Review

ANNALS OF MEDICINE & SURGERY

OPEN

Vitamin D and polycystic ovary syndrome (PCOS): a review

Anmol Mohan, MBBS[a], Ramsha Haider, MBBS[a], Hajar Fakhor, MBBS[e], Fnu Hina, MBBS[d], Vikash Kumar, MD[f], Aleeza Jawed, MBBS[b], Koushik Majumder, MBBS[h,*], Aliza Ayaz, MBBS[a], Priyanka Mohan Lal, MBBS[b], Usha Tejwaney, Pharm. D[g], Nanik Ram, FCPS[c], Saka Kazeem, MD[f]

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 insufficiency causes calcium dysregulation and follicular arrest in women with PCOS, which is connected to menstrual irregularities and fertility issues. Studies have connected PCOS metabolic alterations to VDR polymorphisms such as iApa-I, Taq-I, Cdx2, and Fok-I. Insulin resistance is directly related to Vitamin D, is one of the most distinctive characteristics of the PCOS phenotype. Thus, it is suggested that Vitamin D therapy may help PCOS patients with their insulin sensitivity. In addition to insulin resistance, cardiovascular issues are a second metabolic disturbance that PCOS patients with low Vitamin D levels experience. Dyslipidemia is not linked to an increased risk of cardiovascular disease in PCOS-affected women. 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.

Keywords: menstrual irregularities, PCOS, vitamin D

Introduction

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 symptoms are present, a diagnosis is made[2]. With a prevalence of 4–20% of women of reproductive age globally, it is one of the most frequent endocrine disorders among reproductive-aged women[3]. Many PCOS patients exhibit metabolic syndrome symptoms such as visceral obesity, hyperinsulinemia, and insulin resistance. These factors increase the risk of cardiovascular disease (CVD), type 2 diabetes, and gynaecological cancer, particularly endometrial carcinoma, in PCOS patients[4].

Vitamin D aids in the regulation of calcium and phosphate levels in the body. The nutrients are required to maintain the health of bones, teeth, and muscles[5]. The most frequent medical issue in the world is Vitamin D insufficiency. According to studies, over 1 billion individuals worldwide suffer from Vitamin D

HIGHLIGHTS

- The paper discusses the prevalence of Vitamin D deficiency in women with polycystic ovary syndrome (PCOS) and the potential impact of Vitamin D supplementation on symptoms of PCOS.
- The paper highlights the potential link between Vitamin D deficiency and the development and progression of PCOS, with low Vitamin D levels potentially contributing to insulin resistance and inflammation, which are hallmark features of PCOS.
- The paper highlights that Vitamin D supplementation may help improve symptoms of PCOS, including menstrual irregularities, hirsutism, and insulin resistance.

[a]Karachi Medical & Dental College, [b]Ziauddin University, [c]Aga Khan University Hospital, Karachi, [d]Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan, [e]Asselin Hedelin Hospital, Yvetot, France, [f]The Brooklyn Hospital Center, Brooklyn, NY, [g]Valley Health System, Ridgewood, NJ and [h]Chittagong Medical College, Chittagong, Bangladesh

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article

*Corresponding author. Address: Chittagong Medical College, Chittagong, Bangladesh. Tel.: +880 178 398 3350. E-mail address: majumder382@gmail.com (K. Majumder).

Annals of Medicine & Surgery (2023) 85:3506–3511

Received 10 February 2023; Accepted 13 May 2023

Published online 5 June 2023

http://dx.doi.org/10.1097/MS9.0000000000000879

deficiency, with around half of the world's population suffering from Vitamin D insufficiency[6]. Vitamin D may help to prevent cancer, diabetes, migraine, and autoimmune disorders[7-10]. 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.

PCOS and reproductive cycle

The role of Vitamin D has been observed in the female reproductive health of humans and that of other animals, which has led researchers to believe that Vitamin D may be densely related to the female reproductive cycle hormones as well as organs. The presence of Vitamin D receptors (VDRs) in the granulosa cells and the cumulus oophorus cells of humans and animals[2] supports the claim that Vitamin D plays a significant role in the proper regulation of the female reproductive cycle. VDR and traces of Vitamin D metabolizing enzyme were found in syncytioblast procured from human culturing[12]. VDR was detected in the decidua as well as the placenta[13]. The transcription of dehydroepiandrosterone sulfotransferase and sulfate-conjugation of endogenous hydroxysteroids was also seen to be promoted by VDR in humans[14]. In the case of animals, researchers found VDR expression in the endometrium of mice experiencing the oestrous cycle[15]. Evidence in support of the role of Vitamin D playing a physiological part in the female reproductive cycle is not limited to VDR but extends beyond that. An active form of Vitamin D, 1,25(OH)2D3, was found to regulate the expression and secretion of hormones such as human chorionic gonadotropin hormone and human placental lactogen. Another function of active Vitamin D was found to regulate endometrial decidualization[16,17]. In addition, the active Vitamin D was also found to be a factor that could induce the in-vitro production of hormones such as progesterone, estradiol, and estrone. Oestrogen in females requires Vitamin D for its proper biosynthesis[18].

