ORIGINAL RESEARCH PAPER

Obstetrics & Gynaecology

THE ROLE OF VITAMIN D IN THE MANAGEMENT OF POLYCYSTIC OVARY SYNDROME: A SYSTEMATIC REVIEW

KEY WORDS: PCOS, Vitamin D, Infertility, Polycystic ovary.

Dr. A Vani Swetha Reddy* Resident Department Of Obgy, D Y Patil Hospital, Nerul *Corresponding Author

Dr. Margavi Patel Resident Department Of Obgy, D Y Patil Hospital, Nerul

Dr. Ankita Shahasane Asst Professordepartment Of Obgy, D Y Patil Hospital, Nerul

ABSTRACT

Polycystic ovary syndrome (PCOS) is a prevalent cause of ovarian dysfunction in women experiencing anovulation. It is marked by chronic anovulation, hyperandrogenism, and/or polycystic ovaries visible on ultrasonography. The etiology of PCOS is multifactorial, involving genetic and environmental factors, gonadotropins, and insulin. Vitamin D deficiency is widespread among women with PCOS, with prevalence rates ranging from 67 to 85 percent. This deficiency is linked to metabolic syndrome, posing significant public health concerns. Low levels of 25(OH)D may worsen PCOS symptoms such as insulin resistance, menstrual irregularities, infertility, hyperandrogenism, obesity, and increase the risk of cardiovascular diseases. Although many observational studies indicate a potential inverse relationship between vitamin D status and metabolic disturbances in PCOS, the evidence remains inconclusive due to inconsistent findings from various studies and systematic review meta-analyses.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a prevalent endocrine disorder among women of reproductive age, affecting about 18% of this population[1]. Symptoms typically include menstrual irregularities, elevated androgen levels indicated by lab tests, and clinical signs such as hirsutism and acne, confirmed by the presence of ovarian cysts on ultrasonography[2]. Furthermore, PCOS is often associated with a higher incidence of cardiovascular diseases and metabolic disorders, including obesity, hyperlipidemia, insulin resistance, and diabetes mellitus, which together suggest the diagnosis of PCOS when present in a patient[3].

Human Body Obtains Vitamin D
|
+----------+
| |
Endogenous Sources Exogenous Sources
| |
| |
Cholesterol converted to 7-dehydrocholesterol
| |
Photolysis in the skin by UV light to form Vitamin D_3
| |
In liver: converted to 25OHD by D_3-hydroxylase
|
In kidney: converted to 1,25-dihydroxy vitamin D_3
|
Circulates by binding to vitamin D binding protein
|
Vitamin D Effects on Receptors
|
Recent Research on Vitamin D and PCOS
|
Research Findings on Vitamin D Levels in PCOS
|

- Conflicting results on Vitamin D levels in PCOS vs. healthy controls (higher, lower, same levels)[6–14]
- Average value of vitamin D reported as less than 20ng/ml
- General population shows a decline in vitamin D levels down to 20ng/ml without health problems[15]

Vitamin D_3 and metabolic parameters in PCOS patients

Insulin resistance

The exact mechanism linking vitamin D and insulin remains unclear. Proposed mechanisms include vitamin D enhancing insulin release, upregulating insulin receptors, and inhibiting pro-inflammatory cytokines responsible for insulin resistance. Additionally, improved calcium levels may also contribute to reducing insulin resistance and enhancing insulin secretion[18]. However, recent research indicates no significant correlation between insulin sensitivity and vitamin D unless obesity is present[19]. These conflicting results necessitate further large-scale studies for confirmation. Some studies have shown agreement between insulin resistance and vitamin D levels only in the presence of obesity; this association diminishes once obesity is mitigated[6,9]. Conversely, another study found that PCOS patients with very low vitamin D levels exhibited insulin resistance despite having a normal BMI[7]. Additionally, a statistical study confirmed that the relationship between vitamin D and insulin in PCOS patients is independent of BMI[9]. Most of these studies are cross-sectional, highlighting the need for randomized controlled intervention trials. Limited randomized controlled trials have demonstrated that vitamin D supplementation improves insulin release and sensitivity in PCOS patients, as evidenced by reduced fasting glucose levels[20,21,11].

