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Vitamin D and Polycystic Ovary Syndrome (PCOS): A Narrative Review

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Abstract **Review Article**

Vitamin D, a fat-soluble vitamin synthesized through sunlight exposure, is integral to numerous physiological processes, including immune modulation, insulin sensitivity, and hormonal regulation. Polycystic Ovary Syndrome (PCOS), a prevalent endocrine disorder in women, is characterized by hyperandrogenism, menstrual irregularities, and metabolic dysfunction. Research indicates a significant prevalence of vitamin D deficiency in women with PCOS, implicating its role in pathogenesis and symptom management. Vitamin D influences PCOS-related insulin resistance, reproductive dysfunction, and hyperandrogenism by modulating gene transcription, calcium homeostasis, and inflammatory pathways. Observational and interventional studies reveal potential improvements in insulin sensitivity, menstrual regularity, and fertility with vitamin D supplementation, although the evidence remains inconclusive. Addressing vitamin D deficiency, particularly in obese women with PCOS, may mitigate cardiovascular risks and enhance therapeutic outcomes. Further randomized controlled trials are essential to clarify its efficacy in managing PCOS and associated metabolic disturbances.

Keywords: Vitamin D, PCOS, insulin resistance, reproductive dysfunction, hyperandrogenism, cardiovascular risk, supplementation.

INTRODUCTION

Vitamin D, often referred to as the "sunshine vitamin," plays a crucial role in maintaining overall health and well-being. It is a fat-soluble vitamin primarily synthesized in the skin through exposure to sunlight, with additional sources including dietary intake and supplementation. Beyond its well-known role in calcium homeostasis and bone health, vitamin D is increasingly recognized for its diverse functions in modulating immune responses, insulin sensitivity, and hormonal regulation. Emerging research has highlighted its potential impact on various endocrine disorders, including polycystic ovary syndrome (PCOS) [1-4].

PCOS is one of the most common endocrine disorders affecting women of reproductive age, characterized by hyperandrogenism, irregular menstrual cycles, and polycystic ovarian morphology. It is a multifaceted condition with metabolic, reproductive, and psychological implications. The exact cause of PCOS remains elusive, but it is believed to result from a complex interplay of genetic, environmental, and hormonal factors. Insulin resistance and chronic low-grade inflammation are central features of the syndrome, often exacerbating its clinical manifestations [5-7].

Recent studies have shed light on the potential role of vitamin D in managing PCOS. Vitamin D deficiency is highly prevalent among women with PCOS, suggesting a possible link between the two conditions. Research indicates that vitamin D may influence the pathophysiology of PCOS through its effects on insulin metabolism, ovarian follicular development, and inflammatory pathways. Adequate levels of vitamin D have been associated with improved insulin sensitivity, reduced androgen levels, and better menstrual regularity in women with PCOS.

The interplay between vitamin D and PCOS is an area of active investigation, with researchers exploring its therapeutic potential. While vitamin D supplementation has shown promise in alleviating certain symptoms of PCOS, the evidence is not yet

conclusive, and further studies are needed to establish optimal dosing and long-term benefits. Nonetheless, addressing vitamin D deficiency remains an important consideration in the comprehensive management of PCOS, given its widespread prevalence and impact on overall health [7-11].

Understanding the relationship between vitamin D and PCOS opens new avenues for improving the quality of life in affected women. By targeting underlying metabolic and hormonal imbalances, vitamin D may serve as an adjunctive therapy in the multidisciplinary approach to managing this complex condition.

