

# Vitamin D and Polycystic Ovary Syndrome: an Integrating Review

REVIEW

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## Abstract

**Introduction:** Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age. It causes a metabolic syndrome characterized by insulin resistance, hyperinsulinemia, and dyslipidemia. Vitamin d deficiency and its association with PCOS still represents a controversial subject in the literature.

**Objective:** In this context, this study aimed to understand the association between polycystic ovary syndrome and vitamin d deficiency, and how it occurs.

**Method:** It was an integrative review conducted in the PubMed, Scopus, LILACS, and CINAHL databases from August 2016 to January 2017, with a sample of 7 articles analyzed in their entirety.

**Results:** The evidences according to the studies conducted and the conclusions they identified.

**Conclusions:** It was concluded that we cannot yet assume that vitamin d deficiency contributes to the pathogenesis of PCOS, nor that the syndrome causes vitamin d deficiency, since the studies are controversial and there is a need for research with higher levels of evidence to clarify these doubts.

## Introduction

Polycystic ovary syndrome (PCOS) is an endocrinopathy that affects 5 to 10% of women of reproductive age worldwide, being characterized by chronic anovulation, hyperandrogenism, and polycystic ovaries at ultrasound [1]. Therefore, it is a heterogeneous condition of androgen excess with different degrees of reproductive and metabolic dysfunctions [2, 3].

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## Keywords

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Furthermore, this syndrome is associated with increased risk of infertility and cardiovascular diseases, affecting the quality of life of these women [4]. In this context, vitamin D presents an association with fertility, since its acting mechanism impacts on both reproductive cells and immune system cells [5].

Vitamin d deficiency contributes to the PCOS development, thus promoting insulin resistance, which increases the risk of cardiovascular disease and type 2 diabetes mellitus. On the other hand, other authors state that women with PCOS may present a higher risk to develop vitamin d deficiency, not the opposite [6, 7].

Vitamin d deficiency in women with PCOS is probably due to the obesity of patients with this pathology. Nevertheless, other studies have shown that vitamin d is related to glucose metabolism, through insulin regulation, because of changes in insulin receptor expression and cytokine suppression. Such process may be related to insulin resistance during vitamin d deficiency, consequently resulting in obesity [3, 4, 5, 6, 7, 8].

In this perspective, there is no consensus in the literature regarding the pathophysiology of PCOS and vitamin d deficiency, including if there is a real distinction in serum vitamin d levels in women with and without this disease. Therefore, this study aims to understand the association between polycystic ovary syndrome and vitamin d deficiency, and how it occurs; thus, identifying if there is a difference in serum vitamin d levels in women with and without PCOS, and whether vitamin d deficiency causes or is related to insulin resistance in PCOS patients.

## Methods

This is an integrative review study, as it aims to synthesize a subject, based on the survey of several related studies. The integrative review consists of six stages, starting by establishing the hypothesis or guiding question, followed by literature search, categorization of studies, evaluation of the studies

included in the review, interpretation of the results, and synthesis of the knowledge or presentation of the review [9, 10].

In the first stage of the review, the following guiding questions were designed: "Do women diagnosed with polycystic ovary syndrome present vitamin d deficiency when compared to women without this diagnosis?" and "How to establish the causal relationship between PCOS and vitamin d deficiency?"

