hyperandrogenism is needed for diagnosis, and that oligo-anovulation, and polycystic ovaries are also required to that end (Azziz et al., 2006). Epidemiological studies may yield different results due to protocol-related differences, even though the same criteria are utilized for diagnostic purposes.

PCOS is a highly prevalent disorder among women, with a prevalence rate of 5-10% (Rondanelli et al., 2014). Even though the rate of prevalence of PCOS is 5-7% in women of reproductive age, and 28% in obese woman, it is believed that the rate of prevalence in our country is 6% as per the NIH criteria, 10% as per the Rotterdam criteria, and around 10% as per the AE-PCOS Society (Bozdağ et al., 2016). Of the women diagnosed with PCOS, approximately 40% are faced with the risk of infertility due to ovulation disorders (Diamanti-Kandarakis and Duanif, 2012). Besides reproductive abnormalities, PCOS has also been associated with metabolic comorbidities, many of which are linked to obesity (Yeşilkaya, 2020).

PCOS is genetically inherited, and it is passed through autosomal dominant genes (Atiomo et al., 2003). In a study that analyzed the genetics of PCOS, it was underlined that the dysfunctional β-cell is genetically transmitted, and the polymorphisms in the TNF-R (tumor necrosis factor receptor) and PPAR (peroxisome proliferator-activated receptors) genes were associated with PCOS (Amato and Simpson, 2004).

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Women with PCOS also have metabolic disorders, such as dysfunctional beta cells in the pancreas, insulin resistance, glucose intolerance, visceral obesity, and impaired lipid profile (Amer, 2009). During histopathological analyses, it was observed that the number of follicles in polycystic ovaries tended to increase, and that the cell layers of theca interna contained hypertrophy, luteinization, and a thickened ovarian tunica (Hart et al., 2004). Several studies, which were conducted in regards to abnormal endocrine parameters, such as high insulin resistance, showed increasing Luteinizing Hormones (LH) and increasing androgen concentrations, which may have been associated with a reduced fertilization rate and an abnormal embryological development (Järvelä et al., 2003). A great number of studies have shown that the C-Reactive Protein (CRP) values are positively associated with insulin resistance, body weight, and fat mass in women with PCOS. CRP, IL-6, IL-18 and TNF-α were associated with type 2 diabetes and the risk of developing cardiovascular diseases, which are strongly associated with insulin resistance and body mass amount (Repaci et al., 2011). The levels of TNF-α, IL-6, and CRP in circulation were found to have increased in patients with PCOS, upon the comparison of the number of white blood cells (WBC) and the number of neutrophils to the body mass index (BMI) (Tarkun et al., 2004). IL-6 plays a significant role in the ovarian maturation and implantation process. IL-1β and TNF-α are important indicators that affect ovulation and pregnancy. IL-1 secreted in follicles, can regulate the granulosa cells in order to control the collagenase activity, which plays a significant part in synthesizing prostaglandins, and in ovulation (Xu et al., 2014). TNF-α is an inflammatory cytokine that stimulates and multiplies the theca cells; it plays an important role in regulating the normal activities of the ovaries throughout the follicular and lutein development phases. TNF-α is found in macrophages, oocytes, granulosa cells, atresia, and in theca cells. It was shown that an excessive production of this cytokine in the fat tissues of humans and rodents caused an increase in insulin resistance and in glucose levels (McGrath et al., 2008).

Having an extremely complex pathophysiology, PCOS is a disorder that strongly reduces the quality of life and it is associated with other inflammatory diseases. (Patel, 2018). Major interventions to minimize metabolic risks in PCOS; lifestyle changes, drug therapies, and bariatric surgery. Anti-estrogens such as clomiphene citrate, insulin sensitivity enhancing agents and gonadotropins are often used for ovulation induction in patients with PCOS. Treatments with metformin have been shown to increase insulin sensitivity and lower blood

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sugar and androgen levels. These effects are stronger when combined with lifestyle interventions (Yeşilkaya, 2020).

