Turkish Journal of Clinical Research

Turk J Clin Res. 2026;2(1):48-53
https://doi.org/10.63909/1453043

REVIEW ARTICLE

Vitamin D and its clinical effects in women with polycystic ovary syndrome

Polikistik over sendromlu kadınlarda D vitamini ve klinik etkileri

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Abstract

Polycystic ovary syndrome is a complex endocrine disorder characterized by chronic anovulation and hyperandrogenism. It is one of the most common causes of anovulatory infertility and is widely prevalent among women of reproductive age worldwide. Women with polycystic ovary syndrome experience varying degrees of hirsutism, obesity, and irregular menstrual cycles. Additionally, insulin resistance and the resulting hyperinsulinemia are key metabolic features in the pathogenesis of polycystic ovary syndrome. Vitamin D receptors are distributed across various tissues in the body, including the ovaries and the endometrial layer. This suggests that vitamin D plays an important role in female reproductive functions. Vitamin D enhances insulin synthesis and secretion and increases insulin receptor expression. Recent studies have shown that vitamin D supplementation in women with polycystic ovary syndrome improves insulin resistance, reduces testosterone, LH, and FSH levels, decreases the likelihood of oligo-ovulation and anovulation, and increases pregnancy rates, ovulation rates, and the proportion of mature oocytes. The aim of this review is to evaluate the effects of vitamin D levels and vitamin D supplementation on metabolic, hormonal, and reproductive health in women with polycystic ovary syndrome.

Keywords: Polycystic ovary syndrome, vitamin D, insulin resistance.

Özet

Polikistik over sendromu, kronik anovulasyon ve hiperandrojenizm ile karakterize olan karmaşık bir endokrin bozukluktur. Anovulatuarinfertilitenin en yaygın nedenlerinden birisidir ve dünya genelinde üreme çağındaki kadınların büyük bir kısmında görülmektedir. Polikistik over sendromlu kadınlar değişen derecelerde hirşutizm, obezite ve düzensiz adet dönemleri ile karşı karşıyadır. Aynı zamanda insülin direnci ve bunun sonucunda ortaya çıkan hiperinsülinemi, polikistik over sendromu patogenezinde anahtar metabolik bir özelliktir. D vitamininin reseptörleri vücutta çeşitli dokulara dağılım göstermektedir. Örnek olarak yumurtalık ve endometriyum tabakası verilebilir. Bu da D vitamininin kadınların üreme fonksiyonlarında önemli bir role sahip olduğunu göstermektedir. D vitamini insülin sentezini ve salınımı, insülin reseptör ekspresyonunu artırır. Son zamanlarda yapılan çalışmalarda polikistik over sendromlu kadınlarda D vitamini takviyesinin insülin direncini iyileştirdiği, testosteron, LH, FSH düzeylerini ve oligoovülasyon-anovülasyon görülme olasılığını azalttığı, gebelik, ovülasyon ve olgunlaşmış oosit oranında artış sağladığı gösterilmiştir. Bu derlemenin amacı, polikistik over sendromu olan kadınlarda D vitamini düzeyi ve D vitamini desteğinin metabolik, hormonal ve üreme sağlığı üzerindeki etkilerini değerlendirmektir.

Anahtar Kelimeler: Polikistik over sendromu, D vitamini, insülin direnci.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age. It is characterized by chronic anovulation, hyperandrogenism, hirsutism, and menstrual irregularities (1). Globally, approximately one in every 16 women is affected by PCOS. About half of women diagnosed with PCOS present with abdominal obesity. Both PCOS and obesity are significant risk factors for the development of type 2 diabetes mellitus (T2DM). Additionally, women with PCOS have an increased prevalence of impaired glucose tolerance and T2DM (2). Lifestyle modifications, particularly weight loss achieved through healthy nutrition, contribute to improved glycemic control, reduced insulin resistance, and balanced androgen levels (3). In medical nutrition therapy for PCOS, a diet low in glycemic index, limited in saturated and trans fats, and rich in omega-3 fatty acids is recommended. Additionally, supplementation with chromium and vitamin D may be beneficial (4).

Recently, the role of vitamin D supplementation in the pathogenesis of PCOS has been extensively studied.

