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REVIEW ARTICLE **OPEN ACCESS**

The Efficacy of Nutritional Supplementation in The Therapy of Metabolic Dysfunctions Associated with Polycystic Ovarian Syndrome: A Critical Review

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ABSTRACT
PCOS is a complicated heterogeneous condition with multiple pathological manifestations, including metabolic, endocrine, reproductive, and psychological. However, the aetiology of PCOS is yet unknown. Numerous studies indicate that insulin resistance and hyperandrogenism are critical factors in the pathogenesis of PCOS. As a result, the majority of PCOS treatment techniques focus on lifestyle improvement, including exercise, nutrition, and nutrient supplementation therapy. Recent studies have indicated some nutrients for the treatment of PCOS, including vitamins, minerals, and vitamin-like substances, because each has at least one functional feature in PCOS-induced pathways. As a result, vitamin or mineral deficiency is suggested as a possible cause of PCOS. The purpose of this review is to conduct a comprehensive literature search on nutritional supplements for the treatment of PCOS-related endocrine and metabolic dysfunctions and to examine the role of nutrients in PCOS management in light of clinical trials and experimental investigations. (Turkish Journal of Gynecology and Obstetrics 2018; 19: 220-32).
Keywords: PCOS, insulin sensitivity, hyperandrogenism, metabolism disorder, supplements

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INTRODUCTION

PCOS is one of the most prevalent endocrine disorders, affecting between 5% and 10% of women of adolescent and reproductive age[1,2]. Stein and Leventhal characterised PCOS for the first time in 1935. PCOS is defined by hyperandrogenism, which occurs as a result of increased androgen secretion or activity[3]. However, hyperandrogenism alone is not sufficient to diagnose PCOS. PCOS is described by the Rotterdam criteria as the presence of at least two of the following three criteria: hyperandrogenism, chronic anovulation, and polycystic ovaries on ultrasound findings[4]. Later, the Androgen Excess and PCOS Society reported that hyperandrogenism and ovarian dysfunction (anovulation and polycystic ovaries) to be present in order to diagnose PCOS[5]. PCOS patients present with a variety of symptoms, including menstrual dysfunction, hyperinsulinemia, infertility, glucose intolerance, type 2 diabetes, hirsutism, obesity, acne, metabolic syndrome, an increased risk of developing cardiovascular disease, endometrial cancer, anxiety, obstructive sleep apnea, and abnormal lipid profiles[6,7].Despite substantial research, the origin of PCOS remains unknown because to the poorly understood interplay of genetic and environmental factors[8]. PCOS can be caused by a variety of neuroendocrine abnormalities, including decreased ovarian steroidogenesis, insulin resistance (IR), and elevated cortisol metabolism-related adrenal hyperandrogenism[9-11]. Recent research indicates that IR may lead to metabolic and reproductive problems. As a result, IR is critical in the pathophysiology of PCOS[12].

In a nutshell, insulin is considered a critical hormone for hyperandrogenism in the pathogenesis of PCOS via two distinct pathways:

(1) Insulin stimulates theca cells to produce androgen via luteinizing hormone (LH), and increased androgen production results in hirsutism, acne, and anovulatory infertility.

(2) Insulin's hyperandrogenism-associated function is to limit the synthesis of sex hormone-binding globulin (SHBG) in the liver [13].

SHBG is a plasma protein that binds androgens and estrogens, and so low SHBG levels in PCOS can result in hyperandrogenism. Insulin is critical in controlling glucose metabolism, inhibiting lipolysis, and

activating aminoacid transport[14]. Numerous nutrients are involved in the regulation of the insulin signalling pathway and androgen production.

Sufficient nutrients and energy for growth and reproduction are contingent upon the ideal nutritional composition being defined. It is well established that nutrition-related signaling pathways are critical for the regulation of ovarian follicle growth and ovulation rates[15]. Deficiencies in myo-inositol and vitamin D, in particular, can result in difficulties associated with PCOS pathogenesis [16-18]. Thus, nutritional supplementation may aid in the resolution of PCOS issues such as immature oocytes, infertility, hyperandrogenism, and oxidative stress. The current state of knowledge regarding the efficacy of nutrients in the treatment of PCOS is discussed in light of experimental and clinical studies.