The purpose of this review is to interpret the dietary supplements (unsaturated fatty acids, vitamin D, vitamin E, cinnamon, curcumin, linseed, fennel), and lifestyle changes (a high-protein diet, exercising), which can be used to reduce or treat the complications of PCOS, under the light of scientific facts.

PCOS and Unsaturated Fatty Acids

In a study, which aimed to analyze the fatty acids in the subcutaneous fat tissues of PCOS and non-PCOS women, 13 PCOS women and 32 non-PCOS women, who had similar ages and BMIs, were included. Accordingly; while total monounsaturated fatty acids (MUFA) and the desaturase index were high in women with PCOS, total polyunsaturated fatty acids (PUFA) were found to be significantly higher in non-PCOS women (Emami et al., 2020).

In a study, which investigated the role of nutritional models in the PCOS development, and which was conducted on 281 PCOS patients and 472 healthy volunteers, the nutritional statuses of the participants were determined by using a verified and quasi-quantitative food frequency questionnaire. Accordingly; while the polyunsaturated and monounsaturated fatty acids of the healthy volunteers were at higher levels, the cholesterol and saturated fatty acid levels of the PCOS patients were found to be higher (Eslamian and Hekmatdoost, 2019).

Nevertheless, it must be known that, even though these two case-control studies showed a correlation between nutrition and PCOS, they could not show any causality. Despite the lack of a clinical study, which assesses the complications of PCOS occurring upon the intake of monounsaturated fatty acid supplements, it is understood that the levels of these fatty acids are generally low in women with PCOS. Hence, they may be taken, considering that they have protective effects, yet prospective studies are still needed.

In a study, which associated the food intake with leptin, the satiety hormone, and with ghrelin, the hunger hormone, in women with PCOS, it was found that the MUFA content in the diet was positively correlated with leptin, and negatively correlated with ghrelin in women with PCOS (Polak et al., 2020).

A study, which aimed to investigate the effects of fatty acids on the lipid profiles and androgens of PCOS patients, subjected 31 PCOS patients to a 6-week research. It was ensured that a total of 31 grams of fat were taken on a daily basis by providing one group with almond, which is rich in MUFA, and the other group with walnut, which is rich in PUFA. Accordingly;

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it was found that these dietary intakes positively affected the androgen and plasma lipid levels of PCOS patients, and that the consumption of walnuts increased the sex hormone binding globulin, while almonds reduced the free androgen index (Kalgaonkar et al., 2011).

A study, which aimed to investigate the clinical, hormonal, TNF-α, and resistin levels of the omega-3 supplement administered on women with PCOS, included 45 non-obese women who had PCOS. The participants were given 1,500 mg/day of omega-3 supplements for 6 months. At the end of the study, the hirsutism scores, insulin, insulin resistance, serum LH, testosterone levels tended to decrease, whereas the levels of TNF-α and sex hormone binding globulin increased significantly (Oner and Muderris, 2013).

A study which is aimed to detect the effect of omega-3 supplements visfatin, adiponectin, and anthropometric measurements conducted with 84 women. For 8 weeks, one group was given 3 capsules of omega-3 (180 mg EPA+120 mg DHA), while the other group was given placebo on a daily basis. Accordingly; while the average LH levels decreased in the omega-3 group, the average adinopectin concentration tended to increase. Nonetheless, no significant changes were observed in the average FSH and prolactin levels of both groups (Nadjarzadeh et al., 2015).

PCOS and Vitamins

To assess the effect of vitamin D and omega-3 fatty acids to the PCOS; 50,000 IU of vitamin D administered on all subjects once in two weeks for 12 weeks, one group was given 2000 mg/day of omega-3, while the other group was given equal levels of placebo. Thus, while the gene expressions of CRP, malondialdehyde (MDA), IL-1, and vascular endothelial growth factor (VEGF) reduced, along with the total level of serum testosterone, following the administration of vitamin D and omega-3 fatty acids simultaneously, the total level of antioxidants increased, with an improvement in the mental health parameters (Jamilian et al., 2018).

