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REVIEW

Effects of vitamin D supplementation in women with polycystic ovary syndrome: a review

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ABSTRACT

Increasing evidence supports the contribution of vitamin D deficiency (VDD) in metabolic disturbances among women with polycystic ovary syndrome (PCOS). This review aims to assess the associations between vitamin D levels and metabolic/endocrine dysregulations and to determine the effects of vitamin D supplementation on glucose metabolism, insulin sensitivity, lipid profile, and hormones functionality in PCOS patients. We searched in PubMed human randomized controlled trials (RCTs) published in English between 2016 and 2019 on the effects of vitamin D supplementation on PCOS. Nine studies were included and analyzed. Vitamin D supplementation restored physiological serum 25(OH)D levels in PCOS women in all the studies included. In six studies, it significantly decreased fasting plasma glucose and brought to improvements in insulin resistance (IR) and serum fasting insulin. In addition, four studies reported decreases of serum triglycerides, while discordant data are reported as far as LDL, HDL, and total cholesterol levels. High-doses of vitamin D (4000 IU), compared with low-dose (1000 IU), and placebo, showed beneficial effects on total testosterone, sex hormone-binding globulin (SHBG) and free androgen index (FAI). Vitamin D supplementation at high doses for a period of at least 12 weeks, may lead to improvement in terms of glucose level, insulin sensitivity, hyperlipidemia, and hormonal functionality in PCOS women.

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Vitamin D; polycystic ovary syndrome; insulin resistance; hyperlipidemia; hyperandrogenism

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting approximately 4–18% of women in reproductive age [1]. PCOS is a very heterogeneous androgen excess disorder with different degrees of reproductive and metabolic dysfunctions including infertility, insulin resistance (IR), hyperinsulinemia, and dyslipidemia [2].

Accumulating evidence suggests that vitamin D deficiency (VDD) might be a causal factor in the pathogenesis of IR and the metabolic syndrome in PCOS [3]. Indeed, a relatively high prevalence of VDD is observed among women with PCOS (approximately in the 67–85% women with PCOS) [4]. Additionally, positive associations of VDD with some well-known comorbidities of PCOS including type 2 diabetes, IR, metabolic syndrome, and cardiovascular diseases, are reported [5–7]. This is supported by the fact that the vitamin D receptor (VDR) regulates more than 3% of the human genome, including genes that are crucial for glucose metabolism [8,9]. Vitamin D-associated polymorphisms are correlated with IR and VDD in PCO. More specifically, variants in the VDR Cdx2 and DHCR7 genes are associated with IR and insulin sensitivity and VDR Apa-I variants are associated with testosterone levels in PCOS women [10].

Vitamin D metabolism

Vitamin D is a fat-soluble secosteroid hormone that regulates calcium, magnesium, and phosphate homeostasis and plays a pivotal role as antiproliferative and immunomodulatory mediator. VDRs are expressed in 2776 genomic positions and modulate the expression of 229 genes in more than 30 different tissues, such as skeleton, brain, breast, pancreas, parathyroid glands, immune cells, cardiomyocytes, and ovaries [9,11]. Thus, deficiency of this compound may cause a wide range of extra-skeletal effects with impact on glucose homeostasis, cardiovascular disease, cancer, autoimmune diseases, and psychological disorders [9,12].

Vitamin D supplementation

The rationale for vitamin D supplementation in PCOS women is based on the role vitamin D plays in glucose metabolism enhancing insulin synthesis and release and increasing insulin receptor expression, as well suppressing proinflammatory cytokines [13]. The effect of vitamin D on metabolic and reproductive dysfunctions in PCOS may be mediated by an overall effect on IR. In terms of reproduction, IR increases hyperandrogenism through insulin stimulation of ovarian androgen production and concomitant reduction of sex hormone-binding globulin (SHBG) [14]. In terms of metabolism, IR is associated with impaired glucose tolerance, type 2 diabetes mellitus, and cardiovascular disease [13,15]. Therefore, vitamin D may play a key role in the development of all the clinical features of patients with PCOS [16].