Studies have found that Vitamin D is important for regulating the expression of anti-Mullerian hormone (AMH) in granulosa cells and for follicle selection in hens[19]. In humans, AMH plays a vital role in folliculogenesis and ovarian dysfunction. Higher levels of serum AMH have been observed in women with PCOS compared to non-PCOS women. Therefore, serum AMH has been used as a diagnostic and prognostic tool for the diagnosis of PCOS in women. These findings suggest that Vitamin D may have an indirect impact on the diagnosis of PCOS through its effect on AMH levels[20]. In addition to raised levels of AMH, PCOS patients were also observed to have lower follicular fluid Vitamin D levels[21]. The connection between serum AMH levels and Vitamin D as a vital substance for proper folliculogenesis was seen when Vitamin D treatment decreased serum AMH levels in PCOS patients[22]. In addition to decreasing serum AMH levels, Vitamin D therapy also increased serum anti-inflammatory soluble receptors for end-products of advanced glycation in Vitamin D-deficient PCOS patients[23]. Thus Vitamin D therapy, coupled with metformin therapy and calcium supplementation, could have therapeutic effects on menstrual regularity and ovulation of PCOS patients[24]. Ovarian marker such as AMH is seen to have an essential correlation with Vitamin D. This relationship becomes evident when it was observed that the expression and serum levels of AMH are altered by deficiency of Vitamin D[25-28]. It is speculated that the AMH gene mediation plays a role in the ovulatory dysfunction, thus the impact of Vitamin D serum levels, and deficiency of it, on AMH indirectly affects the ovulatory functions. Upon investigating the correlation between Vitamin D and the female reproductive cycle, Vitamin D was observed to be related to steroidogenesis and serum and cellular AMH levels. It was also observed that the mRNA for VDR and its relative protein levels were found to be increased after the administration of an active form of Vitamin D[23]. A study by Merhi *et al.*[28] revealed that active Vitamin D; 1,25-dihydroxyvitamin D3 had an impact on the AMH sensitivity of granulosa cells in women who had undergone oocyte retrieval in in-vitro fertilization (IVF). Vitamin D also increases the levels of progesterone, estrone, and oestrogen in the blood as; it also increases the level of oestrogen and progesterone in the human placenta. An increase in insulin-like growth factor-binding protein-1 production in the ovarian cells of humans was also noted, according to a study conducted by researchers[2,29].

These findings demonstrate the physiological role of Vitamin D in female reproductive health. Along with these findings, it was also noted that Vitamin D decreased the serum testosterone level while increasing insulin sensitivity[30]. Considering all these physiological effects of Vitamin D on female reproductive health, a positive effect of Vitamin D in PCOS patients was presented. Although there is still a lapse in the extensive investigation of this proposal, it was suggested that Vitamin D has a positive impact on the endometrial alteration of PCOS patients[11].

Aggravation of PCOS symptoms due to Vitamin D deficiency

A growing body of evidence indicates that Vitamin D is essential to reproductive health. Ovarian, endometrial, and placental VDRs have been found. Menstrual imbalance and fertility dysfunction are linked to Vitamin D deficiency, which causes calcium dysregulation and follicular arrest in women with PCOS[31].

In a small uncontrolled study, researchers investigated whether Vitamin D and calcium dysregulation contribute to a follicular arrest resulting in menstrual and reproductive dysfunction. A study of 13 Vitamin D-deficient PCOS women [mean 25(OH)D value of 11–2 ng/ml] showed that combining Vitamin D with calcium boosted 25(OH)D levels within 2–3 months of treatment to within the normal range (30–40 ng/ml). Within 2 months, seven of the nine women with menstrual dysfunction experienced normalized menstrual cycles, two became pregnant, and the other four maintained regular menstrual cycles[31].