SUPPLEMENTS WITH VITAMINS

Vitamin A, commonly known as retinol, is a fat-soluble vitamin. Vitamin A metabolites such as retinoids, retinoic acid, and retinol contribute to antioxidant activity, steroid metabolism, nuclear maturation of oocytes, and prevention of cumulus cell apoptosis[19,20]. It is well established that genes involved in retinoic acid production are differently expressed in theca internal cells isolated from patients with PCOS[21]. To investigate the effects of retinol and retinoids, retinol derivatives were added to theca internal cell culture derived from PCOS and healthy women. Trans retinol treatment of all theca internal cells enhanced dehydroepiandestrone levels and mRNA accumulation of the enzyme cytochrome P450 17 hydroxylase (CYP17), which is implicated in androgen production and retinol biosynthesis[22]. In overweight women with PCOS, obesity and impaired glucose metabolism are related with higher retinol-binding protein 4 (RBP4) levels [23]. Another study examining RBP4 expression in isolated subcutaneous and omental adipose tissue from women with PCOS was published. The authors then proposed that higher 17 estradiol could contribute to the altered gonadal and adrenal steroid profiles by upregulating the RBP4 gene[24].

B group vitamins; the majority of research on this group focuses on B6, B12, and folic acid due to the growing significance of homocysteine (Hcy) in PCOS. Hcy is an important amino acid produced from dietary methionine in this pathway, and increasing total plasma Hcy levels enhance the risk of cardiovascular and reproductive symptoms in PCOS[25]. Additionally, other metabolic pathways required for cell and tissue growth are intimately linked to Hcy[26]. Folic acid, vitamin B6, and vitamin B12 all play a critical role in regulating Hcy. A favourable association between IR and high Hcy levels has been observed in the physiopathology of PCOS[27,28]. Kaya et al. [29] revealed that in women with PCOS, IR, obesity, and elevated Hcy levels were all associated with low serum insulin B12 concentrations. Folic acid supplementation for three months was helpful in lowering serum Hcy levels, particularly in women without IR. However, it is unknown if folic acid supplementation has a dose-dependent effect[30]. Regular exercise has also been associated with a reduction in plasma Hcy levels in the pathophysiology of PCOS. According to Randeva et al. [31], six months of regular exercise results in considerably decreased plasma Hcy levels in young obese and overweight women with PCOS.

Numerous women with PCOS are need to utilise insulin-sensitizing medications such as metformin to improve insulin sensitivity. Metformin inhibits the intrinsic factor-B complex and its receptor, and also causes a drop in serum vitamin B12 and folic acid levels during metformin therapy[32]. Additionally, metformin elevates Hcy levels, increasing the risk of cardiovascular disease in women with PCOS over the long term [33]. Two studies demonstrated an interaction between metformin and B group vitamins: the first demonstrated that daily treatment of folic acid or B group vitamins may be useful in lowering increased Hcy levels in women with PCOS receiving short-term metformin therapy. The investigators did, however, suggest that vitamin supplementation had no influence on androgen and lipid levels in the pathophysiology of PCOS [34]. The second investigation demonstrated that six months of metformin combined with folate supplementation had favourable effects on the vascular endothelium. Because this medication results in decreased Hcy levels, it may be useful in managing long-term consequences of PCOS, such as cardiovascular disease [35].

Inositol and its metabolites are classified as sugar alcohols and are also vitamins of the B complex. Additionally, inositol exists in nine stereoisomers: myo-, cis-, allo-, epi-, muco-, neo-, scyllo-, D-chiro, and L-chiro. Insulin-sensitive metabolites generated from inositol play critical roles in lipid synthesis, signal transduction, oocyte maturation, oogenesis, cell morphogenesis, and cytoskeleton organisation [37]. According to randomised controlled trials including inositol supplementation in women with PCOS, inositol improves nearly all pathologic symptoms associated with the disorder, including the recovery of reproductive anomalies, lowered androgen levels, and improved insulin levels[38].

Interestingly, a combination of inositol isomers such as myo-inositol (MI) and D-chiro inositol (DCI) should be used in a specific ratio, referred to as the plasma physiologic ratio (MI/DCI: 40/1)[39]. Otherwise, immature oocytes may emerge, and inositol's efficacy may be compromised in the

pathophysiology of PCOS[40]. According to several investigations, these pathologic symptoms may be explained by the 'DCI paradox' (41). MI is involved in the follicle-stimulating hormone (FSH) signalling system and glucose uptake homeostasis, whereas DCI stimulates insulin-associated androgen production. Except when the physiologic ratio is exceeded, epimerase performs a functional role in the conversion of MI to CDI, dependent on insulin levels and also on inositol isomerase intake. When hyperinsulinemia is present during the pathogenesis of PCOS, increased epimerase activity might result in anomalies in the FSH signalling pathway, resulting in the development of immature oocytes and hyperandrogenism[42]. Table 1 summarises the contribution of MI to treatment in women with PCOS[43-50]. According to the available literature, therapy of MI improves hyperandrogenism and IR-related indicators, as well as the lipid profile.

