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Overview Of Vitamin D in PCOS Women

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Abstract: ***A common health problem known as polycystic ovarian syndrome (PCOS), is characterized by irregular periods, an excess of androgen production, and polycystic ovaries. It is one of the most prevalent endocrine disorders in women of reproductive age, affecting 4–20% of women worldwide. Numerous studies have found a connection between the onset and symptoms of PCOS and Vitamin D insufficiency. Vitamin D dramatically improves glucose metabolism by increasing insulin production, insulin receptor expression and reducing pro-inflammatory cytokines. The effect of Vitamin D on the metabolic and reproductive dysfunctions associated with PCOS may be mediated by an overall impact on insulin resistance. Vitamin D supplementation improved menstrual periods, increased folliculogenesis, and decreased blood testosterone levels in PCOS patients, all of which had a significant impact on the ability to procreate. As a result, it might be a cutting-edge therapeutic strategy for treating PCOS concurrently The present review introduces the role of vitamin D, its mechanism of action in the management of PCOS. In addition to summarizing the pathophysiology, clinical manifestations, diagnosis and treatment of PCOS from previous published data.***

Keywords: polycystic ovary syndrome; hyperandrogenism; metabolic disorders; vitamin D

1. Introduction to the polycystic ovarian syndrome

Polycystic ovary syndrome (PCOS), is a frequent health issue brought on by an imbalance of reproductive hormones. The ovaries have issues as a result of hormonal imbalance. The ovaries produce the egg discharged each month as part of a regular menstrual cycle. The egg may not mature normally or may not be released during ovulation as it should be if PCOS is present[1].PCOS is a condition that alters the way a woman's ovaries function. PCOS is characterized by irregular periods, an excess of androgen production, and polycystic ovaries. If two of the three deficiency, with around half of the world's population suffering from Vitamin D insufficiency3. Vitamin D may help to prevent cancer, diabetes, migraine, and autoimmune disorders[4]. There's a lot of evidence indicating a link between Vitamin D deficiency and PCOS development and symptoms[11].We attempted to present a short review of recent developments in Vitamin D and PCOS in this paper, including the physiological significance of Vitamin D in female reproduction, the link between Vitamin D and reproductive ability, and PCOS metabolic changes.

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder characterized by anovulation, menstrual disorders, amenorrhea, hirsutism, and infertility. Women with PCOS often have impaired metabolism of androgen and estrogen, and they are frequently obese, insulin resistant, and at risk for type 2 diabetes and cardiovascular disease. The diagnosis of PCOS typically requires the presence of at least two of the following features: clinical and/or biochemical hyperandrogenism, chronic anovulation, and polycystic ovaries as per the Rotterdam consensus.

PCOS can lead to various health complications, including reproductive issues like infertility and miscarriages, metabolic disorders such as type 2 diabetes and metabolic syndrome, and increased risk of cardiovascular diseases. It also has significant psychological impacts, including higher risks of depression and anxiety[(2)]

Treatment for PCOS focuses on normalizing menstrual cycles and addressing clinical features. This can include lifestyle modifications like diet and exercise, hormonal therapy, medications to improve insulin resistance, and assisted reproductive techniques.

Vitamin D supplementation can lower the abnormally elevated serum AMH levels and increase serum anti-inflammatory soluble receptor for advanced glycation end-products in vitamin D-deficient women with PCOS[5]. In particular, vitamin D and calcium supplementation in addition to metformin therapy in women with PCOS could result in the beneficial effects on menstrual regularity and ovulation [6]. However, Garg *et al* 7 recently demonstrated that there was no significant beneficial effect on insulin kinetics and cardiovascular risk factors after supplementation of vitamin D, at a dose of 4,000 IU/day for six months, among women with PCOS treated with metformin. Due to small sample size and the relatively short duration of follow up in previous observational study and clinical trial, the effects of vitamin D supplementation in relieving the symptoms in women with PCOS remain inconclusive [6,7]. Therefore, further research with high quality randomized controlled trials is warranted to establish the impact of vitamin D supplementation on the management of PCOS

Table 1: PCOS phenotypes according to the Rotterdam consensus.