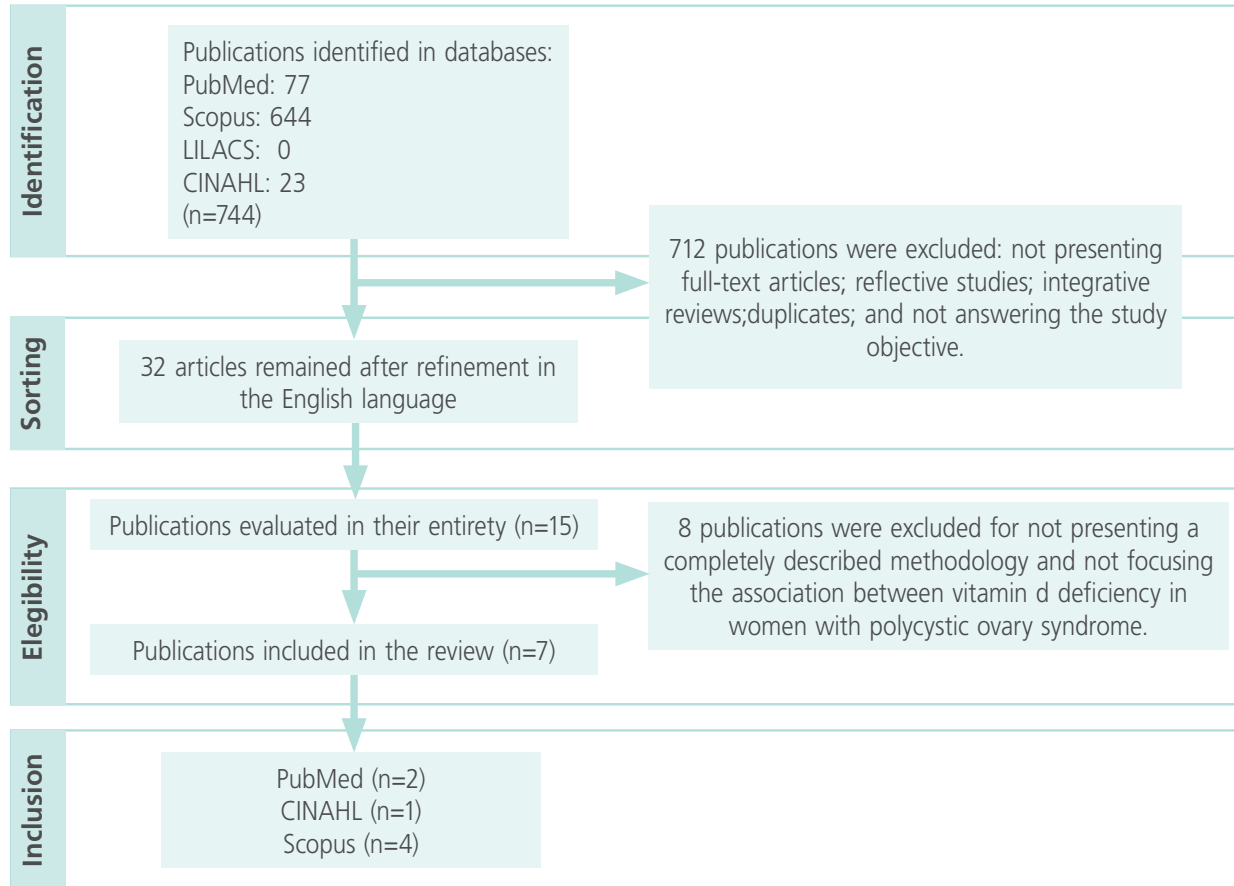
Literature search took place in the National Library of Medicine and National Institute of Health (PubMed), Scopus, Latin American and Caribbean Health Sciences Literature (LILACS), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. Data collection occurred from August 2016 to January 2017, using the controlled descriptors "Polycystic Ovary Syndrome" and "Vitamin D", and the Boolean operator "AND" to combine the descriptors: ("Polycystic Ovary Syndrome") AND "Vitamin D".

Initial sample comprised 744 articles, of which 77 were identified in PubMed database, 23 in CINAHL, 644 in Scopus, and none in LILACS. Next, the following inclusion criteria were applied to refine the search: original articles in the English, Portuguese, or Spanish languages that answered the guiding questions of the study and presented a detailed methodological description and consistent presentation of the results. Moreover, no filter restriction was established for the year of publication of the articles.

To identify the articles that best help to understand the association between PCOS and serum vitamin d levels, a previous selection occurred, in which only the title of the article was read, followed by the abstract and then the full text. The final sample consisted of 7 articles: 2 from the PubMed database, 4 from Scopus, and 1 from CINAHL.

Selected studies were categorized and the necessary information was extracted, which were then organized and entered in a table. The articles un-

**Figure 1:** Flowchart for selecting the publications. Brazil, 2016-2017.



derwent a critical evaluation and analysis, followed by interpretation of the results, discussion, and recommendations. (Figure 1)

## Results

Table 1 presents the results of the publications regarding the identification, title, objectives, design, level of evidence, and the variables of interest of the review.

**Table 1.** Characterization of the articles according to identification, design, level of evidence, and variables of interest of the review. Brazil, 2016-2017.