Vitamin D is critical for skeletal growth, serotonin synthesis regulation, bone mineral density, dental health, lower extremity function, and calcium (Ca) and phosphorus metabolism modulation. Additionally, prior research has indicated that vitamin D may be a substantial and independent predictor of IR[50]. Vitamin D levels drop in obese patients compared to non-obese individuals as a result of IR. In terms of PCOS, a recent review by Krul-Poel et al. [52] on the role of vitamin D in metabolic disturbances associated with the condition confirmed a link between vitamin D and metabolic disturbances. Thus, it was discovered that obese women with PCOS had considerably lower 25-dehydroxy vitamin D levels[53]. Additionally, a cross-sectional study indicated that low D vitamin levels were associated with IR as a result of PCOS's pathophysiology[54].

References	Patients	Treatment	Outcomes
Nestler et al. (43)	44 obese women with PCOS (placebo group n=22, inositol group n=22)	Oral administration of 1200 mg of D-chiro inositol per day for 7-8 weeks	• Plasma triglyceride ↓ • Diastolic and systolic pressure ↓ • DHEA-S ↓ • SHBG ↑
Baillargeon et al. (44)	19 obese women with PCOS	For 4-8 weeks, oral administration of metformin therapy (n=10) (500 mg orally thrice daily) and placebo group (n=9)	• Improvement of insulin mediated release of DCI-IPG
Gerli et al. (45)	92 women with oligomenorrhea and polycystic ovaries	For 12-16 weeks, 400 mcg folic acid intake in placebo group (n=47) and 400 mcg folic acid + 4 g inositol intake in treatment group (n=45)	• Higher ovulation rate • Weight loss • Folicular maturation • Circulating HDL ↑
Papaleo et al. (46)	25 women with PCOS who have oligo or amenorrhea since childbearing age	Myo-inositol + folic acid (inofolic) (2 g twice a day) for 6 months	• Improvement in menstrual cyclicity • Replacement of healthy ovarian activity • Serum free testesterone ↓
Genazzani et al. (47)	20 overweight women with PCOS	Group A (n=10); 2 g myo-inositol + 200 µg folic acid per day Group B (n=10); 200 µg folic acid per day for 12 weeks	• Circulating LH, T, PRL and insulin level ↓ • Ratio of LH/FSH ↓ • Restroration of menstrual cyclicity
Costantino et al. (48)	42 women with PCOS from reproductive age (18-40 years)	Placebo group (n=19): 400 mcg folic acid alone; experiment group (n=23): 4 g myo-inositol + 400 mcg folic acid for 12-16 weeks	• Insulin and androgen level ↓ • Improved glucose tolerance
Minozzi et al. (49)	155 women with PCOS	12 weeks' treatment: placebo group (n=75) oral contraceptive pills (OCP) intake, and the treatment group OCP + myo-inositol (4 g/day) intake	• Insulin sensitivity ↑ • Recovery of hirsutism • Androgen synthesis ↓ • HDL cholesterol level ↑ • LDL cholesterol level ↓
Morgante et al. (50)	Insulin resistant women with PCOS (n=15)	Low dose step-down gonadotropin regimen + Redestop (1500 mg inositol, 100 mg lactoferrin)	• Improved clinical outcomes • Pregnancy rate ↑ • Number of follicles >15 mm in diameter ↓ • Cancellation rate ↓

DHEA-S: Dehydroepiandestrone sulfate; PCOS: Polycystic ovary syndrome; SHBG: Sex hormone-binding globulin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; T: Testosterone; LH: Luteinizing hormone; PRL: Prolactin; DCI-IPG: D-chiro-inositol-containing-inositolphosphoglycan; FSH: Follicle-stimulating hormone; ↓ decreasing; ↑ increasing

Table 1 The effects of myo-inositol compounds in women with polycystic ovary syndrome

The researchers concentrate on vitamin D supplementation as a means of treating women with PCOS in order to demonstrate a link between vitamin D insufficiency and PCOS. A recent investigation on vitamin D replacement therapy in 11 people with PCOS found some favourable benefits on IR but no changes in androgen levels[55]. Additionally, Kotsa et al.[56] examined the effect of vitamin D on PCOS using a vitamin D3 analogue (alphacalcidol). Their findings indicated an increase in insulin secretion during the first phase, a drop in serum triglyceride (TG) levels, and an increase in serum high-density lipoprotein (HDL) cholesterol levels.

