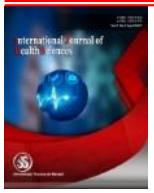

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The Relationship between Vitamins B12, B9, and D and Polycystic Ovarian Syndrome: A Review Article

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, with a constellation of symptoms including hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Approximately 8–13% of women worldwide are diagnosed with PCOS. PCOS affects women of reproductive age, regardless of their ethnic background, although signs and symptoms may vary by ethnicity. Symptoms include obesity, hirsutism, acne, amenorrhea, infertility, and occasionally menorrhagia. It is particularly important to consider the presence of clinical and biochemical signs of hyperandrogenism in female patients. According to previous studies, vitamin deficiencies may play a role in the pathophysiology of PCOS, leading to insulin resistance, inflammation, dyslipidemia, and obesity, all of which are associated with the syndrome. The aim of the study: A review of the effect of some vitamins on polycystic ovary syndrome.

Contents

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1 Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. It is characterized by a variety of symptoms, including hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Worldwide, approximately 8–13% of women are diagnosed with PCOS (Gurkan Bozdag et al., 2016; Singh et al., 2023). The syndrome includes a variety of clinical manifestations, such as acne, hirsutism, alopecia, menstrual irregularities, and ultrasound findings suggestive of polycystic ovarian (PCOM) morphology (Rasquin et al., 2024). In some case-control studies, a cross-sectional study of adolescents and girls in Mumbai reported a prevalence of PCOS as high as 22.5% (Joshi B et al., 2014), 41% in women with menstrual irregularities according to the National Institutes of Health (NIH) criteria (Choudhary et al., 2017), and even 46.8% in euthyroid chronic lymphocytic thyroiditis (CLT) according to the Rotterdam criteria (Ganie et al., 2010) and 73% in obese patients (Deswal et al., 2020). Chronic low-grade inflammation is a well-recognized feature of PCOS, and studies have shown elevated levels of inflammatory markers in affected women (Rudnicka et al., 2021). Interleukins (IL-4, IL-6, IL-10) are anti-inflammatory cytokines that are essential for regulating immune responses and maintaining homeostasis. In PCOS, the balance between anti-inflammatory and pro-inflammatory cytokines is often disrupted in favor of a pro-inflammatory state (Iyer et al., 2012; Rasha A.H. Alathary et al., 2025). Women with polycystic ovary syndrome (PCOS) suffer from a variety of health problems, including obesity, insulin resistance, and dyslipidemia, which in turn increase the risk of hypertension, cardiovascular disease, type 2 diabetes, and non-alcoholic fatty liver disease (Moran et al., 2010; de Groot et al., 2011). The development of PCOS has been associated with multiple genes, especially the methylenetetrahydrofolate reductase gene (MTHFR). This gene encodes an enzyme that is essential for folate metabolism and is also required for DNA methylation (Liew et al., 2015). MTHFR catalyzes the reduction of 5,10-methylenetetrahydrofolate (5,10-methylene-THF) to 5-methyltetrahydrofolate (5-methyl-THF), thereby generating a methyl donor for the conversion of homocysteine (Hcy) to methionine. The enzyme is a key element of one-carbon metabolism (Goyette et al., 1998). In this context, many single-nucleotide polymorphisms (SNPs) associated with the MTHFR gene have been discovered. Among these SNPs, C677T (rs1801133) and A1298C (rs1801131) have the greatest clinical significance because they reduce MTHFR function and increase homocysteine levels, which are both potential risk factors for cardiovascular disease (Xiong et al., 2020). Homocysteine (Hcy) is a sulfur-containing amino acid that plays a mediator role in the metabolic conversion of methionine. Hyperhomocysteinemia (HHcy) is characterized by plasma homocysteine levels ≥15 mmol/l and can be caused by insufficient dietary folate or vitamin B12 intake or mutations in the MTHFR and CBS genes (Jakubowski et al., 2011). A recent meta-analysis found that the overall prevalence of hyperhomocysteinemia (HHcy) in Chinese women was 28% and was on an increasing trend (Zeng et al., 2021). In addition, there was an association between elevated Hcy levels and obesity, insulin resistance, and elevated androgen levels (Asanidze et al., 2019), which contradicts the results of a previous meta-analysis (Meng et al., 2016). Elevated homocysteine levels are associated with insulin resistance and may exacerbate hyperandrogenism, which is a major feature of polycystic ovary syndrome (PCOS) (Meng et al., 2016). After adjusting for age, BMI, insulin resistance, and other variables, multivariate logistic regression analysis showed that serum Hcy significantly increased the risk of PCOS (Bhushan et al., 2022). Therefore, Saadeh N et al. found that serum Hcy was closely associated with PCOS and could be used as an effective predictor for the diagnosis of PCOS (Saadeh et al., 2018). Although some studies have been conducted on the effects of macromolecular nutrients on polycystic ovary syndrome (PCOS), few studies have investigated the importance and role of micronutrients. Some recent studies have shown that adequate micronutrient intake can alleviate PCOS symptoms such as insulin resistance and hyperandrogenism (Günalan et al., 2018; Hager et al., 2019).