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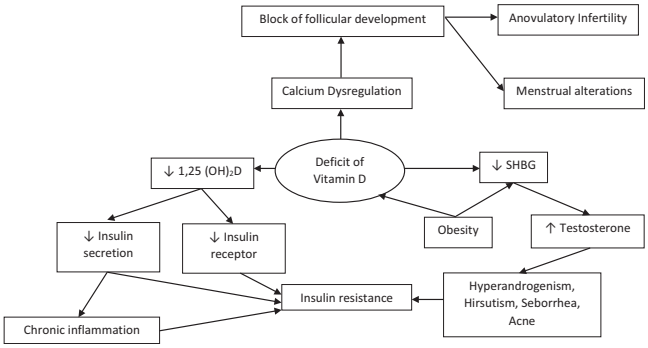
Possible role of vitamin D in the pathogenesis of PCOS



A correlation between low levels of vitamin D and IR, hirsutism, hyperandrogenism, and obesity is reported [4]. Vitamin D has a physiological role in reproduction, with a modulation of follicular development through the influence on the signal of the antimüllerian hormone (AMH), on FSH sensitivity and on the production of progesterone in the ovarian granulosa cells [17]. Vitamin D also appears to be able to modulate the glucose-insulin homeostasis, through the action on its own specific receptors (VDR) located on the pancreatic beta cells and in skeletal muscle, that directly activates transcription of the human insulin receptor gene, activates peroxisome proliferator activator receptor-δ, stimulates the expression of insulin receptor, and enhances insulin-mediated glucose transport *in vitro* [18].

It should be mentioned that in the last years there have been few interventional studies about vitamin D supplementation on PCOS in which some characteristics of this syndrome substantially improved but some others have not changed. Therefore, the objective of this literature review is to summarize the existing evidence and evaluate the effects of vitamin D supplementation on the mitigation of metabolic and hormonal functions in women with PCOS.

Material and methods

To assess the effects of vitamin D supplementation in women with PCOS, we carried out a computerized literature search using PubMed. Eligibility criteria were predetermined by reviewers to prevent bias in the inclusion or exclusion of articles and to improve the precision of the search. We included the most recent experimental studies exclusively published in English between 2016 and 2019, involving women with PCOS classified according to the Rotterdam criteria [19]. We selected the experimental studies who investigated the efficacy of vitamin D supplementation for at least an 8-weeks period.

Results

Throughout the web search strategy, nine randomized controlled trials (RCTs) met the inclusion criteria and were included in the final analysis. Their main features are reported in Table 1.

Although most of the studies were conducted in Iran, the overall population studied was heterogeneous, including mostly Asian, Caucasian, Arab, Hispanic, and Black women.

The number of participants in the studies ranged from 36 to 123. The age of the women ranged from 18 to 40 years and their BMI ranged from 26.6 to 35.5 kg/m^2. The interventions employed the supplementation with cholecalciferol and doses ranging from 1000 IU/d to 60,000 IU/weekly. The supplementations lasted 8, 12, or 24 weeks.

Effects on serum vitamin D levels

All the nine trials included in this review reported that vitamin D supplementation leads to a significant increase in serum 25(OH)D levels (Table 2).

In particular, the study conducted by Gupta et al., 92% of enrolled PCOS subjects were found to have vitamin D level less than 30 ng/ml; the 68% were vitamin D deficient (≤20 ng/ml) out of which the 29% were severely deficient (<10 ng/ml) showing high prevalence of VDD in the PCOS women. After the supplementation, serum level of vitamin D was restored also in severely VDD women (Serum Vit D, mean ± SD: Before 18.56 ± 9.68, After 44.90 ± 9.04, $p = .001$) [23].

Effects on glucose metabolisms

Vitamin D supplementation, compared to the placebo group, significantly decreased fasting plasma glucose (FPG) [21,22,25,27] (Table 2).

Significant improvements were seen in IR, serum fasting insulin. Increased in insulin sensitivity, determined by QUICKI [23,25], increased homeostasis model of assessment-estimated B cell function (HOMA-B) [22,25], reduced HOMA-IR [20,25,27], and increased Matsuda ISI values [26] in the PCOS group after supplementation with vitamin D. On the other hand, no significant changes in FPG levels and insulin sensitivity were found by Lagowska et al. and Irani et al., confirming the controversial results reported by previous metanalysis [28,29].

