

Review Article

Role of Vitamin A and Vitamin D in management of polycystic ovary syndrome

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ABSTRACT

Polycystic ovarian syndrome (PCOS), a very common cause of infertility in reproductive age groups, has increased exponentially in the past few years registering 9% of cases annually worldwide. It is one of the most common syndromes which manifests hormone secretion and its activity. Insulin resistance, obesity, Vitamin and mineral deficiency, etc., are commonly associated with PCOS. Vitamin A is a lipid-soluble vitamin that is useful in antioxidant activity and steroid synthesis is known to prevent the occurrence of PCOS. Vitamin D, a steroid hormone originating from cholesterol is commonly known as “the sunshine vitamin,” is also one of the observed vitamin deficiencies in PCOS women. Supplementation of Vitamins in the diet is essential in the management of PCOS women. This review attempts to brief the role of Vitamin A and Vitamin D as an important agent to overcome the challenges of PCOS by reviewing the investigations of various authors about the potential role of supplementation of Vitamin A and Vitamin D in various model organisms and Randomised Clinical Trials (RCT's).

Key words: PCOS, Insulin resistance, Obesity, Vitamin A, Retinol-Binding protein 4 (RBP4), Vitamin D

INTRODUCTION

PCOS, a common endocrinopathy that affects 5% to 10% of women of reproductive age and is associated with metabolic disorders and reproductive issues, has been reported as one of the major causes of chorionic anovulation and anovulatory infertility (Wood *et al.*, 2007; Dumont *et al.*, 2015). This syndrome can be diagnosed using basic clinical and biochemical parameters, as well as ultrasonography (Lujan *et al.*, 2008). The clinical presentations of PCOS are varied according to age, and it appears that patients may exhibit a variety of symptoms and signs such as menstrual abnormalities, symptoms of, obesity, ovarian impairment, hyperandrogenism and, in some instances, hirsutism. The cause of PCOS syndrome is unclear, although the wide range of patient susceptibilities are undoubtedly determined by several genetic and environmental risk factors, as indicated above (Mohammad & Seghinsara, 2017). The heterogeneity seems to be influenced by a variety of factors, including genetics, uterine diet, prenatal androgen sensitivity, insulin resistance, premature elevated activity of adrenal glands, and variations in body weight (Abbott *et al.*, 2009; Oberfield *et al.*, 2011).

Treatment of PCOS is essential for the manage and overcome chronic conditions associated to PCOS such as obesity, type 2 diabetes, and other metabolically related dysfunctions and

psychological problems to overcome both hyper-androgenism and hyper-insulinemia because PCOS elevates the risk for all these parameters for at least 2-3-fold in women. One of the most interesting comorbidities studied in PCOS women is the vitamin and mineral deficiencies and therefore nutrient supplementations efficiently help in management of PCOS (Zhang *et al.*, 2013). Vitamins have known to act as cofactors in regulating the functions of receptors associated with certain conditions of PCOS like receptors of insulin and androgen. Therefore, supplementation with vitamin or mineral have beneficial effects in management of PCOS associated comorbidities like anovulatory condition, overweight or increased BMI, elevated levels of insulin, cardiovascular disorders, increased androgen levels, along with mental and psychological issues (Günalan *et al.*, 2018; Hoeger *et al.*, 2021).

Vitamin A (Vit A), a water insoluble vitamin is a form of monohydric unsaturated alcohols with an alicyclic ring, but soluble in fat. Vit A's primary biological functions include vision preservation, growth, and epithelial and mucous tissue integrity (Günalan *et al.*, 2018). Retinoids belong to class of small organic molecules that are crucial for certain biological processes pertaining to development including morphogenesis, growth, and cell differentiation (O'Byrne & Blaner, 2013). Presently, data suggests that all-*trans* retinoic acid (RA), is essentially required for male and female reproductive processes as well as for embryonic development,