Associations Between Vitamin D Levels and PCOS Symptoms

Numerous studies have identified correlations between vitamin D levels and various symptoms of polycystic ovary syndrome (PCOS), such as insulin resistance, infertility, and hirsutism. Vitamin D is believed to influence PCOS development by regulating gene transcription and modulating hormones, which affect insulin metabolism and fertility. While some evidence indicates that vitamin D levels are similar in women with and without PCOS, other studies have reported both lower and higher levels in women with the condition. Research has shown that average 25-hydroxy vitamin D (25OHD) levels in women with PCOS range between 11 and 31 ng/ml, with a significant proportion (67–85%) having levels below 20 ng/ml. Vitamin D deficiency is also prevalent globally, affecting 10–60% of adults, which underscores its importance in maintaining systemic health and preventing chronic diseases such as cancer, cardiovascular conditions, autoimmune disorders, and psychological issues like depression and chronic pain [12-14].

Vitamin D Synthesis and Activation

Vitamin D3 is either obtained from dietary sources or synthesized in the skin through sunlight exposure. In the skin, ultraviolet light converts cholesterol to 7-dehydrocholesterol, which undergoes further transformation into vitamin D3. This compound then undergoes two hydroxylation processes—first in the liver, catalyzed by vitamin D-25 hydroxylase, to form 25OHD, and subsequently in the kidneys, regulated by parathyroid hormone, to produce the active form, 1,25-dihydroxyvitamin D3. This active metabolite binds to vitamin D receptors (VDRs), which regulate the expression of 229 genes across various tissues, influencing numerous physiological processes [15].

Variation in Vitamin D Levels Among Women With PCOS

Research examining vitamin D levels in women with PCOS has yielded mixed findings. For instance, Mahmoudi et al. reported higher vitamin D levels in women with PCOS compared to controls, whereas Li et al. observed slightly lower levels in PCOS women. Wehr et al. further reported significantly lower vitamin D levels in PCOS women compared to controls. These inconsistencies could be attributed to differences in age, BMI, and other factors affecting vitamin D metabolism. Despite these variations, the prevalence of vitamin D deficiency appears to be high among both PCOS and non-PCOS populations [16].

BMI and Vitamin D Levels in PCOS

Several studies have noted an inverse relationship between body weight (measured through BMI, body fat, and waist circumference) and serum 25OHD levels in women with PCOS. Obese women with PCOS often have 27–56% lower vitamin D levels compared to their non-obese counterparts, likely due to vitamin D being sequestered in adipose tissue, reducing its bioavailability. Reduced outdoor activity and differences in dietary habits may also contribute to vitamin D deficiency in obese individuals [17-18]. However, conflicting findings exist, with some studies reporting no significant difference in vitamin D levels across varying BMI ranges in women with PCOS. Further research is needed to elucidate the relationship between obesity and vitamin D status in this population.

Vitamin D Levels, Pathogenesis of PCOS, and Insulin Resistance

Emerging evidence suggests that vitamin D deficiency may play a role in the pathogenesis of insulin resistance and metabolic syndrome associated with polycystic ovary syndrome (PCOS). The biological effects of vitamin D are mediated through both genetic and cellular mechanisms. Vitamin D regulates gene transcription via nuclear vitamin D receptors (VDRs), which are widely distributed in various tissues, including the skeleton, parathyroid glands, and ovaries.

The pathogenesis of PCOS has been linked to the influence of VDR polymorphisms (e.g., TaqI, BsmI, FokI, ApaI, and Cdx2) on luteinizing hormone (LH), sex hormone-binding globulin (SHBG), testosterone levels, insulin resistance, and serum insulin levels. Vitamin D deficiency also increases parathyroid hormone (PTH) production, which is regulated by serum calcium and vitamin D levels. Elevated PTH levels have been independently associated with PCOS, anovulatory infertility, and heightened testosterone concentrations.

Vitamin D deficiency, compounded by insufficient dietary calcium, may contribute to the menstrual irregularities commonly seen in PCOS. While sufficient vitamin D levels are thought to be more critical than high calcium intake in maintaining optimal PTH levels, studies suggest that a lower calcium intake is associated with elevated serum testosterone levels in women with PCOS, indicating that dietary calcium insufficiency might further exacerbate hormonal dysregulation in PCOS.