Vitamin D's therapeutic efficacy in PCOS-associated metabolic parameters has been evaluated in several pilot studies. It was reported in a study dated 1990 that seven of nine oligomenorrheic women with PCOS undergoing Vitamin D and calcium supplementation over six months had their menstrual cycle normalized[32]. Similarly, 60 women with PCOS undergoing a later study who were randomized into three groups and given calcium and Vitamin D supplements, metformin, or both confirmed these results. Three months after the treatment, the combination group had more dominant follicles[32].

On 57 women with PCOS in 2011, Wehr and colleagues examined the effects of 20,000 IU Vitamin D weekly for 24 weeks on endocrine and metabolic parameters. Women with PCOS, previously affected by menstrual disturbances (30.4%), reported that their periods had improved after 12 weeks; after 24 weeks, 23 out of 46 women (50.0%), who were at baseline oligo-amenorrheic, reported that their periods had improved. During the study, 4 out of 16 women who were trying to get pregnant at the beginning of the research successfully conceived[33].

As a result of Vitamin D repletion administered weekly or biweekly in combination with the administration of 1500 mg calcium daily, seven out of thirteen premenopausal women with chronic anovulation and hyperandrogenism experienced normalization of menstrual cycles and two became pregnant. Furthermore, all three women with acne vulgaris experienced clinical improvements in their condition[34].

Another study tested 57 women whose glucose metabolism and menstrual frequency were improved, though their BMI did not change as a result of taking Vitamin D3 for 24 weeks[34]. The cardiovascular system may be adversely affected by Vitamin D deficiency, according to emerging research. Vascular smooth muscle and endothelium contain VDRs, and large cohort studies have found a link between Vitamin D deficiency and an increased risk of CVD and mortality. The association between low Vitamin D levels and an increase in CVD risk factors other than insulin resistance has also been demonstrated in PCOS women, including increased levels of total cholesterol, systolic and diastolic blood pressure, glucose, C-reactive protein, triglycerides, high-density lipoprotein cholesterol, total cholesterol[31].

Several PCOS symptoms and potential health issues, including infertility, irregular periods, increased hair growth, obesity, and acne, can contribute potential for mental health problems, including depression. The psychological response to PCOS symptoms may be mediated by hormones and neurotransmitters, making depression and Vitamin D deficiency more fundamentally linked. There was evidence that low 25(OH)D levels are associated with mood disorders (premenstrual syndrome, seasonal affective disorder, unspecified mood disorder, and major depressive disorder) in a review of four studies published in 2008[31].

These studies imply that Vitamin D supplementation may have a role in treating PCOS, although more research is needed. Large randomized controlled trials are needed to further understand the effect of Vitamin D supplementation in women with PCOS.

Effects of Vitamin D deficiency in various genotypes of PCOS

VDR polymorphisms are thought to contribute to or increase the risk for PCOS. In accordance with this theory, 1,25[OH]2D controls several hundred genes, including some relevant to glucose homoeostasis. Studies have linked VDR polymorphisms, such as iApa-I, Taq-I, Cdx2, Bsm-I, and Fok-I, to metabolic changes in PCOS. The rs757343 single-nucleotide polymorphism was also associated with the severity of PCOS symptoms but not with the risk of developing the underlying condition[35].

Despite the relatively small sample sizes, numerous studies suggest an association between VDR polymorphism and PCOS and insulin resistance[36,37,38]. Researchers found differences in the distributions of several VDR gene polymorphisms, including Apa-I and Fok-I, in a cohort of 162 women with PCOS and their controls. The variation in the VDR, which affects the levels of luteinizing hormone (LH) and sex hormone binding globulin (SHBG) and testosterone, may be linked to PCOS[39].

According to research from Iran, the distribution of VDR polymorphisms between people with PCOS and those without did not differ significantly[38]. Nonetheless, other studies have indicated that VDR polymorphisms, such as the Taq-I genotype, are more frequent in PCOS and are associated with higher levels of LH and testosterone. This suggests the Taq-I genotype may be associated with a higher risk of PCOS. According to another study, polymorphisms were similar between PCOS and control groups, but PCOS patients with heterozygous genotypes had lower Vitamin D levels[40].

An Austrian study that included 545 PCOS and 145 control patients found an association between VDR Cdx2 and insulin metabolism, whereas VDR Apa-I was associated with hyperandrogenemia[36]. Polymorphisms related to VDR did not appear to affect PCOS susceptibility. Additionally, a study including 56 PCOS women from Iran identified an association between elevated serum levels of LH and VDR Taq-I as well as a relationship between lower levels of SHBG and VDR Bsm-I[37].