as the main form of vitamin A (Clagett-Dame & Knutson, 2011). Vitamin D is a steroid hormone which is needed in the regulation of calcium phosphate and bone mineralization (Miao *et al.*, 2020). In PCOS women, vitamin D affects metabolism (Krul-Poel *et al.*, 2013). Patients with PCOS have a comparatively greater prevalence of vitamin D insufficiency (Mousa *et al.*, 2015) and recent research has shown that vitamin D deficiency (VDD) in people with PCOS is widespread and that it may be linked to metabolic and endocrine conditions that are connected to PCOS (Wild *et al.*, 2011; Thomson *et al.*, 2012; Trummer *et al.*, 2018). However, the mode of action of Vitamin A and Vitamin D as nutritional supplement for management of PCOS in affected women is an approaching concept. Thus, this review aims to investigate the usefulness of vitamins A and D in treating PCOS.

The design of the study was to review the effects of the Vitamin A and Vitamin D and their beneficiary role in management of PCOS by supplementation. We reviewed different literatures through databases such as PubMed, NCBI, Google Scholar and Various Journals indexed in Web of Science and SCOPUS. We summarized the investigations of different clinical trials and data conducted using model organisms.

ROLE OF VITAMIN A

Vitamin A is a fat-soluble vitamin that is crucial for metabolic activities and is necessary for proper growth and development. It is an iso-prenoid molecule with a 6-membered ring and an 11-carbon side chain. Vitamin A (retinol) is usually consumed as either carotenoids or as retinyl esters which gets metabolized to 11-cis-retinal and all-trans-retinoic acid (ATRA) as active compounds. Retinol being the most biologically active form of the vitamin in the mammalian tissues is essential as it plays an important role in vision. Vitamin A is essentially required for many processes, including reproduction (the production of sexual steroids, spermatogenesis, conception, and placenta formation), differentiation of cellular epithelium, cell division control, bone remodelling, genetic regulation, immune system enhancement, and all stages of lung development (Edem, 2008; Conaway *et al.*, 2013). In addition to their antioxidant effects, retinoid, retinoic acid, and retinol also influence steroid metabolism, oocyte nuclear maturation, and the inhibition of cumulus cell death (Günalan *et al.*, 2018). Chemical compounds known as retinaldehydes (Rh) are essential for the development of many biological and biologically-related activities, including cell differentiation, growth, and morphogenesis. Many issues with the reproductive system, including ovarian and testicular size decrease, can result from vitamin A deficiency in different animals (O'Byrne & Blaner, 2013). Retinoid, which includes retinol and its derivatives, are necessary to maintain barrier function, reproduction, embryogenesis, vision, immunity, reproduction, and cell division and proliferation. The beginning of meiosis in the mammalian foetal ovarian germ cells is also significantly influenced by retinoid signalling. According to recent research,

the ovary's ability to regulate its own retinoid level results in the molecular control of ovarian growth, steroidogenesis, and oocyte maturation. Polycystic ovary syndrome (PCOS), one of the most prevalent ovarian endocrinopathies in reproductive-aged women globally, may, nevertheless, be a patho-physiology of aberrant retinoid signalling (Jiang *et al.*, 2017). Vitamin A deficiency has still remained a problem in developing countries and underdeveloped countries (Humphrey *et al.*, 1992). Studies show that a lack of vitamin A in pregnant rats' diets resulted in the development of placental apoptosis (Clagett-Dame & Knutson, 2011). The relationship between maternal vitamin A deficiency and abnormal placental apoptosis in the trophoblast giant cells, which is induced by Neutrophil-derived TNF-acting through the TNFR1 (p55) and/or a change in the bcl-2/bax ratio, may be explained by the effects of vitamin A deficiency on foetal development. According to their earlier research, it is possible to avoid foetal atrophy by injecting retinol into rat models with vitamin A deficiency soon before the tenth day of pregnancy (Antipatis *et al.*, 2002).

