REVIEW ARTICLE

Are Phenotypes of PCOS and Vitamin D Levels Interlinked

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Abstract

Aim: The present review is done to analyze the serum vitamin D levels in different phenotypes of polycystic ovarian syndrome (PCOS).

Objectives: To estimate the serum levels of vitamin D in women with PCOS and without PCOS. To find out the distribution of different phenotypes of PCOS. To compare the serum vitamin D levels in different phenotypes of PCOS.

Background: Polycystic ovarian syndrome is the most common heterogeneous multisystem endocrinopathy in women of reproductive age. It is further divided into four phenotypes based on Rotterdam criteria. Vitamin D levels are known to be low among women with PCOS. Only limited literature is available related to vitamin D deficiency and the phenotypes of PCOS. This review has highlighted the phenotypes of PCOS and their correlation with vitamin D levels.

Methods: An electronic search strategy was used to select the studies from different databases like PubMed, Google Scholar, SciELO, and ResearchGate. A combination of keywords like vitamin D, PCOS, and phenotypes of PCOS were used to select the studies. Inclusion criteria were studies in English, duration of search of 18 months, case–control studies and cross-sectional studies only.

Results: Phenotype A was the most frequently found phenotype among the different phenotypes of PCOS. After analyzing the data, there was a positive association between vitamin D and PCOS. Obese women were more prone to have vitamin D deficiency. Women with vitamin D deficiency were found to have ovarian dysfunction and insulin resistance. But there was no strong consensus on the association between vitamin D and phenotypes of PCOS.

Conclusion: We found a statistically significant difference in mean serum vitamin D levels among the women with PCOS and without PCOS. The most common phenotype was phenotype A and the least common was phenotype D. There was no significant difference in serum vitamin D levels in respect to different phenotypes of PCOS. Further studies with larger sample size in each phenotype are recommended to conclusively establish the variation of serum vitamin D level in PCOS, particularly related to phenotypes.

Clinical significance: Vitamin D supplementation was found to be beneficial for women with PCOS.

Keywords: Phenotypes of polycystic ovarian syndrome, Polycystic ovarian syndrome, Vitamin D.

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Introduction

Polycystic ovarian syndrome is defined as clinical and/or biochemical hyperandrogenism, ovulatory dysfunction (chronic oligomenorrhea or amenorrhea), and polycystic ovarian morphology after excluding other androgen excess or related disorders based on Rotterdam criteria. The presence of any two of these three features is suggestive of PCOS. Contingently, four unique phenotypes are recognized as per the Rotterdam and Androgen Excess-PCOS (AE-PCOS) Society criteria. The phenotypes prevailing PCOS are A, B, C, and D. Phenotype A has features of hyperandrogenism, ovulatory disturbances, and polycystic ovarian morphology; phenotype B has features of hyperandrogenism and ovulatory disturbances; phenotype C has hyperandrogenism and polycystic ovarian morphology features; whereas phenotype D has ovulatory disturbances plus polycystic ovarian morphology features.[1]

Vitamin D is a fat-soluble secosteroid. Its deficiency has been attributed to various symptoms of PCOS. Wehr et al. in their study stated that women with PCOS were found to have low serum vitamin D levels.[2] The relationship between phenotypes of PCOS and vitamin D was insignificant as stated by Sachdeva et al.[3] However, Davis et al. in his study stated that vitamin D deficiency was seen in phenotype A and there was no association between vitamin D deficiency and phenotype D. Moreover, only limited literatures are available about the association between vitamin D and different phenotypes of PCOS.

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Methods

An electronic search strategy was used to select the studies from different databases like PubMed, Google Scholar, SciELO, and ResearchGate. A combination of keywords like vitamin D, PCOS, and phenotypes of PCOS were used to select the studies. Inclusion criteria were studies in English, duration of search of 18 months, case–control studies, and cross-sectional studies only. However, systemic reviews and meta-analyses were excluded from the review. The total number of articles reviewed was 50; of which only 21 articles fulfilled the inclusion criteria. The selected articles were further assessed for the quality of the research and included in the review.