Moreover, in another study, VDR ApaI gene polymorphisms were linked to testosterone levels in PCOS women, while VDR Cdx2 variants were associated with insulin sensitivity. VDR Bsm-I and VDR Taq-I gene polymorphisms were also linked to low SHBG levels and high LH levels, respectively[41].

It is currently too early to draw any firm conclusions about the relationship between VDR polymorphisms and the severity of PCOS symptoms. Still, continued research into polymorphic variants could allow us to understand more about this common disease.

Vitamin D and insulin resistance

Although the deficiency of Vitamin D prevails in the general public, it is one of the most common findings in PCOS patients[31,36,42]. One of the most characteristic findings of the PCOS phenotype is resistance to insulin, which is closely linked to Vitamin D. Thus, it is said that Vitamin D therapy may improve insulin sensitivity in PCOS patients[43,44,45]. Insulin synthesis and release are said to be enhanced by the increase in the expression of insulin receptors, via Vitamin D therapy[42,46]. In patients with PCOS, the relationship between Vitamin D and insulin resistance does not seem to be aggravated or connected to obesity. According to one of the speculations made by researchers, it can be assumed that Vitamin D appears to have a positive impact on insulin receptors and insulin responsiveness for glucose because active Vitamin D activates the transcription of the insulin gene. This hypothesis is also supported by the fact that there is a promoter region on the human insulin gene, which is responsive to Vitamin D[34,47,48]. Insulin resistance is often associated with increased chances of developing metabolic such as diabetes mellitus as well as cardiac issues[49]. The metabolic disturbances caused in PCOS patients due to Vitamin D deficiency are not fully understood yet and are still being researched[50].

In a recent meta-analysis, it was noted that when Vitamin D is given continuously at doses that are less than 4000 IU/day, it improves glucose metabolism and insulin resistance[51,52]. It also seemed to have beneficial effects on menstrual frequency and

hyperandrogenism[33,53]. In a recent study by Zeeshan *et al.*, Vitamin D supplementation results were placed against a placebo control group; Vitamin D Supplementation showed improvements in alanine aminotransferase and insulin resistance. This study explored the beneficial impacts of Vitamin D supplements, which were found to be modest improvements in insulin resistance characteristics in obsessing Vitamin D-deficient women with PCOS[54].

Vitamin D deficiency and metabolic risk factors in PCOS women

According to a study conducted by Georgopoulos *et al.*[55], women with PCOS were found to have a lower basal metabolic rate compared with women without PCOS. Upon extensive research, it was concluded that Vitamin D plays a vital role in various metabolic pathways. Thus deficiency of Vitamin D leads to many metabolic irregularities, such as causing and aggravating the pathogenesis of insulin resistance and PCOS, as both depend on serum Vitamin D levels[56]. Another study by Thompson *et al.*[31] suggested a link between the level of Vitamin D in females and the hormonal and metabolic disorders found in PCOS cases. Thus based on these findings, it is proposed that Vitamin D supplementation may result in effective modification of hormonal and metabolic disturbances in PCOS patients[57].

In addition to insulin resistance, cardiovascular disorders are another metabolic disturbance observed in patients with PCOS. Vitamin D deficiency was associated with an increased risk of cardiovascular diseases[58,59]. In addition, research conducted on PCOS revealed an inverse relationship between Vitamin D levels and the risk of cardiovascular diseases in women with PCOS[60].

Vitamin D and metabolic diseases

Another downside of PCOS has been found in investigations. A meta-analysis concluded results in support of a pattern of dyslipidemia in PCOS patients[61]. According to a study conducted by Hahn *et al.*[62], the correlation between various patterns of dyslipidemia and Vitamin D deficiency was observed. It was concluded that lower levels of active form of Vitamin D were inconsistent with features of PCOS such as dyslipidemia[63]. Obesity, disturbing levels of triglyceride, and total cholesterol are very frequently characteristic of PCOS. In a study conducted by Rasha *et al.*[64]. it was observed that in Egyptian patients with PCOS, there was a significant decrease in GABA levels compared to normal females. This deficiency of serum GABA was associated with dyslipidemia and low testosterone levels in light of Vitamin D deficiency.