VDRs also play a crucial role in ovarian estrogen production. Vitamin D influences estrogen biosynthesis by directly regulating the expression of the aromatase gene and maintaining extracellular calcium homeostasis. Animal studies have demonstrated that vitamin D deficiency negatively impacts fertility; for example, VDR-null mice exhibit reduced aromatase activity, impaired folliculogenesis, and decreased fertility rates. In human ovarian tissue, 1,25-dihydroxyvitamin D3 has been shown to stimulate estrogen and progesterone production without affecting testosterone production, likely by enhancing aromatase activity [19-21].

In PCOS, aromatase gene expression is reduced in follicles compared to controls, resulting in increased LH levels and decreased follicular production of progesterone and estradiol in preovulatory follicles. This hormonal imbalance is likely due to the hyperluteinized microenvironment characteristic of PCOS. These findings suggest that vitamin D deficiency may exacerbate the symptoms of PCOS by disrupting normal hormonal regulation and follicular function. Addressing vitamin D insufficiency in women with PCOS could potentially mitigate some of these adverse effects and improve metabolic and reproductive outcomes.

Although the precise mechanisms linking vitamin D to insulin resistance remain unclear, several cellular and molecular pathways have been proposed to explain their relationship. The biologically active form of vitamin D, 1,25-dihydroxyvitamin D (1,25OHD), may enhance insulin action by stimulating insulin synthesis and release, increasing insulin receptor expression, and suppressing pro-inflammatory cytokines that contribute to insulin resistance. Additionally, vitamin D may influence insulin sensitivity by improving calcium status, enhancing local production of 25OHD for transcriptional regulation of specific genes, or reducing serum levels of parathyroid hormone (PTH), which is implicated in metabolic dysfunction. However, a recent study employing gold-standard methods to assess peripheral insulin sensitivity found that while vitamin D deficiency was linked to obesity, it was not directly associated with insulin resistance. Despite substantial evidence suggesting a connection between vitamin D and insulin sensitivity, further research is needed to elucidate these mechanisms [20,18-19].

Vitamin D levels have also shown negative correlations with markers of insulin resistance, such as fasting insulin and HOMA-IR. However, in several studies, these associations diminished after controlling for BMI, highlighting the confounding role of adiposity. For instance, Hahn et al. found that lower 25OHD levels in women with PCOS were associated with insulin resistance and obesity, suggesting that obesity may mediate the relationship between vitamin D deficiency and insulin resistance in PCOS. Conversely, some studies have reported that severe vitamin D deficiency in women with PCOS is independently linked to increased insulin resistance, regardless of BMI or waist-to-hip ratio (WHR). Furthermore, research has shown that both obese and non-obese women with PCOS exhibit a negative correlation between 25OHD levels, BMI, and HOMA-IR, reinforcing the notion that vitamin D status may influence insulin resistance independently of adiposity.

Wehr *et al.*, demonstrated that 25OHD levels are a significant independent predictor of HOMA-IR, alongside BMI, based on multivariate regression analyses. These findings suggest that while vitamin D deficiency is closely tied to obesity, it may also directly contribute to insulin resistance in women with PCOS.

Despite these associations, the evidence is primarily derived from cross-sectional studies, limiting the ability to establish causation. To address this, randomized controlled trials (RCTs) are needed to evaluate the effects of vitamin D supplementation in women with PCOS. Existing intervention studies, though limited, have shown promising results. For example, a small study involving 15 obese women with PCOS reported that supplementation with alphacalcidol (1-α-hydroxyvitamin D3) for three months increased insulin secretion, correlating with improvements in 25OHD levels. Another trial found that a single high dose of vitamin D significantly decreased HOMA-IR in obese women with PCOS, with most participants achieving sufficient vitamin D status. A more recent pilot study in relatively lean women with PCOS reported improved glucose metabolism but no significant changes in fasting or stimulated insulin levels after 24 weeks of weekly cholecalciferol supplementation. However, the absence of a control group and high baseline vitamin D levels may have influenced the outcomes.