Effects on lipid profile

In addition, four studies reported significant decreases in the mean of serum triglyceride (TG) [25–28], however, only the study conducted by Foroozanfard et al. found that different doses of vitamin D supplementation (4 000 and 1 000 IU) compared with placebo, led to significant decreases in VLDL (−2.0 ± 1.5 *vs.* −0.7 ± 2.9 and +1.4 ± 4.8 mg/dl, respectively, $p = .001$), LDL (−10.8 ± 8.3 vs. −5.7 ± 21.9 and + 6.8 ± 28.2 mg/dl, respectively, $p = 0.005$), and total/HDL-cholesterol ratio (−0.2 ± 0.3 *vs.* −0.1 ± 0.6 and +0.2 ± 0.7 mg/dl, respectively, $p = .003$) [27] (Table 2).

Moreover, vitamin D replacement significantly decreased serum VEGF levels correlating with a decrease in serum TG [28] and also led to significant reductions in serum high-sensitivity C-reactive protein (hs-CRP), plasma total antioxidant capacity (TAC) levels [24,25], and plasma malondialdehyde (MDA) levels [25], showing that VDD women with PCOS phenotype have beneficial effects on chronic inflammation and oxidative stress after vitamin D supplementation.

Discordant with the above presented results are those reported by 4 RCTs include in the review, that found no changes in LDL, HDL, and total cholesterol [20,21,23,28].

Effects on hormonal function

Jamilian et al. demonstrated that high-dose vitamin D (4000 IU) supplementation, compared with low-dose (1000 IU) and placebo, had beneficial effects on total testosterone, SHBG, free androgen index (FAI) compared with low-dose vitamin D and placebo groups [24]. Serum androstenedione levels decreased

Table 1. Characteristics of the included studies and study populations.

Study	Country	Population	N° of cases	Intervention/control	Vitamin D dose and regimen	Duration (weeks)
[20]	UK	Caucasian	40	Vitamin D ($n = 20$) Placebo ($n = 20$)	3200 IU/daily	12
[21]	Austria	Caucasian	123	Vitamin D ($n = 119$) Placebo ($n = 61$)	20,000 IU/weekly	24
[22]	Iran	Asian	36	Vitamin D ($n = 19$) Placebo ($n = 17$)	50,000 IU/weekly	8
[23]	India	Asian	50	Vitamin D ($n = 25$) Placebo ($n = 25$)	60,000 IU/weekly	12
[24]	Iran	Asian	90	Vitamin D ($n = 30$) Placebo ($n = 30$)	1000 IU/daily 4000 IU/daily	12
[25]	Iran	Asian	70	Vitamin D ($n = 35$) Placebo ($n = 35$)	50,000 IU every 2 weeks	12
[26]	Turkey	Arab	121	Vitamin D ($n = 67$) Placebo ($n = 54$)	50,000 IU/weekly 1500 IU/d	8 4
[27]	Iran	Asian	90	High dose ($n = 30$) Low dose ($n = 30$) Placebo ($n = 30$)	4000 IU/daily or 1000 IU/daily	12
[28]	USA	Hispanic Asian Black	53	Vitamin D ($n = 35$) Placebo ($n = 18$)	50,000 IU/weekly	8

Table 2. Effects of Vitamin D supplementation on glucose metabolism, lipid profile, and hormonal status.

Study	Vit D doses	Weeks	Serum Vit D	Glucose metabolism	Lipid profile	Hormones status
[25]	3200 IU/d	12	Increased 25hydroxyvitamin D	No changes in FPG, serum insulin levels, HOMA-IR	No changes in cholesterol, LDL, HDL, TG,	No changes of SHBG, testosterone and FAI
[22]	20,000 IU/w	24	Increased 25hydroxyvitamin D	Decreased PG after 60 min during OGTT, No changes in HbA1c, HOMA-IR, QUICKI	No changes in cholesterol and TG	No changes of total and free-testosterone, Increased menstrual regularity
[21]	50,000 IU/w	8	Increased 25hydroxyvitamin D	Decreased FPG, serum insulin levels, HOMA-IR	NA	Decreased SHBG, total testosterone and FAI
[20]	60,000 IU/w	12	Increased 25hydroxyvitamin D	Decreased FPG, IR, fasting serum insulin, Improvement of HOMA-IR, QUICKI, Increased insulin sensitivity	No changes in cholesterol, HDL, TG	Increased menstrual regularity, 40% decrease in antral follicles count No changes of FSH, LH, Estradiol, cortisol, prolactin, TSH, testosterone, 17a-OH progesterone, DHEAS
[29]	4000 IU/d 1000 IU/d	12	Increased 25hydroxyvitamin D	Decreased FPG, serum insulin levels, HOMA-IR	NA	Decreased total testosterone, FAI, hirsutism and hs-CRP Increased SHBG and total antioxidant capacity No changes in DHEAS, NO, GSH and MDA
[23]	25,000 IU/w	12	Increased 25hydroxyvitamin D	Decreased FPG, serum insulin levels, HOMA-IR, HOMA-B, increased QUICKI	Decreased cholesterol after controlling for age and baseline BMI	Decreased serum hs-CRP and plasma MDA levels
[26]	50,000 IU/w 1500 IU/d	8	Increased 25hydroxyvitamin D	Decreased FPG, HOMA-IR, Increased Matsuda ISI values	Decreased cholesterol	Decreased testosterone, androstenedione, SHBG
[24]	4000 IU/d 1000 IU/d	12	Increased 25hydroxyvitamin D	Decreased FPG, serum insulin levels, HOMA-IR, No changes in QUICKI	Decreased TG, VLDL, LDL, total/HDL cholesterol ratio No changes in HDL	NA
[28]	50,000 IU/w	8	Increased 25hydroxyvitamin D	No Changes in FPG, fasting insulin, HOMA-IR	Decreased TG, No changes in LDL, HDL, cholesterol	Decreased FGS, intermenstrual intervals, No changes in DHEAS, free testosterone, FSH, LH, LH/FSH,