Significant factors were mentioned in a compilation that analyzed the developments taking place between vitamin D and the pathophysiological process of PCOS. It was emphasized that there was a negative correlation between vitamin D levels and serum androgen levels in PCOS patients, that the thickness of endometrium was reduced by diminishing the Anti-Müllerian Hormone (AMH) and serum androgen levels through vitamin D supplements, and that it fixed the menstrual cycle. Similarly, it was reported that the vitamin D level was negatively correlated with insulin resistance (IR) and body fat mass, and that these parameters

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were improved with vitamin D supplements. It was further reported that vitamin D supplements also positively affected the mental health of PCOS patients (Mu et al., 2021).

A study, which aimed to investigate the effects of omega-3 and vitamin E supplements on insulin resistance and hormonal parameters of PCOS patients, included 68 women, aged 18-40, and one group was administered 400 mg of α-Linolenic acid and 400 IU of vitamin E supplements, while the other group received equal levels of placebo for 12 weeks. The insulin resistance decreased in the group that received omega-3 and vitamin E supplements, compared to the placebo group, whereas the insulin sensitivity was improved. It was observed that, hormonally, the levels of total and free testosterone reduced significantly in the same group (Ebrahimi et al., 2017).

A study, which aimed to make a qualitative assessment of the dietary components of women with PCOS, included 54 women. The analysis, which was based on the 3-day food consumption records of the women, calculated the average intakes of energy, vitamin, minerals, cholesterol, and dietary fibers. Consequently, upon the comparison of these patients to the national dietary guidelines, it was found that the levels of calcium, potassium, magnesium, folic acid, vitamin C, vitamin $B_{12,}$ and vitamin D were low, whereas the average daily intake of fats, saturated fatty acids, and sucrose was high. Moreover, it was found that the waist circumference and BMI values were high in those women, while their average protein intake was low (Szczuko et al., 2016).

PCOS and Cinnamon

A study, which aimed to investigate the effects of cinnamon supplements on the blood parameters of obese women with PCOS, was conducted on 84 overweight or obese women, aged 20-38, who had PCOS. Throughout the study that lasted 8 weeks, one group was given 3 capsules of cinnamon (500 mg), while the other was given placebo on a daily basis. Consequently, cinnamon increased the serum total antioxidant capacity, while had reducing effects on the MDA levels. Furthermore, significant improvements were observed in the total serum levels of cholesterol, LDL-C, and HDL-C of the group that received cinnamon supplements. Hence, it was shown that cinnamon could reduce the risk factors in PCOS by diminishing the complications of PCOS (Borzoei et al., 2018).

In a meta-analysis that is reported the effects of cinnamon on the metabolic parameters of PCOS, it was reported that the body weight and BMI in patients with PCOS were not affected by the cinnamon supplements, and fasting insulin and fasting blood sugar, LDL, total

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cholesterol and triacylglycerol reduced significantly, while the HDL serum concentration improved significantly (Heydarpoura et al., 2020).

PCOS and Fennel

It was intended to investigate the effects that high-protein diets with energy restriction, and fennel could effect on the body fat and muscle percentages and insulin resistances of women with PCOS. Fennel is known as an antioxidant plant that has high contents of polyphenol and flavonoid. The energy restriction improved the body fat and muscle percentage, as well as the insulin resistance index, in women with PCOS, regardless of the dietary components, whereas high-protein diets and fennel did not impose any significant effects on these parameters (Hosseini Marnani et al., 2020).