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Cite as: Elveda Demirhan E. Vitamin D and its clinical effects in women with polycystic ovary syndrome. Turk J Clin Res. 2026;2(1):48-53

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Received: 11 February 2026 | **Accepted:** 29 April 2026 | **Published:** 31 May 2026

Turk J Clin Res. 2026;2(1):48-53
https://doi.org/10.63909/1453043

Approximately 67–85% of patients with PCOS have concomitant vitamin D deficiency. This deficiency has been positively associated with well-known comorbidities of PCOS, including T2DM, metabolic syndrome, and cardiovascular diseases (5). The aim of this review is to evaluate vitamin D levels and the effects of vitamin D supplementation on metabolic, hormonal, and reproductive health in women with PCOS. This study is a review and includes current literature findings examining the relationship between polycystic ovary syndrome and vitamin D.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is an endocrine disease seen in women of reproductive age, characterized by hyperandrogenism and chronic anovulation, resulting from the interaction of genetic predisposition and environmental factors, and associated with hormonal and metabolic irregularities (6,7). Considered one of the leading causes of infertility worldwide, this syndrome was first described by Stein and Leventhal and is also referred to as Stein-Leventhal syndrome in the literature. Clinical findings such as amenorrhea, oligoamenorrhea, hirsutism, and acne, which develop due to increased androgen levels, are among the main features of the disease (8,9). Dysfunction in the theca cells of the ovaries leads to increased androgen production, resulting in various biochemical and clinical symptoms. Furthermore, irregularities in gonadotropin-releasing hormone (GnRH) secretion cause an increase in luteinizing hormone (LH) levels and a decrease in follicle-stimulating hormone (FSH) (10,11). This hormonal imbalance disrupts follicular development and can lead to ovulation problems.

Polycystic Ovarian Syndrome Symptoms and Diagnosis

Hyperandrogenism is defined as the appearance of cystic structures in the ovaries, weight gain, male-pattern hair growth on the face and body, acne formation, and hair loss due to excess androgens. It is reported that elevated androgen levels in the blood lead to irregularities in the menstrual cycle, particularly affecting the ovulation phase. Therefore, oligoovulation or anovulation is frequently observed in women diagnosed with PCOS. According to current diagnostic criteria, the presence of at least two of the following is considered sufficient for diagnosis: oligoanovulation (cycles shorter than 21 days or longer than 35 days), clinical or biochemical hyperandrogenism, and polycystic ovarian morphology findings (12).

In addition, high serum anti-Müllerian hormone (AMH) levels, although there is no universally established threshold value, are considered an important biochemical indicator for PCOS (13). There is a positive correlation between AMH levels and hyperandrogenism (9). Markers of hyperandrogenism in women with PCOS are free testosterone and free androgen index. It has also been stated that increased total testosterone levels and decreased E2/T (serum estradiol/serum testosterone) index play a role in the pathogenesis of atherosclerosis. Aromatase enzyme is one of the essential enzymes that convert androgens to estrogens in the steroidogenesis process. However, it is reported that there is a decrease in the activity of aromatase enzyme in individuals diagnosed with PCOS and that this contributes to the disruption of androgen-estrogen balance (14).

Pathophysiology of Polycystic Ovary Syndrome and Its Relationship with Other Diseases

The fetal programming hypothesis is proposed as one of the fundamental etiological mechanisms of PCOS, characterized by hyperandrogenism and insulin resistance, and it is stated that this process can lay the groundwork for the development of various diseases in adolescence, adulthood, and later life (13). Experimental animal studies have shown that high levels of androgen exposure during the intrauterine period can alter follicle development and contribute to the emergence of clinical findings of PCOS in adolescence (15). Maternal obesity, diabetes, insulin resistance, and increased gestational weight gain during pregnancy are reported to be important determinants of high birth weight in newborns. It is stated that these conditions may also be associated with hyperandrogenism and, when combined with increased androgen exposure during the fetal period, may increase the risk of developing PCOS later in life in infants with high birth weight (16). It is stated that approximately 75% of anovulation-related infertility cases are associated with PCOS (17). With advancing age, the condition, initially manifesting as menstrual irregularities and fertility problems, can gradually

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https://doi.org/10.63909/1453043

transform into a clinical picture where metabolic complications come to the forefront (13).