significantly ($p = .007$) and negative correlations between 25(OH)D levels and total testosterone ($r = -0.306$; $p < .01$) and androstenedione ($r = -0.275$; $p < .01$) levels are reported by Karadağ et al. [26].

The most recent randomized, double-blind, placebo-controlled study conducted by Javed et al. and published in 2019, found no differences in cardiovascular risk factors or hormones [20] (Table 2).

Discussion

We have presented the effects of vitamin D supplementation on glucose metabolism and IR, hyperlipidemia and hormonal status in women with PCOS. Although our results are quite heterogeneous, we can summarize that vitamin D supplementation helped restoring physiological serum 25(OH)D levels in VDD women, in fact, taking into account that approximately 67–85% of women with PCOS have insufficient levels of vitamin D [16], this supplementation should be recommended to all the PCOS women.

Vitamin D supplementation might also be helpful to improve glucose metabolism and insulin sensitivity of women diagnosed with PCOS in terms of glucose concentration and HOMA-IR, reduction of hyperlipidemia and regulation of menstrual cycles.

A recent systematic review, published in 2018, compared the effects of supplementation with vitamin D alone (dose from 1000 IU/d to 60,000 IU/week) or with co-supplements to the administration of placebos in women diagnosed with PCOS. Eleven studies that involved 601 women diagnosed with PCOS were analyzed. Vitamin D as a co-supplement was found to significantly decrease fasting glucose concentrations and the HOMA-IR value [29].

Evidence from RCTs suggests that the supplementation of PCOS patients with continuous low doses of vitamin D (<4000 IU/d) or supplementation with vitamin D as a co-supplement may improve insulin sensitivity in terms of the fasting glucose concentration (supplementation with vitamin D in combination with other micronutrients) and HOMA-IR (supplementation with vitamin D in continuous low daily doses or as co-supplement) [29].

This indicates that doses and timing have a significant weight on the effectiveness of the supplementation, justifying the heterogeneous results found among the studies included in this literature review and in the previously published systematic reviews and metanalysis [16,29].

Among the studies included in this review, the better outcomes have been obtained with high doses of vitamin D (≥4000 IU/d) administered for a period of at least 12 weeks. With this posology in fact, improvement in terms of glucose level, insulin sensitivity, hyperlipidemia, and hormonal functionality has been achieved.

Population characteristics (BMI, ethnicity) and basal levels of vitamin D and hormones are also variables that need to be considered in the decision of supplementing vitamin D.

Conclusion

Multiple studies have illustrated a beneficial effect of vitamin D supplementation on plasma vitamin D levels, and glucose metabolism, in terms of fasting glucose levels and insulin sensitivity. An inverse association between the vitamin D status, and hyperandrogenism and IR is also reported. Consequently, intervention with vitamin D at doses as high as (≥4000 IU/d) administered for a period of at least 12 weeks have provided improvements in the hyperinsulinemia, and androgenic and fertility factors in PCOS women. Overall, high dose vitamin D supplementation has shown promising results in improving the treatment of the PCOS patients.

Disclosure statement

The authors report no conflicts of interest.

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