Results

Kim et al. in a case–control study stated that women with PCOS showed no differences in the level of 25-hydroxy vitamin D [25(OH)D] (19.6 ± 6.6 ng/mL in patients vs 20.1 ± 7.4 ng/mL in controls, respectively, $p = 0.696$) or prevalence of vitamin D deficiency (57.9% in patients vs 56.5% in controls, respectively, $p = 0.880$).[9]

In 2018, a case–control study done by Davis et al. stated that 59.9% of PCOS cases lacked sufficient vitamin D levels. The odds of vitamin D deficiency in all PCOS cases were twice that of controls; however, the association was attenuated after adjusting for body mass index (BMI) and race/ethnicity. When examining PCOS phenotypes exhibiting androgen excess, crude associations were observed for deficient vitamin D levels; however, the association decreased after adjustment for BMI and race/ethnicity.[20]

In a cross-sectional study by Krul et al., serum 25(OH)D was significantly lower in PCOS women compared to controls (mean 25(OH)D of 49.0 vs 64.5 nmol/L).[15]

In 2017, Diamanti et al. analyzed the phenotypic spectrum of PCOS and stated that classic PCOS phenotype was more frequent (85.96%) than the nonclassical phenotype (14.04%).

Discussion

Phenotypes of PCOS

PCOS was first diagnosed in 1935. Later, based on Rotterdam criteria, four unique phenotypes of PCOS were identified. Currently, only limited literatures are available about PCOS and its phenotypes. Zhang et al. in a study to analyze the phenotypic spectrum of PCOS stated that phenotype A accounts for 26.8%, phenotype B 7.6%, phenotype C 13.4%, and phenotype D 52.2%.[4] A prospective study done by Diamanti et al. stated that classic phenotype (chronic anovulation with biochemical hyperandrogenemia and/or hyperandrogenism) was 85.96% and nonclassical phenotype (polycystic ovaries and/or chronic anovulation or polycystic ovaries and biochemical hyperandrogenemia and/or hyperandrogenism) was 14.4%.[5] Pehlivanov et al. conducted a study among the Bulgarian population and stated that the percentages of phenotypes A, B, C, and D in their study were 58.6, 11.4, 10.0, and 20.0%, respectively.[6] In another study done by Clark et al., the prevalence of Frank PCOS was 66%, ovulatory PCOS was 13%, normoandrogenic PCOS was 11%, and non-PCO PCOS was 9%.[7] In a study done in India by Sachdeva et al., the most prevalent phenotype was phenotype A of 67.7% and the least prevalent was phenotype D of 3.6% (Table 1).[3]

Vitamin D and PCOS

Vitamin D deficiency, obesity, and insulin resistance are strongly linked to the development of PCOS. The probable mechanism is decreased protein-bound vitamin D altering calcium homeostasis by decreasing the absorption of calcium, resulting in increased parathyroid hormone secretion. This increased parathyroid hormone binds to G-cell protein receptor, causing increased cyclic adenosine monophosphate, resulting in phosphorylation of insulin receptor substrate 1 (IRS-1). This decreases the sensitivity of insulin receptors, resulting in insulin resistance and altered glucose homeostasis and ultimately resulting in hyperandrogenism and menstrual irregularities which is one of the features of PCOS. Hence, vitamin D plays a major role in the development of PCOS. Due to the constant correlation between obesity, insulin resistance, and PCOS, few studies have mentioned the probable mechanism and the positive and/or negative correlation among the three.