	Severe PCOS	Mild PCOS	Ovulatory PCOS	Hyperandrogenism and Chronic Anovulation
Periods	Irregular	Irregular	Normal	Irregular
Ovaries on Ultrasonography	Polycystic	Polycystic	Polycystic	Normal
Androgen concentration	High	Mildly raised	High	High
Insulin concentrations	Increased	Normal	Increased	Increased
Risks	Potential long term	Unknown	Unknown	Potential long term

Pathogenesis

By the time the diagnosis is established, PCOS presents as a phenotype reflecting a self-perpetuating vicious cycle involving neuroendocrine, metabolic, and ovarian dysfunction. Over the years, numerous hypotheses have been proposed regarding the proximate physiologic origins for PCOS. PCOS reflects the interactions among multiple proteins and genes influenced by epigenetic and environmental factors (Fig. 1) [8]. Specific sections of this article deconstruct the factors contributing to the development of PCOS in humans and preclinical models. Clinical and biochemical hyperandrogenism are major features of PCOS.

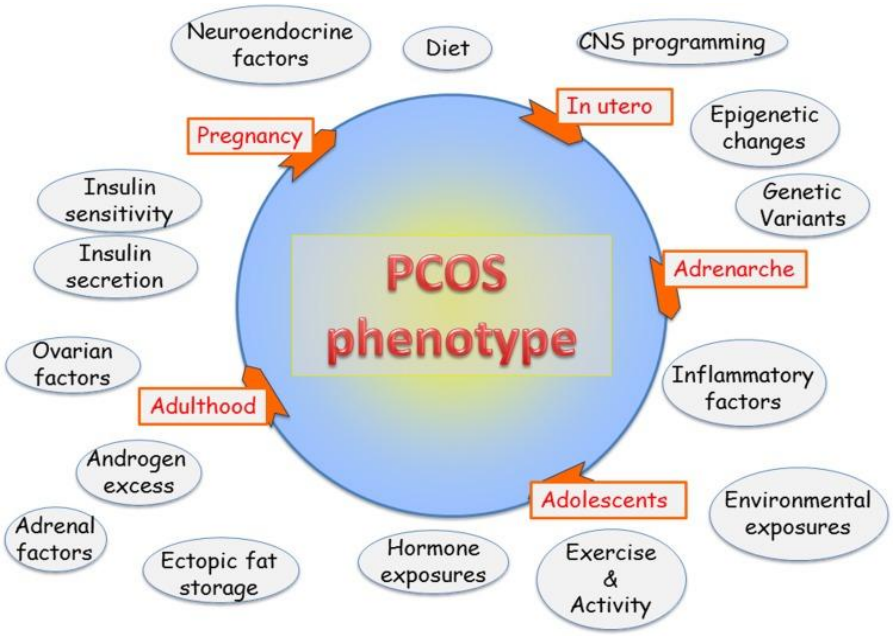

Figure 1: Factors contributing to PCOS phenotype. PCOS encompasses a woman's life cycle. Factors potentially impacting the pathophysiology of PCOS are shown in circles. Not all factors affect each individual. PCOS epitomizes a biologic network of interacting neuroendocrine, hormonal, metabolic, genetic, and environmental influences

Clinical Features and Diagnosis of PCOS:

A biochemical and clinical hyperandrogenism of ovarian origin and to a lesser extent adrenal is evident in about 60–80% of PCOS patients, resulting in one of the main features of the syndrome Ovarian hyperandrogenism is mainly due to a defect in the intrinsic steroid synthesis in ovarian thecal cells. Extra-ovarian factors, such as high levels of LH and insulin and low levels of FSH, and intraovarian factors, such as anti-Müllerian hormone (AMH) and inhibin, may enhance the hyperandrogenism state. Also high levels of androgens are recognized as one of the possible causes of PCOS insulin resistance. An excess of androgens during intrauterine life and in the immediate postnatal period may lead to accentuate visceral adiposity and insulin resistance. Medications with anti-androgenic activity may improve insulin resistance. Androgens by acting directly on the insulin signaling system may contribute to the peripheral insulin resistance in patients with PCOS. Insulin resistance and compensatory hyperinsulinaemia are involved in all three main clinical aspects of the syndrome: hyperandrogenaemia, ovarian dysfunction and metabolic alterations [9]

The prevalence of PCOS varies according to the diagnostic criteria used which usually include extension of hirsutism, level of circulating androgens, degree of irregularity of the menstruation and ultrasound morphology of the ovary.