The retinol binds to the retinol-binding proteins and helps in solubilizing retinol to be delivered to target tissues and thus helps in maintaining the retinol plasma concentrations (Dawson, 2000). Studies demonstrate a correlation between higher Retinol-binding protein 4 (RBP4) levels and variables such as obesity and poor glucose metabolism in overweight PCOS women (Hahn *et al.*, 2007; O'Byrne & Blaner, 2013). Another RBP4-based investigation found RBP4 expression in PCOS women's isolated subcutaneous and omental adipose tissue. By activating the RBP4 gene, the scientists proposed that elevated 17-beta estradiol may be responsible for the changed gonadal and adrenal steroid profiles (Tan *et al.*, 2007). According to research, androgen biosynthesis, CYP17, CYP11A1, and StAR gene expression are all differentially regulated by retinol and retinoids in PCOS and normal theca cells. This information shows that retinoids have an impact on both the normal and PCOS theca cells' ability to produce androgen and the expression of steroidogenic enzymes. The results of several research taken together show that retinoids can control the expression of steroidogenic enzymes and androgen biosynthesis in both normal and PCOS theca cells. They also suggest that they may be a factor in PCOS's excessive theca-derived androgen production (Wood *et al.*, 2004). In conclusion, the relative vitamin A levels in females during conception and pregnancy are an important factor in determining the success of reproduction, and a vitamin A shortage may result in absolute infertility prior to implantation, fetal resorption, or deformity (Clagett-Dame & Knutson, 2011). Genes related to Retinoic acid synthesis were expressed differently in Theca interna cells obtained from PCOS patients (Wood *et al.*, 2003). Applying retinoids, which are retinol derivatives, to theca interna cell cultures obtained from PCOS and healthy women allowed researchers to study the effects of these compounds. All trans retinol-treated theca interna cells showed a rise in dehydroepiandrosterone levels and mRNA accumulation of cytochrome P450 17 hydroxylase (CYP17),

implicated in androgen production and retinol biosynthesis (Wickenheisser *et al.*, 2005). The preantral and antral follicles as well as the oocyte diameter were observed to be enhanced in healthy mice after receiving an injection of retinoic acid (0.05 g/L) (Jiang *et al.*, 2017). Hyper-androgenism is impacted by using inositol, vitamin A, carnitine, omega-3 fatty acids, and NAC supplements (Moayeri *et al.*, 2020). According to studies, adding retinoic acid accelerated primary follicle development and raised the percentage of mature oocytes, and it also boosted the number of blastocysts fertilized in a primary follicle culture (Tahaei *et al.*, 2011; Pu *et al.*, 2014). According to research, all-trans retinoic acid (ATRA) prevents apoptosis in cumulus cells by up regulating the expression of the Bcl-2 and catalase (CAT) genes while down regulating the expression of caspase-8. ATRA also increased oocyte survival and nuclear maturation when compared to controls.

In conclusion, the findings from this investigation suggest that the injection of Retinols as promising new therapy to treat women with PCOS as it has both protective and ameliorative effects. As a result, treating PCOS in women with these supplements improves hyper-insulinemia and boosts insulin sensitivity (Tahaei *et al.*, 2011; Pu *et al.*, 2014). In short, supplementation of vitamin A has shown wider impacts along with, enhancing vision, reproduction and immune functions accounting to its beneficiary effect on human health in saving countless lives (Humphrey *et al.*, 1992).