These findings underscore the potential role of vitamin D supplementation in mitigating insulin resistance and metabolic disturbances in PCOS, though larger, well-designed RCTs are necessary to confirm these benefits and clarify the underlying mechanisms.

Table-1: The effect of vitamin D supplementation in women with polycystic ovary syndrome [1]

Study	Rashidi *et al.*, 42	Thys-Jacobs *et al.*, 19	Wehr *et al.*, 22	Selimoglu *et al.*, 20	Kotsa *et al.*, 21
n	60	13	46	11	15
Intervention	1000 mg calcium + 400 IU vitamin D daily; 1000 mg calcium + 400 IU vitamin D + 1500 mg/day metformin; 1500 mg/day metformin	1500 mg calcium carbonate daily + 50,000 units ergocalciferol weekly or biweekly to reach targeted 25OHD levels	20,000 IU cholecalciferol weekly	Single dose of vitamin D3 (300,000 IU)	1 µg/day alphacalcidol (1-α-hydroxyvitamin D3)
Study Design	RCT	Single arm	Single arm	Single arm	Single arm
Intervention Duration	3 months + 3 months follow-up	6 months (2–3 months to reach desired levels)	24 weeks	3 weeks	3 months
25OHD Before Treatment (ng/ml)	Not measured	11.2 ± 6.9	28.0 ± 11.0	16.9 ± 16	15.2 ± 7.2
25OHD After Treatment (ng/ml)	Not measured	30–40	52.4 ± 21.5	37.1 ± 14.6	28.6 ± 6.6
CVD Risk Factors	–	–	↓ Fasting and stimulated glucose, triglycerides, hip circumference − Fasting and stimulated insulin, HOMA, BMI, HDL, waist circumference, blood pressure ↑ Total cholesterol, LDL	↓ HOMA − Glucose, insulin levels	↑ Insulin secretion, HDL − Glucose, insulin, BMI ↓ Triglycerides
Reproductive Function	↑ Number of dominant follicles (≥14 mm) during follow-up in calcium–vitamin D–metformin group − Rates of pregnancy and menstrual regularity ↓ Menstrual irregularities most noticeable in vitamin D–calcium–metformin group	7/9 women normalized menstrual cycles 4 maintained normal cycles 2 women became pregnant Improved acne vulgaris in 3/3 women	23/46 oligo- or amenorrheic women improved menstrual frequency 4/16 women seeking pregnancy conceived	6 pregnancies (46% of those who desired)	–
Hyperandrogenism	–	− Other clinical outcomes of hyperandrogenism	− Testosterone, free testosterone, SHBG, FAI	− DHEAS, total and free testosterone, androstenedione	–

Insulin Resistance and Vitamin D in Women with PCOS

Research suggests that lower 25OHD levels are associated with higher insulin resistance. Two small uncontrolled studies indicate that vitamin D therapy may improve insulin resistance and insulin secretion in obese women with PCOS. However, an uncontrolled pilot study reported no significant effect in relatively lean women with PCOS without severe insulin resistance. Further research through randomized controlled trials is required to clarify the role of vitamin D supplementation in managing insulin resistance in women with PCOS.

Vitamin D and Reproductive Function in Women with PCOS

Emerging evidence highlights the significant role of vitamin D in reproductive function. Vitamin D receptors (VDRs) are expressed in the ovary, endometrium, and placenta. Studies have shown that vitamin D deficiency, often associated with calcium dysregulation, can contribute to follicular arrest, menstrual irregularities, and fertility issues in women with PCOS. In VDR-null mutant mice, impaired folliculogenesis was observed, supporting the importance of vitamin D in ovarian function [21-24].