The aim of the study
A review of the effect of some vitamins on polycystic ovary syndrome.

2 Pathophysiology of polycystic ovarian syndrome

The pathophysiology of polycystic ovary syndrome (PCOS) is multifactorial and remains a mystery. Impaired ovarian steroidogenesis, insulin resistance (IR), neuroendocrine defects, and adrenal hyperandrogenism caused by increased cortisol metabolism are the main mechanisms. Although the root cause of PCOS is still unclear, androgens and insulin are two key factors in its pathogenesis. Therefore, the treatment of PCOS involves improving hyperandrogenism and hyperinsulinemia. Nutrients serve as cofactors to maintain insulin and androgen receptor function (Rawat, 2020).

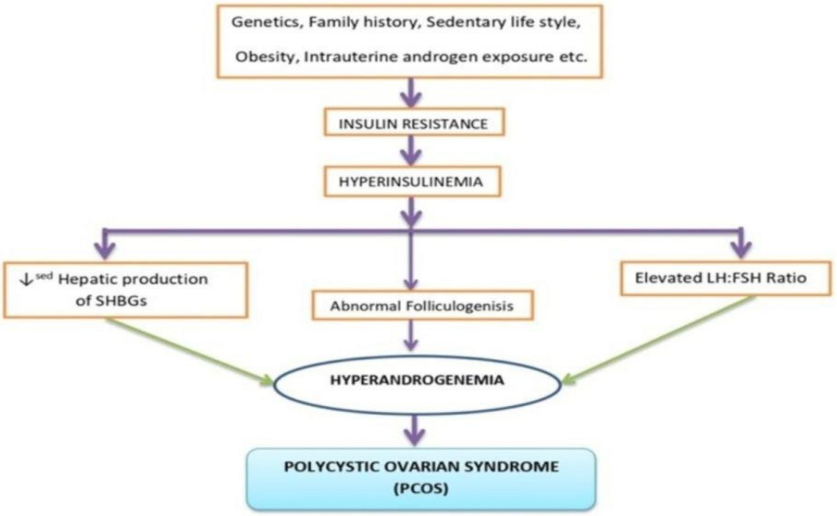

Figure 1. Pathophysiology of polycystic ovarian syndrome

3 Vitamin B12 with Polycystic Ovarian Syndrome

The B vitamins are a class of water-soluble vitamins that play an important role in cellular metabolism and red blood cell synthesis. They form a class of chemically diverse compounds. Dietary supplements that contain all eight vitamins are called vitamin B complex. Each B vitamin is either a cofactor (usually a coenzyme) for important metabolic processes or a precursor required for these processes (Hanna et al., 2022). Vitamin B12 is essential for the function and development of various body parts such as the brain, neurons, and blood cells. Methylcobalamin is the biologically active form of vitamin B12. Cyanocobalamin must be converted by the body to its active form and is the most commonly used form in dietary supplements. Vitamin B12 is often used to treat vitamin B12 deficiency and elevated homocysteine levels in the blood. The reduced vitamin B12 levels observed in women with PCOS and insulin resistance suggest that vitamin B12 may play a role in hyperinsulinemia, insulin resistance, and hyperhomocysteinemia. The importance of vitamin B12 in the remethylation of homocysteine to methionine is well recognized, and hyperhomocysteinemia is a characteristic of vitamin B12 deficiency (McCarty, 2000). Previous studies have shown a causal relationship between reduced vitamin B12 levels and increased risk of PCOS (Shen et al., 2023), as vitamin B12 deficiency leads to increased Hcy levels. Multiple studies have confirmed the association between increased Hcy levels and PCOS and have shown that Hcy levels in circulating plasma and follicular fluid are significantly increased in PCOS patients (Eskandari et al., 2016; Qi et al., 2017). Studies on PCOS patients with recurrent miscarriage have shown that high Hcy levels in serum and follicular fluid trigger granulosa cell apoptosis and impair villous angiogenesis, leading to embryo implantation defects and early miscarriage (Nelen et al., 2000). Increased Hcy levels in PCOS patients are also associated with poor oocyte maturation, reduced fertilization rates, and decreased embryo quality, which can negatively affect fertility (Nafiye et al., 2010). Studies have shown that folic acid and vitamin B12 treatment can improve insulin resistance in patients with metabolic syndrome (Kilicdag et al., 2005). Kaya et al. reported that insulin resistance, obesity, and increased

homocysteine levels were associated with decreased serum vitamin B12 concentrations in PCOS patients (Kaya et al., 2009).