Insulin resistance is detected in approximately 50–70% of women diagnosed with PCOS. Genetic disorders in insulin signaling pathways, along with decreased levels of insulin receptors and glucose transporter protein-4 (GLUT4) in adipose tissue, contribute to the exacerbation of insulin resistance in these individuals (18). Increased body weight poses a significant risk for the development of hyperinsulinemia, impaired glucose tolerance, and type 2 diabetes (12). The progression of insulin resistance stimulates androgen synthesis in the ovaries while simultaneously suppressing the production of sex hormone binding globulin (SHBG) in the liver; as a result, circulating free testosterone levels increase, contributing to hyperandrogenism (13). Increased androgen excess further deepens insulin resistance, while the accompanying hyperinsulinemia also increases androgen production through cogonadotropic effects. Thus, hyperandrogenism and hyperinsulinemia form a mutually reinforcing mechanism. This hormonal environment disrupts adipose tissue functions, promoting the conversion of preadipocytes into mature adipocytes, particularly increasing visceral fat accumulation and perpetuating the vicious cycle associated with obesity (11,19). It is also reported that the increase in pro-inflammatory factors accompanying visceral fat accumulation plays a role in the pathogenesis of insulin resistance and increases tumor necrosis factor-alpha levels. In addition, interleukin-6 (IL-6) gene polymorphisms have been found to show a positive correlation with total testosterone levels and lipid parameters in women with PCOS (18).

In one study, it was found that serotonin levels were lower in individuals diagnosed with PCOS, and it was reported that this may be related to an increased luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio. Decreased serotonin levels; It has been shown to be associated with psychological symptoms such as low self-esteem, anxiety, and frequent mood swings (20). In more than thirty cross-sectional studies conducted in different countries, the relationship between PCOS and symptoms of depression and anxiety has been examined using various assessment and screening scales. It has been reported that the prevalence of depression is approximately 20% higher in the PCOS group compared to the control group; and that anxiety symptoms are approximately 30% more frequent. In addition, it has been stated that women with PCOS who have anxiety symptoms have higher free testosterone levels than those who do not have these symptoms (21). A meta-analysis also revealed that the incidence of clinical depression, anxiety disorder, bipolar disorder, and obsessive-compulsive disorder is significantly increased in women with PCOS (22).

The Relationship Between Vitamin D and Polycystic Ovary Syndrome

Vitamin D is a fat-soluble vitamin with hormonal functions. Vitamin D receptors are found in different cells in our body (23,24). Vitamin D exhibits antiproliferative and immunomodulatory effects. As a steroid hormone, its active metabolite is calcitriol. It is also known for its effect on endocrine function (25). Vitamin D exists in two forms: ergocalciferol (D2) and cholecalciferol (D3). Vitamin D3 is synthesized endogenously in the human body. Ultraviolet radiation from sunlight acts on the skin, converting 7-dehydrocholesterol into a pre-vitamin form. This form is then converted into vitamin D. Vitamin D deficiency is defined as 25-OH-D levels <20 ng/mL, and insufficiency as 20-30 ng/mL (26). The primary role of vitamin D is to regulate calcium-phosphorus balance and bone metabolism (27). Vitamin D increases insulin synthesis and secretion, insulin receptor expression, and suppresses pro-inflammatory cytokines. From a reproductive perspective, insulin resistance increases hyperandrogenism by stimulating ovarian androgen production with insulin and the accompanying reduction of sex hormone-binding globulin (SHBG) (5, 28).

The vitamin D receptor regulates more than 3% of the human genome, primarily genes with important roles in glucose metabolism. Vitamin D receptors are expressed at 2776 genomic positions. It regulates gene expression in many tissues such as the brain, pancreas, skeleton, breast, parathyroid glands, cardiomyocytes, ovaries, and immune cells. Therefore, vitamin D deficiency can cause imbalances in blood glucose, cardiovascular diseases, cancer, and autoimmune diseases (5). Vitamin D receptors are distributed in various tissues in the body. For example, the ovary and endometrium layer can be given (27). Vitamin D protects our body against oxidative stress. It maintains calcium ion levels, ensuring the

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https://doi.org/10.63909/1453043

resting potential of our cells. It is beneficial in fertilization and placenta formation in women (29). This shows that vitamin D has an important role in the reproductive functions of women. In particular, approximately 67-85% of PCOS patients have accompanying vitamin D deficiency (5).