Dyslipidemia is inconsistent with an increased risk of cardiovascular disease in women with PCOS. According to Jiaxi *et al.*[65]. it was found that Vitamin D supplements demonstrated a reduction in lipid metabolism in patients with PCOS. The effects of Vitamin D supplementation on the regulation of dyslipidemia and improvement of lipid metabolism in PCOS patients have been proven only statistically via meta-analysis. Still, they have yet to be proven in a significant manner in clinical trials. In accordance with the increased prevalence of Vitamin D deficiency and dyslipidemia seen in PCOS, a linkage between the two has been established. Thus Vitamin D supplements are considered a viable therapy option that may be utilized in patients with dyslipidemia due to PCOS, as it may prove to be an add-on therapy with decreased risks.

Therapeutic use of Vitamin D in PCOS

Vitamin D has been proven to have therapeutic uses in PCOS based on the prognosis of PCOS. Vitamin D significantly enhances insulin synthesis and increases insulin receptor expression while suppressing pro-inflammatory cytokines, thus improving glucose metabolism[66]. Vitamin D's influence on PCOS metabolic and reproductive dysfunctions might be mediated through an overall effect on insulin resistance. Compared with the placebo group, Vitamin D treatment significantly reduced fasting plasma glucose; insulin resistance, or serum fasting insulin, showed significant improvement. In addition, four investigations found that the mean blood triglyceride level decreased significantly[67].

In a study conducted by Dastorani *et al.*[68]. infertile women with PCOS who were candidates for IVF were given 50 000 IU of Vitamin D every other week for 8 weeks, which resulted in significant reductions in blood levels of AMH and insulin. Overall, this study showed that taking 50 000 IU of Vitamin D every other week for 8 weeks improved insulin metabolism and several lipid profile measures in infertile women with PCOS who were candidates for IVF.

Menstrual regularity was shown in 70% of the patients who took calcium, Vitamin D, and metformin, and the follicular response was seen in 28% of the patients, even though there was no statistically significant difference between the two groups following therapy, according to Raziah *et al.*[69]. Treatment with Vitamin D might compensate for Vitamin D insufficiency, significantly raise vitamin levels, and lower BMI. In addition, Vitamin D supplementation may be beneficial in treating PCOS patients, not just for improving insulin resistance and infertility.

Conclusion

We outlined how Vitamin D affects PCOS-related metabolic changes, reproductive ability, and mental wellness. The Vitamin D levels in PCOS patients' serum and follicular fluid were lower in prior research. Serum testosterone levels, IR parameters, and body fat mass all had unfavourable correlations with Vitamin D levels. Vitamin D therapy enhances IR and lipid metabolism, lessening PCOS patients' metabolic problems. Additionally, Vitamin D supplementation helps PCOS patients with their mental issues. To fully understand the effect of Vitamin D in PCOS, more research including cell culture, animal models, and ultimately human studies is required. Clinicians need clinical trials to identify the best therapy protocols.

In conclusion, it was highlighted in this review how PCOS and circulating 25(OH)D are related, as well as how Vitamin D affects PCOS women's capacity to conceive, metabolic changes, and mental health. Therefore, when treating PCOS patients, especially those who also had metabolic syndrome, hypovitaminosis D should be taken into consideration. Patients with PCOS who took Vitamin D supplements had improved menstrual cycles and folliculogenesis as well as lower serum testosterone levels, which were all positive effects on their capacity to reproduce. Therefore, it might be a novel therapeutic approach for treating PCOS in combination.

Ethical approval

Not applicable.

Consent

Consent was not required.

source of funding

Not applicable.

Author contribution

All authors equally contributed to this work.

Conflicts of interest disclosure

No conflict of interest declared.

Research registration unique identifying number (UIN)

It is not a human study.

Guaranto

Koushik Majumder.