4 Vitamin B9 with Polycystic Ovarian Syndrome

Dietary folate is the natural form of vitamin B9 and is a water-soluble vitamin. On the other hand, folic acid (FA) is the synthetic form that is added to staple foods and dietary supplements to meet folate requirements. In addition, the gut microbiota plays a role in folate biosynthesis, which in turn affects the overall folate status of an individual (Engevik et al., 2019). Folate and one-carbon metabolism are essential for regulating cellular function in all tissues. This process includes the synthesis of nucleic acids, the production of amino acids, and the synthesis of methyl donors such as S-adenosylmethionine (Lyon et al., 2020). Folate and fatty acids have been shown to reduce the risk of neural tube defects. Therefore, many countries have introduced mandatory folic acid fortification guidelines to increase folate intake in women of childbearing age. Chile has implemented a mandatory enrichment policy since 2000, which is considered a safe, cost-effective, and sustainable measure (Murphy et al., 2020). However, studies have shown that folic acid supplementation can mitigate the effects of Hcy (Di Simone et al., 2004). Blood folate levels are often reduced in women with PCOS, and folic acid alone or in combination with B vitamins can improve fasting insulin levels and other outcomes (Cowan et al., 2023). Supplementation with B vitamins and folic acid can reduce blood homocysteine levels in women with PCOS (Thornburgh et al., 2022).

5 Vitamin D with Polycystic Ovarian Syndrome

Vitamin D plays a physiological role in reproductive processes, including follicular development and luteinization, by altering anti-Müllerian hormone (AMH) signaling, follicle-stimulating hormone sensitivity, and progesterone production in human granulosa cells (Irani et al., 2014). In addition, it affects glucose homeostasis in multiple ways. Possible effects of vitamin D on glucose homeostasis include the presence of specific vitamin D receptors (VDRs) in pancreatic β cells and skeletal muscle, expression of the enzyme 1-α-hydroxylase, which catalyzes the conversion of 25-hydroxyvitamin D [25(OH)D] to 1,25-dihydroxyvitamin D, and the presence of a vitamin D response element in the promoter of the human insulin gene (Alvarez et al., 2010). The prevalence of vitamin D deficiency in women with polycystic ovary syndrome (PCOS) is approximately 67–85%, with serum 25(OH)D concentrations <20 ng/ml (Thomson et al., 2012). Although there were no significant differences in 25(OH)D levels between women with PCOS and normal controls, a high prevalence of vitamin D deficiency is associated with metabolic syndrome, which may have significant public health implications (Moini et al., 2015). Low 25(OH)D levels can aggravate PCOS symptoms, including insulin resistance, ovulatory and menstrual irregularities, infertility, hyperandrogenism, and obesity, and increase the risk of cardiovascular disease. Many observational studies have suggested that vitamin D may play a role in the inverse association between vitamin D status and metabolic disorders in PCOS (Krul-Poely et al., 2013). Low 25(OH)D levels were significantly associated with insulin resistance in women with PCOS2. Therefore, researchers believe that genes involved in vitamin D metabolism are potential susceptibility genes for PCOS. It has been reported that some polymorphisms in VDR genes (e.g., Cdx2, Taq1, Bsm1, Apa1, and Fok1) play an important role in insulin secretion and sensitivity in women with PCOS (Al-Daghri et al., 2014). Vitamin D supplementation can reduce abnormally elevated serum AMH levels and increase soluble anti-inflammatory receptor for advanced glycation end products in serum in women with PCOS who are vitamin D deficient (Irani et al., 2014). In particular, vitamin D and calcium supplementation in addition to metformin treatment may have a beneficial effect on menstrual regularity and ovulation in women with PCOS (Rashidi et al., 2009). Recent studies by Garg et al. showed that supplementation with 4,000 IU of vitamin D daily for six months in women with PCOS treated with metformin had no significant beneficial effects on insulin dynamics or cardiovascular risk factors. The effect of vitamin D supplementation on symptom relief in women with PCOS is unclear due to the small sample size and relatively short follow-up period of previous observational studies and clinical trials (Rashidi et al., 2009; Garg et al., 2015). According to previously published studies,

serum vitamin D levels in women with PCOS may be higher, lower, or not significantly different from healthy controls. This leads to the conclusion that the contribution of vitamin D to the etiology of PCOS is unclear (Legro et al., 2013). Therefore, further high-quality randomized controlled trial studies are needed to determine the effect of vitamin D supplementation in the treatment of PCOS.

6 Conclusion

In conclusion, patients with polycystic ovary syndrome (PCOS) represent a unique population group characterized by specific hormonal profiles that differ from healthy individuals. Concentrations of vitamins B12, B9, and D may differ in patients with PCOS compared with healthy women. Further research and investigation are needed to gain new insights into PCOS.

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