Patients with polycystic ovary syndrome experience abnormal changes in calcium and phosphorus metabolism. In these patients, associated with obesity, phosphorus and parathyroid hormone (PTH) levels are high, while vitamin D levels are low. Supplementing vitamin D in PCOS patients increases serum 25(OH)D levels while decreasing PTH levels. It also reduces the likelihood of oligoovulation-anovulation. When vitamin D supplementation is used in combination with metformin in PCOS patients, it improves reproductive functions. These include regulating follicle development in the ovaries and menstrual cycles (27). In another study, it was reported that the combined use of vitamin D and metformin may be a more effective approach in relieving menstrual irregularities in women with PCOS compared to metformin treatment alone (30).

Studies comparing patients diagnosed with PCOS with healthy individuals have reported that serum vitamin D levels are lower in women with PCOS, and this may be associated with preeclampsia and infertility (31). Furthermore, significant correlations have been shown between vitamin D levels and body mass index, serum testosterone, and dehydroepiandrosterone-sulfate levels in women with PCOS (32). A negative correlation has been found between vitamin D levels and the severity of hirsutism, which develops due to high testosterone levels (33).

Studies examining the effects of vitamin D supplementation on metabolic parameters have reported that 300,000 IU of vitamin D administration improved insulin resistance in obese women with PCOS (33). Similarly, a study in infertile women diagnosed with PCOS showed that vitamin D supplementation reduced insulin resistance, which was associated with improved embryo quality (34). In a randomized controlled trial, it was reported that a combination of 50,000 IU of calcium and vitamin D weekly reduced triglyceride and LDL cholesterol levels in women with PCOS (35).

It has been reported that serum vitamin D levels are lower in women diagnosed with PCOS compared to healthy fertile women, and this decrease may be related to insulin resistance and dyslipidemia (36). In addition, an inverse relationship was found between vitamin D concentrations and waist-hip ratio, fasting insulin level, and LDL cholesterol values (37). In meta-analyses conducted on women with PCOS, it was shown that vitamin D supplementation significantly reduced fasting plasma glucose and insulin resistance indicators (38). In another meta-analysis, it was found that pregnancy, ovulation, and mature oocyte rates increased in the group receiving vitamin D supplementation; It has been reported that testosterone, LH, FSH and premature birth rates are reduced (29). When current data are evaluated, it is seen that the best results from vitamin D supplementation in women with PCOS are obtained by administering ≥4000 IU of vitamin D daily for at least 12 weeks (5,28).

CONCLUSION

This review evaluates current studies examining the relationship between vitamin D levels and metabolic, hormonal, and reproductive health in women with polycystic ovary syndrome (PCOS). Current findings indicate that vitamin D deficiency is common in women with PCOS, and low vitamin D levels may be associated with clinical findings such as insulin resistance, dyslipidemia, hyperandrogenism, and oligoovulation.

Vitamin D supplementation is reported to have positive effects, particularly on insulin resistance, fasting blood glucose, and lipid profiles; it may also offer benefits for reproductive health, such as decreased testosterone levels and increased ovulation and pregnancy rates. However, the heterogeneity in the literature regarding dose, duration, sample size, and concomitant treatments limits the ability to make definitive clinical recommendations.

Based on current evidence, vitamin D supplementation can be considered a supportive approach in PCOS management. It is thought that supplementation at appropriate doses and durations may be beneficial for metabolic and reproductive parameters, especially in women with PCOS who have vitamin D deficiency. However, larger sample sizes, longer duration, and

Turk J Clin Res. 2026;2(1):48-53
https://doi.org/10.63909/1453043

randomized controlled trials are needed to determine the optimal dose and duration of treatment.

Acknowledgement: None.

Ethical Approval: Ethical approval was not required for this study since it is a review article.

Author Contributions: Idea/Concept: E.E.D.; Design: E.E.D.; Supervision: E.E.D.; Resources: E.E.D.; Materials: E.E.D.; Data Collection and/or Processing: E.E.D.; Analysis and/or Interpretation: E.E.D.; Literature Review: E.E.D.; Written by: E.E.D.; Critical Review: E.E.D.

Conflict of Interest: There is no conflict of interest.

Financial Disclosure: No financial support was received for this study.

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