In another study that analyzed the effects of fennel on PCOS, however, it was reported that it regulated the estrous cycle, increased the number of antral follicles, reduced the ovarian cysts, increased the number of corpus luteum follicles, decreased the nitric oxide concentration, increased the Ferric Reducing Antioxidant Power (FRAP) levels, while improving the regulation of the T-cells (Tregs) (Seif Amirhoseiny et al., 2020).

PCOS and Curcumin

In a study, which aimed to investigate the effects of curcumin supplementation on IL-6, CRP, and TNF-α in patients with polycystic ovaries, 72 female Wistar rats were used. Ovaries were taken for histological evaluation following a 60-day curcumin supplementation. Consequently, it was found that, compared to the control group, the theca layer reduced, the corpus luteum (CL) diameter increased, while the expression of IL-6, CRP, TNF-α, and follicle and ovarian cysts in the follicular fluid decreased in the group that received curcumin supplementation (Mohammadi et al., 2017).

The study, which aimed to investigate the effects of curcumin on body weight, glycemic control, and serum lipids in women with PCOS, included 60 PCOS patients, aged 18-40, and for 12 weeks, one group was given 500 mg/day of curcumin, while the other group was provided with equal amounts of placebo. Based on the parameters analyzed at the beginning of the study and after 12 weeks of administration, significant levels of improvements were observed in the BMI, serum insulin, insulin resistance, insulin sensitivity, peroxisome proliferator-activated receptor gamma (PPAR-y), low density lipoprotein receptor (LDLR), HDL, LDL, and total cholesterol levels (Jamilian et al., 2020).

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In another study, through which it was intended to investigate the effects of curcumin on letrozole-induced PCOS, it was observed that curcumin supplementation in Wistar rats reduced the abnormalities in the serum sex steroid profile, lipid profile, glucose, and glycosylated hemoglobin levels. Furthermore, curcumin rehabilitated all the parameters in the ovaries, thus eliminating the cysts (Reddy et al., 2016).

Nutritional and Lifestyle Changes with PCOS

Lifestyle changes for women with PCOS is dimetional. In studies examining the effect of lifestyle changes on insulin resistance in patients with PCOS; It has been found that short-term low-energy diets, which lead to a weight loss of 5% to 9%, reduce insulin resistance. It is stated that in obese patients with PCOS in which anovulation develops, reducing body weight by 2-5% helps increase insulin sensitivity, initiation of ovulation and pregnancy. It has been reported that moderate weight loss (5-10%) improves ovulation and menstrual functions by normalizing gonadotropin and androgen metabolism, and reduces the risk of developing hyperandrogenism, cardiovascular disease and type 2 DM (Yeşilkaya, 2020)**.**

A study, through which it was aimed to analyze the effects of high-protein diets on the body composition and several biochemical parameters of PCOS patients, included 20 women. Of these patients whose weight loss-oriented energy calculations were made, one group was given a diet with protein with a normal range, while the other group received a high-protein diet. Accordingly; the group that received a high-protein diet experienced significant levels of weight loss, with reductions in their BMIs, waist circumferences, waist/hip ratios, while significant improvements were achieved regarding their body compositions; nevertheless, no significant results could be achieved in regards to biochemical and hormonal parameters. Although the fact that this study was conducted in a limited period of 6 weeks, could be a determinant factor, it could be thought that high-protein diets could be effective in healing PCOS complications (Şanlı Ak, 2017). In another study, however, it was found that the insulin sensitivity of 60 PCOS patients, who administered a modified, high-protein diet for 12 weeks, increased significantly, while their CPR levels reduced (Mehrabani et al., 2012).

In a set of works regarding obese people with PCOS, it was reported that 12 weeks of high-energy, high-protein diets ensured weight loss, and that the levels of insulin, free testosterone, triacylglycerol, and LDL reduced, while the sex hormone binding globulin level (SHBG) increased (Moran et al., 2011). A meta-analysis of randomized control trials set forth that high-protein diets with moderately low carbohydrates could lead to weight loss in patients

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with impaired glucose metabolism, while yielding some positive effects on HbA1c and blood pressure (within 6 months) (Dong et al., 2013).