Data availability statement

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Polycystic ovary syndrome | Office on Women's Health [Internet] [cited 2022 Dec 23]. https://www.womenshealth.gov/a-z-topics/polycystic-ovary-syndrome
[2] 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;42:754–7.
[3] Deswal R, Narwal V, Dang A, *et al*. The prevalence of polycystic ovary syndrome: a brief systematic review. J Hum Reprod Sci. 2020 ;13():261.
[4] Polycystic ovary syndrome and metabolic syndrome - PubMed [Internet] [cited 2022 Dec 23]. https://pubmed.ncbi.nlm.nih.gov/26265416/
[5] Vitamin D - NHS [Internet] [cited 2022 Dec 23]. https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/
[6] Siddiqee MH, Bhattacharjee B, Siddiqi UR, *et al*. High prevalence of vitamin D deficiency among the South Asian adults: a systematic review and meta-analysis. BMC Public Health 2021;21:118.
[7] Kayaniyil S, Vieth R, Harris SB, *et al*. Association of 25(OH)D and PTH with Metabolic Syndrome and Its Traditional and Nontraditional Components. J Clin Endocrinol Metab 2011;96:168–75.
[8] Pittas AG, Dawson-Hughes B, Sheehan P, *et al*. Vitamin D Supplementation and Prevention of Type 2 Diabetes. N Engl J Med 2019;381:520–30.
[9] Ghorbani Z, Togha M, Rafiee P, Ahmadi ZS, Rasekh Magham R, Haghighi S, *et al*. Vitamin D in migraine headache: a comprehensive review on literature. Neurol Sci [Internet]. 2019;40:2459–77.
[10] Artaza JN, Mehrotra R, Norris KC. Vitamin D and the cardiovascular system. Clin J Am Soc Nephrol 2009;4:1515–22.
[11] Mu Y, Cheng D, Yin Tl, *et al*. Vitamin D and polycystic ovary syndrome: a narrative review. Reprod Sci 2021;28:2110–7.
[12] Tuan RS, Moore CJ, Brittingham JW, *et al*. In vitro study of placental trophoblast calcium uptake using JEG-3 human choriocarcinoma cells. J Cell Sci 1991;98:333–42.
[13] Avila E, Díaz L, Halhali A, *et al*. Regulation of 25-hydroxyvitamin D3 1α-hydroxylase, 1,25-dihydroxyvitamin D3 24-hydroxylase and vitamin D receptor gene expression by 8-bromo cyclic AMP in cultured human syncytiotrophoblast cells. J Steroid Biochem Mol Biol 2004;89–90:115–9.
[14] Somjen D, Katzburg S, Stern N, *et al*. 25 hydroxy-vitamin D3-1α hydroxylase expression and activity in cultured human osteoblasts and their modulation by parathyroid hormone, estrogenic compounds and dihydrotestosterone. J Steroid Biochem Mol Biol 2007;107(3–5):238–44.
[15] Zarnani AH, Shahbazi M, Salek-Moghaddam A, *et al*. Vitamin D3 receptor is expressed in the endometrium of cycling mice throughout the estrous cycle. Fertil Steril 2010;93:2738–43.
[16] Stephanout A, Ross R, Handwergek S. Regulation of human placental lactogen expression by 1,25-dihydroxyvitamin D3. Endocrinology 1994;135:2651–6.
[17] Barrera D, Avila E, Hernández G, *et al*. Calcitriol affects hCG gene transcription in cultured human syncytiotrophoblasts. Reprod Biol Endocrinol 2008;6:1–8.
[18] Kinuta K, Tanaka H, Moriwake T, *et al*. Vitamin D Is an Important Factor in Estrogen Biosynthesis of Both Female and Male Gonads. Endocrinology 2000;141:1317–24.
[19] Wojtusik J, Johnson PA. Vitamin D regulates anti-mullerian hormone expression in granulosa cells of the hen. Biol Reprod 2012;86:91–2.
[20] Qi X, Pang Y, Qiao J. The role of anti-Müllerian hormone in the pathogenesis and pathophysiological characteristics of polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2016;199:82–7.
[21] Aghadavod E, Mollaei H, Nouri M, *et al*. Evaluation of relationship between body mass index with vitamin D receptor gene expression and vitamin D levels of follicular fluid in overweight patients with polycystic ovary syndrome. Int J Fertil Steril 2017;11:105–11.
[22] Kuyucu Y, Çelik LS, Kendirlinan Ö, *et al*. Investigation of the uterine structural changes in the experimental model with polycystic ovary syndrome and effects of vitamin D treatment: An ultrastructural and immunohistochemical study. Reprod Biol 2018;18:53–9.
[23] Irani M, Merhi Z. Role of vitamin D in ovarian physiology and its implication in reproduction: a systematic review. Fertil Steril 2014;102:460–68.e3.
[24] Lin MW, Wu MH. The role of vitamin D in polycystic ovary syndrome. Indian J Med Res 2015;142:238.
[25] Merhi ZO, Minkoff H, Feldman J, *et al*. Relationship of bariatric surgery to Müllerian-inhibiting substance levels. Fertil Steril 2008;90:221–4.
[26] Merhi ZO. Impact of bariatric surgery on female reproduction. Fertil Steril 2009;92:1501–8.
[27] Merhi ZO, Seifer DB, Weedon J, *et al*. Circulating vitamin D correlates with serum antimüllerian hormone levels in late-reproductive-aged women: Women's Interagency HIV Study. Fertil Steril 2012;98:228–34.
[28] Merhi Z, Doswell A, Krebs K, Cipolla M. Vitamin D Alters Genes Involved in Follicular Development and Steroidogenesis in Human Cumulus Granulosa Cells. J Clin Endocrinol Metab [Internet]. 2014;99:E1137–45. https://academic.oup.com/jcem/article/99/6/E1137/2537382
[29] Barrera D, Avila E, Hernández G, *et al*. Estradiol and progesterone synthesis in human placenta is stimulated by calcitriol. J Steroid Biochem Mol Biol 2007;103(3–5):529–32.
[30] Pal L, Berry A, Coraluzzi L, *et al*. Therapeutic implications of vitamin D and calcium in overweight women with polycystic ovary syndrome. Gynecol Endocrinol 2012;28:965–8.
[31] Thomson RL, Spedding S, Buckley JD. Vitamin D in the aetiology and management of polycystic ovary syndrome. Clin Endocrinol (Oxf) 2012;77:343–350.
[32] Anagnostis P, Karras S, Goulis DG. Vitamin D in human reproduction: a narrative review. Int J Clin Pract 2013;67:225–35.
[33] 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;34:757–63.
[34] Lerchbaum E, Obermayer-Pietsch B. Mechanisms in endocrinology: vitamin D and fertility: a systematic review. Eur J Endocrinol 2012;166:765–78.