The biochemical mechanism through which vitamin D supplementation improves PCOS is unknown at the moment. However, a recent investigation reported that supplementing with vitamin D3 improved several biochemical indicators in women with PCOS by increasing the amount of soluble receptor for Advanced

Glycosylated Ends (AGEs). As a result, vitamin D3 reduces the progression of inflammation in the pathogenesis of PCOS. Additionally, vitamin D3 therapy promotes folliculogenesis by lowering increased anti-mullerian hormone levels[57]. Interestingly, Jafari-Sfidvajani et al.[58] demonstrated that when vitamin D supplementation was combined with a low-calorie diet, no statistically significant changes in the androgen profile occurred; however, menstrual frequency improved.

Vitamin E is a lipid-soluble antioxidant and free radical scavenger that helps maintain a healthy balance of antioxidant and oxidant systems[59]. Additionally, fresh studies indicated that vitamin E can increase endometrial thickness in women with unexplained infertility, with the effects linked to the vitamin's anticoagulant and antioxidant properties[60]. Additionally, coenzyme q10 and vitamin E cotreatment for eight weeks improved SHBG values in patients with PCOS[61]. Another study found that co-supplementing vitamin E (400 IU) and omega-3 fatty acids (1000 mg) for 12 weeks significantly improved IR and androgen levels in women with PCOS[62].Vitamin E is a lipid-soluble antioxidant and free radical scavenger that helps maintain a healthy balance of antioxidant and oxidant systems[59]. Additionally, fresh studies indicated that vitamin E can increase endometrial thickness in women with unexplained infertility, with the effects linked to the vitamin's anticoagulant and antioxidant properties[60]. Additionally, coenzyme q10 and vitamin E cotreatment for eight weeks improved SHBG values in patients with PCOS[61]. Another study found that co-supplementing vitamin E (400 IU) and omega-3 fatty acids (1000 mg) for 12 weeks significantly improved IR and androgen levels in women with PCOS[62].

VITAMIN-LIKE NUTRIENT SUPPLEMENTATION IN PCOS:

Alpha-Lipoic Acid (a-LA) is a powerful antioxidant, an essential cofactor in the citric acid cycle, and a weight-regulating agent (63,64). Interestingly, Masharani et al. [65] discovered that regulated release of -LA was not associated with an increase in plasma antioxidant capacity or a decrease in plasma oxidation metabolites in six nondiabetic women with PCOS. To examine the effect of -LA and DCI (DCA) in the short-term therapy of PCOS, both metabolites were administered for 180 days to 46 women (26 with PCOS and 20 female controls). They suggested that certain reproductive features such as menstrual periods, ovarian cysts, and progesterone levels improved. From a metabolic standpoint, IR improved dramatically in participants with PCOS, while poor lipid metabolism was significantly improved[66].

OTHER SUPPLEMENTS:

Melatonin (MT) is a pineal gland-secreted neuroendocrine hormone. It is critical for circadian rhythm regulation. Due to its potent free radical scavenger activity, high amounts of MT have been detected in follicular fluid, affecting physiologic processes in the ovaries such as folliculogenesis, follicular atresia, ovulation, steroidogenesis in theca cells, and corpus luteum development [67-69]. Additionally, Wei et al. [70] found that low-dose MT supplementation promotes nuclear maturation of oocytes in vitro. As a result, MT may enhance oocyte quality and boost conception rates[71]. In women with PCOS, the concentration of MT in pre-ovulatory follicular fluid is decreased. Kim et al. [72] reported that MT treatment may be beneficial in enhancing the success of in vitro fertilisation and improving the clinical results of PCOS.

LIMITATIONS:

Our study was limited by the large number of related publications published: the doses, types, and combinations of supplemented nutrients are significantly varied, depending on the investigated group, making it difficult to evaluate the results. Another problem is the low nutritional doses employed in the trials, as well as the inadequacy of the PCOS diagnosis criteria. Additionally, each woman with PCOS requires a unique supplements regimen based on her signs and symptoms and physiologic anomalies. For example, some people experience infertility as a result of PCOS, while others suffer from endocrine and metabolic disorders. However, the majority of studies on nutrient supplementation is focused on the metabolic components of PCOS. As a result, this review focused mostly on the treatment effects on metabolic and endocrine dysfunctions rather than on infertility, which was also a constraint in this study. Large-scale molecular investigations might be organised to shed light on the altered signalling pathways associated with PCOS. By employing a molecular targeting technique, nutrients can be employed effectively to control all elements of PCOS.

CONCLUSION

In conclusion, vitamin and mineral supplements may help alleviate symptoms associated with PCOS, such as immature oocytes, hyperinsulinemia, hyperandrogenism, higher BMI, cardiovascular illnesses, and mental and psychological issues.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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