Patients suffering from PCOS most frequently complain of:

1) Menstrual irregularities: usually associated with anovulation which is the cause of oligomenorrhoea (less than nine menstrual cycles per year; cycles of average duration exceeding 36–40 days). Anovulation in 30% of cases is accompanied by secondary amenorrhoea (no menstrual periods for three or more consecutive months) which occurs after a period of variable oligomenorrhoea.
2) Hyperandrogenism. The most characteristic clinical presentations are hirsutism and acne. Total testosterone is the best to reflect the androgenic status as the free testosterone level may not be very accurate. Total testosterone can be measured on any day of the menstrual cycle [32]. Other laboratory investigations that can be made are:
   - Free androgen index (FAI) is the ratio between total testosterone and SHBG.
   - Androstenedione is the direct precursor of testosterone, produced by the ovaries, adrenals and

peripheral tissues. In women with PCOS, androstenedione levels can be increased even when the total testosterone is normal [33].

- DHEA-S is almost exclusively of adrenal origin and is increased in about 20–30% of PCOS patients. Hyperandrogenaemia, therefore, is predominantly of ovarian origin and supported by the increased activity of the P450c17 enzyme complex in thecal cells, which has two activities, 17α-hydroxylase, which converts progesterone to 17-OH-P, and 17–20 lyase, which transforms the latter into androstenedione (Figure 2). Androstenedione will then be converted into testosterone by 17β-hydroxysteroid dehydrogenase. In particular, the activity of 17α-hydroxylase is increased. Furthermore, it appears to be an adrenal contribution to hyperandrogenaemia, again due to the excessive activation of the same microsomal enzyme P450c17, predominantly in the activity of 17–20 lyase, although a hyper-responsiveness to ACTH is not to be excluded. Insulin is able to directly stimulate the enzymatic activity of P450c17, both at the adrenal and ovarian level . A recent study has shown that androstenedione and total testosterone level helps to better assess the risk of developing metabolic syndrome in women with PCOS (9)

Introduction to Vitamin D

Vitamin D is a fat-soluble vitamin well known for its essential role in bone health. It is converted in the body into several biologically active metabolites and interacts with the genome to produce both calcemic and nonracemic effects. Several studies have been proven that vitamin D influences several body functions including cellular proliferation, differentiation, immune function, vascular tone, insulin secretion, the renin angiotensin aldosterone system, and fertility. It has been proposed that hypovitaminosis D is linked to an increased risk for cancer Chandra, autoimmune diseases, diabetes, and cardiovascular diseases and PCOs[10].

Synthesis of Vitamin D

Vitamin D, a pivotal nutrient, undergoes a unique biosynthesis process that is intricately linked to ultraviolet (UV) radiation. This synthesis is not just confined to humans but extends to various animals and fungi. Here's a detailed and sequential explanation of this process:

- **Photochemical Synthesis**: The synthesis of vitamin D in both animals and fungi is rooted in photochemistry. Specifically, many animals convert 7-dehydrocholesterol to vitamin D3, while many fungi transform ergosterol to vitamin D2.
- **Synthesis in the Skin**: The skin, specifically its epidermal strata, plays a central role in vitamin D3 production. The precursor, 7-dehydrocholesterol, is abundantly produced and reacts with UVB light, which has wavelengths ranging from 290–315 nm.
- **Evolutionary Perspective**: From an evolutionary standpoint, vitamin D synthesis is ancient. It began with photosynthesizing phytoplankton in the ocean over 500 million years ago
- **Industrial Synthesis**: On an industrial scale, vitamin D3 is produced by exposing 7-dehydrocholesterol to UVB and UVC light, followed by a purification process. This 7-dehydrocholesterol can be sourced from fish organs or wool grease from sheep[11]