[35] Trummer C, Pilz S, Schwetz V, *et al*. Vitamin D, PCOS and androgens in men: a systematic review. Endocr Connect 2018;7:R95.
[36] Wehr E, Trummer O, Giuliani A, *et al*. Vitamin D-associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome. Eur J Endocrinol 2011;164:741–9.
[37] Ranjzad F, Mahban A, Shemirani AI, *et al*. Influence of gene variants related to calcium homeostasis on biochemical parameters of women with polycystic ovary syndrome. J Assist Reprod Genet 2011;28:225–32.
[38] Ranjzad F, Mahmoudi T, Irani Shemirani A, *et al*. A common variant in the adiponectin gene and polycystic ovary syndrome risk. Mol Biol Rep 2012;39:2313–9.
[39] Grundmann M, von Versen-Höynck F. Vitamin D - roles in women's reproductive health? Reprod Biol Endocrinol 2011;9:146.
[40] Chen Y, Zhi X. Roles of vitamin D in reproductive systems and assisted reproductive technology. Endocrinology [Internet] 2020;161:bqaa023.
[41] Voulgaris N, Papanastasiou L, Piaditis G, *et al*. Vitamin D and aspects of female fertility. Hormones 2017;16:5–21.
[42] He C, Lin Z, Robb SW, *et al*. Serum vitamin D levels and polycystic ovary syndrome: a systematic review and meta-analysis. Nutr 2015;7:4555–77.
[43] Belenchia AM, Tosh AK, Hillman LS, *et al*. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. Am J Clin Nutr 2013;97:774–81.
[44] Tzotzas T, Papadopoulou FG, Tziomalos K, *et al*. Rising serum 25-hydroxyvitamin D levels after weight loss in obese women correlate with improvement in insulin resistance. J Clin Endocrinol Metab 2010;95:4251–7.
[45] 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 Investig 2010;33:234–238.
[46] Teegarden D, Donkin SS. Vitamin D: emerging new roles in insulin sensitivity. Nutr Res Rev 2009;22:82–92.
[47] Maestro B, Dávila N, Carranza MC, *et al*. Identification of a Vitamin D response element in the human insulin receptor gene promoter. J Steroid Biochem Mol Biol 2003;84(2–3):223–30.
[48] Maestro B, Molero S, Bajo S, *et al*. Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D3. Cell Biochem Funct 2002;20:227–32.
[49] Ruige JB, Assendelft WJJ, Dekker JM, *et al*. Insulin and risk of cardiovascular disease. circulation 1998;97:996–1001.
[50] Trummer C, Schwetz V, Kollmann M, *et al*. Effects of vitamin D supplementation on metabolic and endocrine parameters in PCOS: a randomized-controlled trial. Eur J Nutr 2019;58:2019–28.
[51] Seyyed Abootorabi M, Ayremlou P, Behroozi-Lak T, *et al*. The effect of vitamin D supplementation on insulin resistance, visceral fat and adiponectin in vitamin D deficient women with polycystic ovary syndrome: a randomized placebo-controlled trial. Gynecol Endocrinol [Internet] 2018;34:489–94.
[52] Łagowska K, Bajerska J, Jamka M. The role of vitamin D oral supplementation in insulin resistance in women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Nutr 2018;10:1637.
[53] Irani M, Seifer DB, Grazi RV, *et al*. Vitamin D supplementation decreases TGF-β1 bioavailability in PCOS: a randomized placebo-controlled trial. J Clin Endocrinol Metab 2015;100:4307–14.
[54] Javed Z, Papageorgiou M, Deshmukh H, *et al*. A randomized, controlled trial of vitamin d supplementation on cardiovascular risk factors, hormones, and liver markers in women with polycystic ovary syndrome. Nutrients 2019;11:188.