Androgen levels

Several studies have linked elevated androgen levels with lower plasma levels of vitamin D_3 (25OHD). Low plasma vitamin D concentrations have been observed in hirsute females with or without PCOS compared to normal controls[22]. Conversely, non-hirsute females with PCOS typically show normal vitamin D values[9]. Moreover, PCOS patients have shown a positive association between plasma vitamin D_3 levels and sex-hormone-binding globulin (SHBG)[2,9,10], and a negative correlation with testosterone levels[8]. Additionally, SHBG levels are inversely correlated with low vitamin D levels in PCOS patients[2,10]. To further validate these links between vitamin D and androgen in PCOS, vitamin D supplementation in PCOS women has been shown to normalize vitamin D concentrations and reduce acne[23].

Body weight and body mass index (BMI)

Studies in PCOS patients have reported an inverse relationship between BMI and plasma vitamin D concentrations[6,8,19]. Recent reports confirm that vitamin D precursors are lower in overweight females with PCOS[19]. This

suggests that vitamin D deficiency in PCOS may primarily be linked to obesity[10]. Considering the lipophilic nature of vitamin D, it tends to accumulate in adipose tissue, leading to higher concentrations in overweight individuals[24]. Similarly, the utilization and metabolism of vitamin D may differ between overweight and lean subjects.

Vitamin D and reproductive function in PCOS patients

The influence of vitamin D on reproductive function is underscored by the presence of vitamin D receptors (VDRs) in reproductive tissues such as ovaries, placenta, and endometrium[25]. Low plasma vitamin D levels can lead to hypocalcemia, which has been associated with inhibition of folliculogenesis in PCOS patients. This can result in menstrual irregularities and impaired fertility[26],[27]. Vitamin D supplementation in PCOS patients focuses on its role in metabolic pathways including glucose metabolism, insulin receptors, and proinflammatory cytokines[18]. Vitamin D primarily influences insulin resistance, leading to reduced hyperandrogenism, which in turn decreases ovarian androgen production and increases sex-hormone-binding globulin. This comprehensive approach aims to alleviate all complications associated with PCOS (Figure 1)[28]. Vitamin D also influences reproduction through molecular mechanisms that enhance follicular sensitivity to follicle-stimulating hormone (FSH) and increase progesterone production[29]. Vitamin D and systemic diseases in PCOS patients

Cardiovascular diseases

Inadequate vitamin D levels adversely impact the cardiovascular system, as vitamin D receptors (VDRs) are abundant in endothelial cells of blood vessels and the heart. Vitamin D deficiency is associated with increased risk of cardiovascular morbidity and mortality[30],[31],[32],[33]. Plasma vitamin D concentrations inversely correlate with cardiovascular risk factors such as insulin resistance, impaired glucose tolerance, dyslipidemia, elevated C-reactive protein, triglycerides, low high-density lipoprotein (HDL), and leptin[5]. Observational studies have shown a coexistence of metabolic syndrome and low vitamin D levels in PCOS patients[9]. Furthermore, vitamin D supplementation in patients with cardiovascular diseases and metabolic disturbances has resulted in decreased triglyceride levels, improved insulin sensitivity and glycemic control, and increased total cholesterol and low-density lipoprotein (LDL) levels. However, no significant changes were observed in blood pressure, waist circumference, and HDL levels[11],[21].

Psychological diseases

Clinical features associated with PCOS (menstrual irregularities, infertility, hirsutism, acne, and obesity) contribute to mood disturbances in women. Studies suggest that mood changes in PCOS may partly stem from vitamin D deficiency, as vitamin D modulates neurotransmitter release and function[34],[35],[36]. A review highlighted four studies demonstrating mood disturbances associated with low plasma vitamin D levels in PCOS, including seasonal affective disorder, depression, and low mood[37]. Moreover, vitamin D supplementation improved mood disorders in up to 50% of patients, with improvements correlating with increased plasma vitamin D levels[38].

DISCUSSION

Excessive androgen production by the ovaries and adrenal glands is a primary characteristic of PCOS. PCOS serves as a natural model demonstrating the impact of excess androgens on bone health in females[39]. In women with PCOS, the adverse effect of amenorrhea on bone health is offset by the overproduction of androgens[40]. Insulin resistance and systemic hyperinsulinemia play a significant role in driving hyperandrogenism in this syndrome. Insulin, in conjunction with LH, stimulates androgen synthesis by ovarian theca cells in vitro. Hyperinsulinemia, characterized by reduced insulin-mediated glucose metabolism, has been observed in 10-25% of overweight individuals during complex insulin secretion studies[41]. Conversely, there is evidence suggesting subdued insulin sensitivity in lean individuals with PCOS, contrasting with overweight individuals where these changes are clinically significant, underscoring the substantial contribution of adiposity to insulin resistance in PCOS[42],[43].