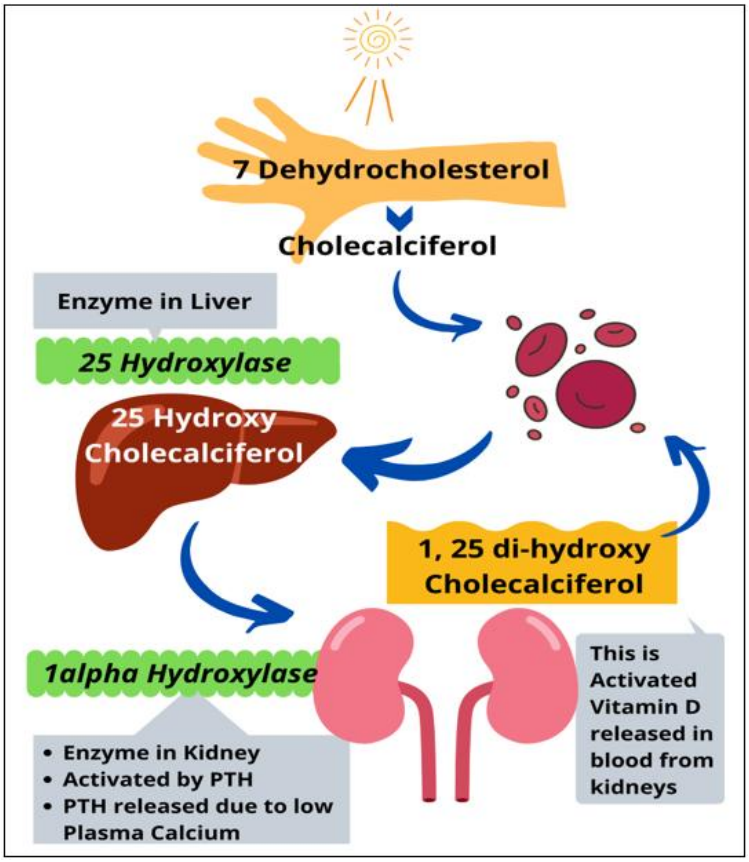

Figure 2: Vitamin D metabolism and functions

Effect of Genetic Variants of Vitamin D Metabolizing Enzymes and Proteins on PCOS Clinical Features

In women, VDR mRNA has been shown to be expressed in the ovaries [9], the pituitary gland [40], as well as in human endometrium [41]. Thus, indicating a role of vit D in steroidogenesis of sex hormones [18] Mahmoudi found an association of VDR Apa-I polymorphism with PCOS susceptibility in a cohort including 162 PCOS and 162 control women from Tehran. Moreover, in a study conducted in Iran, there was an association of VDR Taq-I with elevated serum levels of LH as well as an association between decreased levels of SHBG and VDR Bsm-I (Mahmoudi 2009). Furthermore, several polymorphisms in the VDR gene, such as Cdx2, Taq1, Bsm1, Apa1, and Fok1, were reported to play an important role on insulin secretion and sensitivity in PCOS women[12]

2. Conclusion

This review has concluded that vitamin D intake is important for restoration of normal vitamin D plasma level and inadequacy could be a causative agent for initiation or progression of important diseases including PCOS.

3. Recommendation

Administration of vitamin D could be part of the entangled therapy of PCOS patients who have overweight and low vitamin D, not only to boost insulin resistance but to also decrease other vast events. Randomized, controlled, prospective studies are justified to investigate the potential beneficial impact of vitamin D administration in overweight people either with or without PCOS, particularly if vitamin D can avert type 2 and type 1 diabetes mellitus. Diabetic was shown to have an unfavourable relationship with vitamin D levels

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