[55] Georgopoulos NA, Saltamavros AD, Vervita V, *et al*. Basal metabolic rate is decreased in women with polycystic ovary syndrome and biochemical hyperandrogenemia and is associated with insulin resistance. Fertil Steril 2009;92:250–5.
[56] Ngo DTM, Chan WP, Rajendran S, *et al*. Determinants of insulin responsiveness in young women: Impact of polycystic ovarian syndrome, nitric oxide, and vitamin D. Nitric Oxide 2011;25:326–30.
[57] Faghfoori Z, Fazelian S, Shadnoush M, *et al*. Nutritional management in women with polycystic ovary syndrome: a review study. Diabetes Metab Syndr Clin Res Rev 2017;11:S429–32.
[58] Rahimi-Ardabili H, Pourghassem Gargari B, Farzadi L. Effects of vitamin D on cardiovascular disease risk factors in polycystic ovary syndrome women with vitamin D deficiency. J Endocrinol Invest 2013;36:28–32.
[59] Karadağ C, Yoldemir T, Yavuz DG. Effects of vitamin D supplementation on insulin sensitivity and androgen levels in vitamin-D-deficient polycystic ovary syndrome patients. J Obstet Gynaecol Res 2018;44:270–7.
[60] Atasayan K, Yoldemir T. The effect of PCOS status on atherosclerosis markers and cardiovascular disease risk factors in young women with vitamin D deficiency. Gynecol Endocrinol [Internet]. 2021;37:225–9.
[61] Wild RA, Rizzo M, Clifton S, *et al*. Lipid levels in polycystic ovary syndrome: Systematic review and meta-analysis. Fertil Steril 2011;95:1073–79.e11.
[62] Hahn S, Haselhorst U, Tan S, *et al*. Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes [Internet] 2006;114:577–83.
[63] Policisti^nih S, Korelacije J, Vitaminom DSA, *et al*. Anti-müllerian hormone as a diagnostic marker in egyptian infertile polycystic ovary syndrome females: correlations with vitamin D, total testosterone, dyslipidemia and anthropometric parameters antimilerov hormon. J Med Biochem 2018;37:448–55.
[64] Radwan RA, Abuelezz NZ, Abdelraouf SM, *et al*. Decreased serum level of gamma-amino butyric acid in egyptian infertile females with polycystic ovary syndrome is correlated with dyslipidemia, total testosterone and 25 (OH) vitamin D levels. J Med Biochem 2019;38:512–8.
[65] Luo J, Li T, Yuan J. Effectiveness of vitamin D supplementation on lipid profile in polycystic ovary syndrome women: a meta-analysis of randomized controlled trials. Ann Palliat Med 2021;10:11429–129.
[66] Angellotti E, D'Alessio D, Dawson-Hughes B, *et al*. Vitamin D supplementation in patients with type 2 diabetes: the vitamin D for established type 2 diabetes (DDM2) study. J Endocr Soc 2018;2:310–21.
[67] Menichini D, Facchinetti F. Effects of vitamin D supplementation in women with polycystic ovary syndrome: a review. Gynecol Endocrinol [Internet] 2020;36:1–5.
[68] Dastorani M, Aghadavod E, Mirhosseini N, *et al*. The effects of vitamin D supplementation on metabolic profiles and gene expression of insulin and lipid metabolism in infertile polycystic ovary syndrome candidates for in vitro fertilization. Reprod Biol Endocrinol 2018;16:1–7.
[69] Firouzabadi Rd, Aflatoonian A, Modarresi S, *et al*. Therapeutic effects of calcium & vitamin D supplementation in women with PCOS. Complement Ther Clin Pract 2012;18:85–8.