In a research, which analyzed the responses of PCOS patients to dietary treatment, it was reported that symptoms, such as acnes, and hirsutism, healed in a short period of time as a result of weight loss. The chance of getting pregnant is also increased. That provided protection against cardiovascular diseases, cancer, chronic inflammatory diseases, such as Type 2 DM, in the long period of life (Moran et al., 2013). In another study, which was aimed to analyze the effects the linseed powder supplements, given to 41 women with PCOS. It was observed that body weight, insulin resistance, insulin concentration, triglyceride, CRP, and leptin reduced significantly with the linseed powder, and lifestyle changes like diet and exercising, while insulin sensitivity, HDL, and adiponectin increased significantly. The same study found that the linseed supplements and lifestyle changes were more effective on PCOS patients, in regards to biochemical and anthropometric variables, compared to lifestyle modifications alone (Haidari et al., 2020). In a study that was conducted on 20 adolescents with PCOS, a weight loss diet was administered in addition to the metformin treatment, and the consequential 5% decrease in the body weight led to a decrease in insulin resistance, while fixing the menstrual cycle, and reducing the testosterones (Glueck et al., 2009). In a study conducted on adolescents with PCOS, it was reported that a low-glycemic index diet led to more weight loss (Wong et al., 2015).

The 5αR1 enzyme has specific effects on insulin resistance, and this enzyme is capable of synthesizing dihydrotestosterone by metabolizing testosterone. In a study that investigated the effects of exercising on the 5αR1 enzyme and intracellular signal of PCOS, 54 rats with PCOS were used, and specific groups were subjected to controlled exercises. Accordingly; it was observed that exercising could activate the signaling paths of the glucose metabolism in the skeletal muscle by reducing the 5αR1 expression (Wu et al., 2018).

Conclusion and Recommendations

PCOS is an extremely complex disorder, which is prevalent in women of reproductive age and which does not have any clear treatment so far. It has highly common symptoms, such as insulin resistance, hyperinsulinemia, high androgen levels, polycystic ovaries, hirsutism, acnes, obesity, gonadotropin abnormalities, adipose tissue disorders, not being able to become pregnant, or highly risky gestation. This review that we authored analyzes the food

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supplements, and possible changes in nutrition and lifestyle for reducing the complications of PCOS.

Women with PCOS are highly likely to develop abdominal obesity, and insulin resistance in the event that they persist on keeping their unhealthy dietary habits. There is no optimal nutritional treatment that is defined for PCOS so far. Nonetheless, considering the results of the study, we can say that foods that are rich particularly in omega-9 (olive oil) and omega-3 (sea products), prevent the formation of PCOS, or reduce its complications.

When we analyze the pathophysiology of PCOS, we see a quite complex picture. It is possible to say that it bears a resemblance to other inflammatory diseases (obesity, insulin resistance, Type 2 DM, cardiovascular diseases), rather than its unique characteristics. Thus, there is a vicious cycle, in which these diseases trigger PCOS, or PCOS triggers them. The most effective way to have strong immune system against such inflammatory diseases is to lose weight or to be in an ideal range of BMI, in particular. To that end, women with PCOS are required to exercise as a lifestyle, and to ensure a weight control by spending energy. It is known that high-protein and low glycemic index diets are also effective in sustaining the weight loss (Larsen et al., 2010). These types of changes that PCOS patients would impose on their nutritional habits, will also show protective and therapeutic effects.

Specific antioxidant- or anti-inflammatory foods (curcumin, linseed, cinnamon, fennel), and vitamins (D, E) are also among the dietary supplements that women with PCOS would prefer, in that they prevent the formation of inflammatory cytokines, rehabilitate intracellular receptors, and ensure weight control.

Conflict of Interest

The authors declare that for this article they have no actual, potential or perceived the conflict of interest.

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