ROLE OF VITAMIN D IN PCOS

Vitamin D is a crucial fat-soluble vitamin that serves as a precursor for important hormones involved in key processes like controlling the metabolism of calcium and phosphate in combination with parathyroid hormone, which is required for bone growth and development as well as for controlling immune response and protein synthesis. The term "vitamin D" refers to both ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃), both of which can be obtained from bright plant sources and sunlight, respectively. Ergocalciferol (vitamin D₂) is converted into the biologically active form 25(OH) D (calcidiol), which represents the serum concentration of the precursor to the active steroid hormone, while cholecalciferol (vitamin D₃) is obtained from (Kulda, 2012; Chiang *et al.*, 2017). According to studies, less than 20 ng/mL of 25(OH)D serum concentrations have been found to be associated with metabolic syndrome, illustrating the strong association between Vitamin D deficiency and PCOS and its serious impact on health. Additionally, 67-85% of women with PCOS have significant Vitamin D deficiency. Low 25(OH) D levels increase the risk of cardiovascular illnesses while exacerbating PCOS symptoms including insulin resistance, hyper-androgenism, ovulatory abnormalities, infertility, and obesity (Menichini & Facchinetti, 2020). More than 900 genes involved in various physiological processes are controlled by the intracellular vitamin D receptor (VDR), which is bound by 1,25(OH)₂D, the physiologically active form of vitamin D (Bizzaro *et al.*, 2017). Literature shows that the influence of the

VDR polymorphisms in women with PCOS related to vitamin D metabolism. They also illustrated the role of Vitamin D with respect to BMI and Insulin resistance in Women with PCOS discussing that there is a need for a placebo controlled RCT to be conducted due to inconsistent data (Krul-Poel *et al.*, 2013).

According to research, potential genes linked to PCOS include genes involved in vitamin D metabolism. In PCOS women, the VDR gene polymorphisms Cdx2, Taq1, Bsm1, Apa1, and Fok1 have an impact on insulin sensitivity and secretion (Al-Daghri *et al.*, 2014). In PCOS women of Taiwanese ancestry, the VDR 1a promoter polymorphisms were found to be related to blood levels of 25(OH)D (Lin *et al.*, 2012). Further research on the relationships between VDR genotypes and the clinical or biochemical characteristics of PCOS in women in India revealed that the Cdx2 genotypes affected testosterone levels, and the Fok1 polymorphism substantially predicted infertility. They also said that the two haplotypes, ACCA and ACTA, made up of four polymorphisms, were shown to be substantially related with PCOS. The relevance of these VDR gene variations in the patho-physiology of insulin resistance and PCOS is still unknown due to a lack of evidence, despite reports suggesting that they may play a significant role in PCOS (Lin & Wu, 2015).

The effect of vitamin D supplementation on plasma vitamin D levels, glucose metabolism, and insulin sensitivity has all been previously reported in studies. Hyper-androgenism and IR women with PCOS have also been found to be negatively correlated with vitamin D supplementation, as have fasting glucose levels and insulin sensitivity. At a minimum of 12 weeks, women with PCOS who received vitamin D administration at dosages as high as (4000 IU/d) had positive changes in their hyper-insulinemia, androgenic and fertility levels. Supplementation of vitamin D to women with PCOS showed reduction in insulin resistance, hyperandrogenism and also improved the lipid metabolism in them according to data available from the randomized controlled trials (RCT's).

In conclusion, there is evidence to support the hypothesis that functional genetic variations in the VDR, CYP2R1, and CYP24A1 genes of vitamin D are caused by vitamin D₃ administration, which results in an increase in blood 25(OH) D concentrations (Bizzaro *et al.*, 2017). Overall, high dose vitamin D supplementation has shown promising results in improving the treatment of the PCOS patients. Therefore, vitamin D supplementation is seeking higher attention for PCOS therapy (Menichini & Facchinetti, 2020; Miao *et al.*, 2020).

CONCLUSION

Suggestions from different investigations show that Vitamin A (Retinols) and Vitamin D are a promising therapy in future for management of the PCOS by treating the Vitamin deficiencies. This review summarizes that Vitamin A and Vitamin D, the essential Vitamins must be supplemented with diet in PCOS women for symptomatic reliefs. The inconsistent

date also shows that there is a much need for more Randomized Clinical Trials (RCT's) and more investigations for evidential support of the investigations reviewed here.

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