Table 1: Proportion of each phenotype in individual studies

Authors	*Phenotype A*	*Phenotype B*	*Phenotype C*	*Phenotype D*
Zhang et al.	26.8%	7.6%	13.4%	52.2%
Pehlivanov et al.	58.6%	11.4%	10.0%	20.0%
Clark et al.	66%	9%	13%	11%

A cross-sectional study done by Kayaniyil et al. showed a positive correlation between low serum vitamin D levels, insulin resistance, and beta-cell dysfunction.[8] In contrast to the results of the studies mentioned, studies done by Kim et al. and Jedrzejuk et al. stated that there was no statistically significant relationship between vitamin D and PCOS.[9,10] Jia et al. conducted a study to correlate serum vitamin D and PCOS. The study concluded that vitamin D deficiency was more prevalent in women with PCOS. It also stated a negative association between insulin resistance and PCOS.[11] Another such study done by He et al. in 2015 compared the vitamin D levels in women with PCOS (cases) and without PCOS (controls). It was found that serum vitamin D levels were low in cases compared to controls. It also stated that there was a significant alteration in glucose homeostasis in cases with the prevalence of insulin resistance accounting for 50–70%.[12]

Sidabutar et al. conducted a cross-sectional comparative study on 23 women with PCOS and 23 women without PCOS. This study stated that PCOS women with waist–hip ratio >0.85 had lower vitamin D levels and the levels were significantly lower in the cases than in the controls. Vitamin D also plays a key role in the pathogenesis of type 2 diabetes mellitus.[13] Research related to phenotypes of PCOS was done to see the beneficial effect of vitamin D supplementation in a specific phenotype of PCOS. It was a randomized double-blind trial conducted by Maktabi et al. done among 70 vitamin D deficient (<20 ng/mL) PCOS cases belonging to phenotype B. Thirty-five cases received vitamin D every 2 weeks for 12 weeks and the rest belonged to the placebo group. After the 12th week, it was observed that vitamin D supplementation had beneficial effects on women with PCOS.[14]

A cross-sectional study done by Krul et al. with a total of 639 cases (women with PCOS) and 449 controls (women without PCOS) stated a positive association between vitamin D deficiency and PCOS.[15] It also stated that women in the PCOS group had higher insulin resistance, as stated by the previous study done by He et al. A study done by Jukic et al. assessed the menstrual cycle length and the association between individual phases and the effect of vitamin D supplementation on the menstrual cycle. Vitamin D deficiency was more in women among mid-30s and was associated with a longer menstrual cycle and follicular phase with a shorter luteal phase. A direct association between vitamin D supplementation and improvement in cycle length was noted.[16] A research done by Lagowska et al. stated that vitamin D deficiency is associated with an imbalance in androgen, resulting in menstrual disorders and alteration of insulin levels.[6] Vitamin D in the adipose tissue raises high-density lipoprotein levels, helps adipokine profile, and increases leptin levels.

A case–control study done by Shah et al. concluded that there was a significant relationship between PCOS and low vitamin D. It also states that low vitamin D levels are associated with menstrual irregularities, hirsutism, and hyperandrogenism.[17] There are few other studies (Wehr et al., Hahn et al., and Elkhoy et al.) which stated a positive correlation between vitamin D and PCOS.[2,18,19] Only a few studies were done to correlate the vitamin D levels with

different phenotypes of PCOS. Davis et al. conducted a case–control study to evaluate the associations between vitamin D and different phenotypes of PCOS. They have concluded that a higher proportion (59.9%) of PCOS cases had low vitamin D levels than controls (47.6%, $p = 0.06$) and vitamin D deficiency occurred more frequently in PCOS cases with androgen excess, thus the phenotype of PCOS with hyperandrogenism as a feature.[20]

A retrospective study was done to assess serum vitamin D levels in different phenotypes of PCOS by Eftekhar et al. in 200 infertile women who were further divided into four phenotypes of PCOS, with 50 normal subjects being also recruited in the control group with normal ovulatory function. Higher serum vitamin D levels were noted in the control group whereas there was no significant difference in serum vitamin D levels among different phenotypes.[21]

The aim of the present review is to find literatures associated with phenotypes of PCOS and vitamin D.

Conclusion

We found a statistically significant difference in mean serum vitamin D levels among women with and without PCOS. The most common phenotype was phenotype A and the least common was phenotype D. There was no significant difference in serum vitamin D levels in respect to different phenotypes of PCOS. Although vitamin D deficiency among women with PCOS is well established, the variation in different phenotypes is not established. Further studies on PCOS phenotypes with larger sample sizes are recommended to establish associations with lower vitamin D levels.

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