Title	Objectives	Design	Level of Evidence	Sample	Results	Diagnostic Criteria
Effect of vitamin d on clinical and biochemical parameters in polycystic ovary syndrome women: a meta-analysis [11]	To investigate the association between the serum level of vitamin d and PCOS, and the therapeutic effect of vitamin d in patients with PCOS.	Systematic review with meta-analysis	I	Not available	The serum level of vitamin d is associated with the risk of PCOS, but the therapeutic effect of vitamin D3 supplementation on PCOS remains to be further explored.	Rotterdam

Title	Objectives	Design	Level of Evidence	Sample	Results	Diagnostic Criteria
Intrinsic factors rather than vitamin d deficiency are related to insulin resistance in lean women with polycystic ovary syndrome [12]	To investigate the correlation between insulin resistance and serum 25-OH-vit d concentrations in lean women with polycystic ovary syndrome.	Cross-sectional	IV	90 women (of which 50 were diagnosed with PCOS)	An association between 25-OH-Vit d levels and insulin resistance is not evident in women with PCOS; insulin resistance is related to levels of C-reactive protein, luteinizing hormone, and total testosterone in women with PCOS.	Rotterdam
Vitamin d deficiency in women with polycystic ovary syndrome [13]	To investigate the prevalence of vitamin d deficiency in Korean women with PCOS; and investigate the relationship between vitamin d status and clinical or metabolic features of patients with PCOS.	Cross-sectional	IV	38 women with PCOS and 109 women in control group	The study found no differences in the absolute level of serum vitamin d between PCOS patients and matched controls; additionally, it did not find any correlations between serum vitamin d level and clinical or metabolic profiles between PCOS patients and control group.	Rotterdam
Association of vitamin d receptor gene variants with polycystic ovary syndrome: A case control study [14]	To investigate the possible associations between gene variants with insulin resistance and serum insulin levels.	Case-control	III	70 women (35 with PCOS and 35 without PCOS)	The results showed an association between the VDR gene variants and PCOS risk. These data also indicated that the INSR "NN" genotype was a marker of decreased insulin in women with PCOS. However, further studies are needed to confirm the findings and elucidate the biological mechanisms by which these polymorphisms influence the PCOS risk.	National Institute of Child Health and Human Development criteria
Comparison of 25-hydroxyvitamin d and calcium levels between polycystic ovarian syndrome and normal women [15]	To investigate the correlation between vitamin d levels and PCOS; find a correlation between body mass index (BMI), hyperandrogenism and metabolic syndrome with serum level of 25(OH)D in PCOS patients.	Cross-sectional	IV	242 women (125 with PCOS and 117 healthy individuals)	The final result implicates to not only an association between vitamin d and metabolic syndrome, but also a real peril of pandemic of severe vitamin d deficiency which is considered as real threats for women of reproductive age. Although a direct association between PCOS and vitamin d was not found.	Rotterdam
Association of hypovitaminosis d with metabolic disturbances in polycystic ovary syndrome [16]	To extend the currently rare knowledge about the association of vitamin d in PCOS women.	Cross-sectional	IV	206 women with PCOS	There was no correlation of 25(OH)D levels with total testosterone or free testosterone. Our observations did not find any differences among PCOS and healthy women with respect to 25(OH)D levels.	Rotterdam
Serum vitamin d levels and polycystic ovary syndrome: A systematic review and meta-Analysis [17]	To determine whether serum vitamin d levels are lower in PCOS women than in non-PCOS women.	Systematic review with meta-analysis	I	Not available	Vitamin d deficiency is common among PCOS women; there is no evidence that vitamin d deficiency is causally linked to the development of PCOS; dysregulation of vitamin d metabolism may be a consequence of PCOS.	Not reported on the study

Regarding the year of publication, four articles (57.1%) were published in 2015; two (28.5%), in 2014; and one (14.2%), in 2009. All articles were in English. As for the methods, there were four (57.1%) with a cross-sectional design, two (28.5%) systematic reviews with meta-analysis, and one (14.2%) case-control.

Regarding the level of evidence, 28.5% presented level I; 14.2%, level III; and 57.1%, level IV. Level of evidence I represents strong evidence, in which at least one systematic review of many studies with a randomized controlled design can be identified. Level of evidence III indicates strong evidence of randomized study, time series, matched case-controls, among others. As for the level of evidence IV, it shows non-experimental studies that present a good delineation and that take place in more than one research site [18].

Rotterdam criteria were used as diagnostic reference for the polycystic ovary syndrome in five (71.4%) of the studies. As to the research site, two studies (28.5%) took place in Iran and one (14.2%) in Korea, the other studies did not mention it. Regarding the sample size, three studies (42.8%) comprised less than 100 patients; and only two (28.5%), more than 200. Another important aspect worth highlighting is that four studies (57.1%) included women with PCOS and control groups (without PCOS) for comparison.