According to a study by Dunaif et al.[44], women with PCOS exhibit significant insulin resistance independent of obesity, body shape distortions, and glucose homeostasis impairment. However, significant disparities in insulin resistance have been noted between lean and overweight women with PCOS, highlighting obesity as the factor most severely impacting insulin resistance[8]. Both hyperinsulinemia and adiposity likely contribute to the development of PCOS. Low calcium intake has been proposed as a potential contributor to obesity[45]. However, our study did not find differences in calcium levels between overweight and lean women with PCOS. Serum 25-OH-D_3 concentrations were significantly lower in overweight postmenopausal women compared to healthy controls. Reduced sunlight exposure due to decreased mobility in obese individuals, increased vitamin D sequestration in adipose tissue, and suppression of hepatic vitamin D production due to elevated 1,25-dihydroxyvitamin D levels may contribute to the low levels of 25-OH-D_3 in overweight individuals[46]. Obesity-related vitamin D deficiency may have functional implications, as evidenced by anticipatory hyperparathyroidism observed in overweight individuals with low 25-OH-VD concentrations[47]. Consistent with our findings, Hahn et al.[7] demonstrated that increasing body mass was significantly associated with lower 25-hydroxyvitamin D concentrations in PCOS patients. Low levels of 25-OH-VD may play a role in the development of diabetic complications[48]. Oral administration of 1,25-dihydroxyvitamin D_3 prevented lean diabetic mice from developing insulin-dependent diabetes, as reported by Zella et al.[49]. Women with PCOS are at increased risk of developing hyperglycemia and type 2 diabetes (T2DM)[8]. Vitamin D deficiency is prevalent in women with T2DM[40]. Supplementation with vitamin D has been shown to improve insulin levels[21].

CONCLUSION

This review concludes that maintaining adequate vitamin D levels is crucial for preventing or managing significant diseases, including PCOS. Vitamin D deficiency may contribute to the initiation or progression of these conditions.

Recommendation

Administration of vitamin D should be considered as part of comprehensive therapy for overweight PCOS patients with low vitamin D levels, aiming not only to improve insulin resistance but also to mitigate other associated complications. Randomized controlled prospective studies are warranted to explore the potential beneficial effects of vitamin D supplementation in overweight individuals, with or without PCOS, particularly in preventing type 1 and type 2 diabetes mellitus. There is an unfavorable relationship between vitamin D levels and diabetes that merits further investigation.

REFERENCES:

1. March WA, Moore VM, Willson KJ, et al. The prevalence of polycystic ovary syndrome in a community sample assessed under different diagnostic criteria. *Hum Reprod.* 2010;25(2):544–51.
2. Lam PM, Johnson IR, Raine-Fenning NJ. Three-dimensional ultrasound features of the polycystic ovary and the impact of phenotypic variations on these parameters. *Hum Reprod.* 2007;22(12):3116–23.
3. Talbott EO, Zborowski JV, Boudreaux MY. Do women with polycystic ovary syndrome have an increased risk of cardiovascular disease? A review of the evidence. *Int Congr Ser.* 2004;1266(C):233–40.
4. Ramagopalan SV, Heger A, Berlanga AJ, et al. A ChIP-seq defined genome-wide map of vitamin D receptor binding: Associations with disease and evolution. *Genome Res.* 2010;20(10):1352–60.
5. Thomson RL, Spedding S, Buckley JD. Vitamin D in the etiology and