Two observational studies have explored vitamin D levels in infertile women, including those with PCOS. One study (n = 67) found significantly lower vitamin D levels in 13 women with PCOS compared to infertile women with normal ovulation. Each unit increase in vitamin D (normalized for BMI) reduced the likelihood of a PCOS diagnosis by 96%. Another study (n = 84) of women undergoing IVF showed that higher follicular fluid levels of 25OHD significantly predicted pregnancy success. Women with the lowest tertile of follicular fluid 25OHD levels were 75% less likely to conceive compared to those in the highest tertile.

Studies have also examined the effects of vitamin D supplementation. One intervention study supplemented 13 vitamin D-deficient women with PCOS with vitamin D and calcium, normalizing their 25OHD levels within 2–3 months. Seven of nine women regained regular menstrual cycles, two became pregnant, and the remaining four maintained normal cycles. This suggests a potential therapeutic role for vitamin D and calcium in addressing menstrual dysfunction in vitamin D-deficient women with PCOS.

In a randomized clinical trial, 60 infertile women with PCOS received one of three treatments: calcium and vitamin D, calcium and vitamin D combined with metformin, or metformin alone. The calcium–vitamin D–metformin group showed the highest number of dominant follicles during follow-up, although no significant differences were observed in pregnancy or menstrual regularity rates. Another pilot study (n = 46) found that weekly cholecalciferol supplementation improved menstrual frequency in 50% of women with oligo- or amenorrhea. These findings highlight the potential role of vitamin D in improving reproductive outcomes, though more evidence is needed.

Vitamin D and Hyperandrogenism in Women with PCOS Studies have shown an association between lower 25OHD levels and markers of hyperandrogenism in women with PCOS. Women with hirsutism had significantly lower 25OHD levels compared to BMI-matched controls, and those with PCOS and hirsutism had lower levels than non-hirsute PCOS women. Additionally, 25OHD levels were positively associated with SHBG and negatively associated with free androgen index (FAI) and testosterone levels. However, these associations diminished after adjusting for BMI, suggesting obesity may be a confounding factor.

Limited intervention studies on vitamin D supplementation have shown no significant changes in testosterone, SHBG, or FAI levels. However, in one study, clinical improvements in acne vulgaris were observed in three vitamin D-deficient women with PCOS after supplementation with vitamin D and calcium. Randomized trials are needed to evaluate the potential of vitamin D in managing hyperandrogenism in women with PCOS [22-24].

Vitamin D and Cardiovascular Risk in Women with PCOS

Vitamin D deficiency has been linked to increased cardiovascular risk. Observational studies in women with PCOS report adverse associations between low vitamin D levels and elevated CVD risk factors, including glucose levels, triglycerides, and HDL cholesterol. In one study (n = 206), PCOS women with metabolic syndrome had significantly lower 25OHD levels compared to those without metabolic syndrome.

Small intervention studies have reported mixed effects of vitamin D supplementation on CVD risk factors. While triglycerides and HDL levels improved, BMI and blood pressure remained unchanged. Another study found that atorvastatin increased 25OHD levels in women with PCOS, correlating with reduced high-sensitivity C-reactive protein. These findings suggest potential cardiovascular benefits of vitamin D supplementation, warranting further investigation.

CONCLUSION

Vitamin D deficiency is highly prevalent among women with PCOS and is linked to a range of symptoms, including insulin resistance, cardiovascular risk factors, infertility, and hirsutism. Emerging evidence suggests that vitamin D deficiency may contribute to the development of insulin resistance and PCOS. Observational studies have associated lower 25OHD levels with obesity, insulin resistance, menstrual irregularities, reduced pregnancy success, hirsutism,

hyperandrogenism, and elevated cardiovascular risk factors. Preliminary intervention studies suggest that vitamin D supplementation may improve insulin resistance and menstrual dysfunction, although its benefits for pregnancy remain inconclusive. These findings indicate a potential role for vitamin D supplementation in PCOS management; however, large-scale randomized controlled trials are necessary to confirm these effects and establish clear guidelines.

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