Conducted a systematic review with meta-analysis that showed that vitamin d concentration in PCOS patients is lower than in women without PCOS, thus suggesting that vitamin d concentration was negatively associated with insulin resistance in PCOS, but failed to detect the effect of vitamin D3 supplementation on PCOS [11].

A study of 2014, however, identified that the difference in the 25(OH)D concentration among women with and without PCOS was not statistically significant. In addition, serum vitamin d levels have no correlation with insulin resistance. Corroborating this research, Kim et al [13] did not verify differences

between serum vitamin d levels in women with and without PCOS; it also found no relationship between the 25(OH)D concentration and the hormonal and metabolic profile of these patients [12].

Performed a cross-sectional study with 206 women diagnosed with PCOS and did not identify any difference in these patients regarding vitamin d concentration, nor in vitamin d levels with total testosterone and free testosterone [19].

Conducted a research to investigate, among other genes, the association of polymorphisms in the vitamin d receptor (VDR) and the risk of developing polycystic ovary syndrome. They found that the gene variants responsible for the VDR may be used to indicate susceptibility to PCOS, but further studies are needed to determine how these polymorphisms influence the PCOS risk [12].

Found that women of reproductive age are at high risk for vitamin d deficiency in a global context, thus not identifying a direct association between PCOS and vitamin d levels [14].

A systematic review to determine whether serum vitamin d levels are lower in women with PCOS than in women without PCOS and concluded that vitamin d deficiency is common among PCOS patients. Nonetheless, there is no scientific evidence to prove that this vitamin deficiency is associated with the development of polycystic ovary syndrome, but rather that vitamin d deficiency is probably one of the consequences of PCOS [17].

## Discussion

The prevalence of vitamin d deficiency in women with PCOS is still uncertain, and serum 25(OH)D levels in women with this syndrome, portrayed in some studies, are still inconsistent [20]. This data corroborates those found by this research, since the existing studies on this subject are still very inconclusive.

Studies show the association between vitamin d and fertility, so it may be related to the outco-

me of some pathologies, such as endometriosis and polycystic ovary syndrome. Nonetheless, the pathophysiology of PCOS usually presents hyperinsulinemia and obesity, which represent disorders of the endocrine system. Therefore, insulin resistance is common in PCOS, not being caused by vitamin d deficiency as some of the studies surveyed in the review suggest [21].

Unlike these findings, the National Health and Nutrition Program identified an association between serum 25(OH)D levels and the development of the metabolic syndrome. It also states that the vitamin d concentration is inversely related to the risk of hyperglycemia and insulin resistance [22].

Women with PCOS are more susceptible to severe complications, which include insulin resistance, hyperinsulinemia, and dyslipidemia. With calcium and vitamin d supplementation for eight weeks, PCOS patients presented a significant change in insulin concentration [3].

Study found that obese women with PCOS had lower vitamin d levels than non-obese women with PCOS, and that 25(OH)D deficiency was related to the development of insulin resistance in these patients, thus impairing their glucose tolerance [23].

A systematic review concluded that the association between vitamin d and metabolic disorders in women with PCOS remains obscure. Although the literature reports an inverse relationship between vitamin d levels and insulin resistance in PCOS patients, these studies are still very heterogeneous, hence hindering a conclusion [24].

On the other hand, other studies already investigated the effect of calcium and vitamin d supplementation in women with PCOS, noting that this therapy improves the hormonal environment and sequelae related to the syndrome. Nevertheless, it also suggests the need for further studies to better understand these benefits [25].

That the variety of phenotypes of PCOS patients and the heterogeneity of available studies make it difficult to draw conclusions and suggest the con-

duction of clinical trials with well-defined populations [26].

## Conclusions

It is noticed that, despite the great amount of studies conducted on the subject, there is not a single conclusion that is shared between authors, quite the contrary, some are even contradictory. Therefore, it is concluded that vitamin d levels in PCOS patients remain a controversial subject, in which some authors argue that there is no difference between vitamin d levels in women with and without PCOS, as well as this vitamin deficiency is not related to insulin resistance.

In this context, it is imperative to wait for further studies with higher levels of evidence to understand how the association between polycystic ovary syndrome and vitamin d deficiency occurs and to clarify doubts in order to provide a more qualified and targeted assistance.

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