management of polycystic ovary syndrome. *Clin Endocrinol (Oxf).* 2012;77(3):343–50.
6. Panidis D, Balaris C, Farmakiotis D, et al. Serum parathyroid hormone concentrations are increased in women with polycystic ovary syndrome. *Clin Chem.* 2005;51(9):1691–7.
7. Yildizhan R, Kurdoglu M, Adali E, et al. Serum 25-hydroxyvitamin D concentrations in obese and non-obese women with polycystic ovary syndrome. *Arch Gynecol Obstet.* 2009;280(4):559–63.
8. Wehr E, Pilz S, Schweighofer N, et al. Association of hypovitaminosis D with metabolic disturbances in polycystic ovary syndrome. *Eur J Endocrinol.* 2009;161(4):575–82.
9. Li HWR, Brereton RE, Anderson RA, et al. Vitamin D deficiency is common and associated with metabolic risk factors in patients with polycystic ovary syndrome. *Metabolism.* 2011;60(10):1475–81. Available from: http://dx.doi.org/10.1016/j.metabol.2011.03.002
10. Wehr E, Pieber TR, Obermayer-Pietsch B. Effect of vitamin D3 treatment on glucose metabolism and menstrual frequency in polycystic ovary syndrome women: A pilot study. *J Endocrinol Invest.* 2011;34(10):757–63.
11. Mazloomi S, Sharifi F, Hajihosseini R, et al. Association between Hypoadiponectinemia and Low Serum Concentrations of Calcium and Vitamin D in Women with Polycystic Ovary Syndrome. *ISRN Endocrinol.* 2012;2012:1–6.
12. Lerchbaum E, Giuliani A, Gruber HJ, et al. Adult-type hypolactasia and calcium intake in polycystic ovary syndrome. *Clin Endocrinol (Oxf).* 2012;77(6):834–43.
13. Mahmoudi T, Gourabi H, Ashrafi M, et al. Calciotropic hormones, insulin resistance, and the polycystic ovary syndrome. *Fertil Steril.* 2010;93(4):1208–14. Available from: http://dx.doi.org/10.1016/j.fertnstert.2008.11.031
14. Prentice A. Vitamin D deficiency: A global perspective. *Nutr Rev.* 2008;66(SUPPL.2):153–64.
15. Lips P. Worldwide status of vitamin D nutrition. *J Steroid Biochem Mol Biol.* 2010;121(1–2):297–300. Available from: http://dx.doi.org/10.1016/j.jsbmb.2010.02.021
16. Mahmoudi T. Genetic variation in the vitamin D receptor and polycystic ovary syndrome risk. *Fertil Steril.* 2009;92(4):1381–3. Available from: http://dx.doi.org/10.1016/j.fertnstert.2009.05.002
17. Teegarden D, Donkin SS. Vitamin D: Emerging new roles in insulin sensitivity. *Nutr Res Rev.* 2009;22(1):82–92.
18. Muscogiuri G, Policola C, Prioletta A, et al. Low levels of 25(OH)D and insulin-resistance: 2 unrelated features or a cause-effect in PCOS? *Clin Nutr.* 2012;31(4):476–80.
19. Selimoglu H, Duran C, Kiyici S, et al. The effect of vitamin D replacement therapy on insulin resistance and androgen levels in women with polycystic ovary syndrome. *J Endocrinol Invest.* 2010;33(4):234–8.
20. Kotsa K, Yavropoulou MP, Anastasiou O, et al. Role of vitamin D treatment in glucose metabolism in polycystic ovary syndrome. *Fertil Steril.* 2009;92(3):1053–8. Available from: http://dx.doi.org/10.1016/j.fertnstert.2008.07.1757
21. Glintborg D, Andersen M, Hagen C, et al. Higher bone mineral density in Caucasian, hirsute patients of reproductive age. Positive correlation of testosterone levels with bone mineral density in hirsutism. *Clin Endocrinol (Oxf).* 2005;62(6):683–91.
22. Thys-Jacobs S, Donovan D, Papadopoulos A, et al. Vitamin D and calcium dysregulation in the polycystic ovarian syndrome. *Steroids.* 1999;64(6):430–5.
23. Lagunova Z, Porojnicu LC, Lindberg F, et al. The dependency of vitamin D status on body mass index, gender, age and season. *Anticancer Res.* 2009;29(9):3713–20.
24. Stumpf WE, Denny ME. Vitamin D (soltriol), light, and reproduction. *Am J Obstet Gynecol.* 1989;161(5):1375–84. Available from: http://dx.doi.org/10.1016/0002-9378(89)90699-6
25. Parikh G, Varadinova M, Suwandhi P, et al. Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. *Horm Metab Res.* 2010;42(10):754–7.
26. Sander VA, Hapon MB, Sícaro L, et al. Alterations of folliculogenesis in women with polycystic ovary syndrome. *J Steroid Biochem Mol Biol.* 2011;124(1–2):58–64.
27. Menichini D, Facchinetti F. Effects of vitamin D supplementation in women with polycystic ovary syndrome: a review. *Gynecol Endocrinol.* 2020;36(1):1–5. Available from: https://doi.org/10.1080/ 09513590.2019.1625881
28. Irani M, Merhi Z. Role of vitamin D in ovarian physiology and its implication in reproduction: A systematic review. *Fertil Steril.* 2014;102(2). Available from: http://dx.doi.org/10.1016/j.fertnstert.2014.04.046
29. Zittermann A, Schleithoff SS, Koerfer R. Putting