The Correlation between Vitamin D and Polycystic Ovary Syndrome

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ABSTRACT

Background: A deficiency of Vitamin D not only causes poor bone mineralization but also has been implicated in many other chronic diseases. Recent studies have suggested a relevance of vitamin D to reproductive physiology. Moreover, recent evidence is establishing to support the hypothesis that vitamin D status may contribute to the development of metabolic disturbances in PCOS.

Aim of the Study: To investigate the relationship between Vitamin D level and polymorphisms related to metabolic disturbances particularly Insulin resistance in women with PCOS.

Methods: A review of the scientific literature (PubMed Search 1960 to 2017)

Pubmed, Embase and CENTRAL were searched to identify randomized controlled trials that investigated The Correlation between Depression and Folate Deficiency as the primary outcome. Identification of papers and data extraction were performed by two independent researchers.

We searched for relevant trials in the Cochrane Library, MEDLINE (from 1960), Embase (from 1960), and ongoing trial databases; all searches current to October 2017.

Results: Eight studies were included enrolling 1225 women; 779 patients with depression and 446 control subjects. Univariate regression analyses of the weighted means indicated a significant correlation between vitamin D and IR predictability in both PCOS and control women. However, the significance was neutralized after factoring BMI in PCOS women.

Conclusion: There is a growing body of evidence suggesting an inverse association between vitamin D status and metabolic disturbances in PCOS in the current literature yet heterogeneity of the conducted studies made it difficult to come out with a solid conclusion. Nevertheless, normalization of vitamin D levels is recommended generally and especially for PCOS patients.

Keywords: Vitamin D; Insulin resistance; Infertility; PCOS women.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common heterogeneous endocrine disorder characterized by irregular menses, hyper androgenism, and polycystic ovaries. PCOS is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. However, there is considerable interindividual variation in presentation. Although not required for diagnosis, the presence of insulin resistance and hyperinsulinemia is common and places those affected at increased risk of diabetes and cardiovascular disease[1] . Thus, PCOS adversely affects endocrine, metabolic, and cardiovascular health.

Approximately 90%–95% of anovulatory women presenting to infertility clinics have PCOS. Women with PCOS have a normal number of primordial follicles and primary and secondary follicles are significantly increased. However, due to derangements in factors involved in normal follicular development, follicular growth becomes arrested as follicles reach a diameter of 4–8 mm. Because a dominant follicle does not develop, ovulation does not ensue [2].

In addition, spontaneous abortion occurs more frequently in PCOS with incidences ranging from 42%–73%[3].

On a separate note, Vitamin D is a fat-soluble vitamin that belongs to the family of steroid hormones. The biological actions of vitamin D are exerted through a soluble protein, the vitamin D receptor (VDR). VDR is a transcription factor located in the nuclei of target cells that mediates the genomic action of the active form of vitamin D

(1,25(OH)2D3) [4]. This transcription factor is distributed in various tissues, including the reproductive system. The presence of VDR in female reproductive tissue suggests that vitamin D is involved in female reproduction.

More evidence suggested that vitamin D deficiency disrupts female reproductive physiology[5]. Nuclear localization of $1,25(OH)_2D$ and VDR are described in a variety of female reproductive organs including the hypothalamus, pituitary gland, uterus, oviduct, ovary, mammary gland and the placenta. Diet-induced vitamin D deficiency in female rats results in severely compromised fertility: a 45–70% reduction in the probability of becoming pregnant, 67–100% reduction in the number of viable pups and 0–33% probability of rearing normal sized and healthy litters are described in experimental models of vitamin D deficiency [5].

The growing incidence of pre-diabetes and clinical type 2 diabetes, in part characterized by insulin resistance, is a critical health problem with consequent devastating personal and health-care costs [6].Vitamin D status, assessed by serum 25OHD levels, is inversely associated with diabetes in epidemiological studies. Several clinical intervention studies also supported that Vitamin D, or its active metabolite 1,25(OH)2D3, improves insulin sensitivity, even in subjects with normal glucose tolerance. The mechanisms proposed which may underlie this effect include potential relationships with improvements in lean mass, regulation of insulin release, altered insulin receptor expression and specific effects on insulin action [7].These actions may be mediated by systemic or local production of 1,25(OH)2D3 or by suppression of parathyroid hormone, which may function to negatively affect insulin sensitivity. Thus, substantial evidence supported a relationship between Vitamin D status and insulin sensitivity; however, the underlying mechanisms require further exploration [8].

There have been some studies done regarding PCOS and Vitamin D levels. A study done at the Medical University of Graz in Austria showed that almost three of every four women with PCOS may have vitamin D deficiencies. The study looked at 206 women affected by PCOS and found that 72.8% had insufficient vitamin D levels[9].

In a very small Columbia University study of 13 women with PCOS, five were found to have obvious vitamin D deficiency and three others had borderline-low vitamin D status[10]. All 13 women were treated with vitamin D2 at a dose of 50,000 IU once or twice a week, and also received 1,500 mg of supplemental calcium per day. Of the nine women with irregular periods prior to vitamin D treatment, seven experienced a more normal cycle within two months and the other two became pregnant. The authors of the study suggested that abnormalities in calcium balance may be responsible, in part, for the arrested follicular development in women with PCOS [10].

MATERIALS AND METHODS

A review of the scientific literature (PubMed Search 1960 to 2017)

Pubmed, Embase and CENTRAL were searched to identify randomized controlled trials that investigated The Correlation between Depression and Folate Deficiency as the primary outcome. Identification of papers and data extraction were performed by two independent researchers.

We searched for relevant trials in the Cochrane Library, MEDLINE (from 1960), Embase (from 1960), and ongoing trial databases; all searches current to October 2017.

This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, systematically identifying and appraising peer-reviewed RCTs reporting on the relationship between Vitamin D deficiency and PCOS with the objectives of investigating:

- The primary evidence of Vitamin D deficiency in PCOS women
- Type of studies (sample size, study location and year of publiction)
- Metabolic data of subjectsBMI and IR for included subjects
- Methodological quality of the studies
- Estimates of the size of the effect.

Search Approach

A systematic search for relevant observations studies and RCTs was performed evaluating Vitamin D levels and their correlation with Insulin resistance and PCOS predisposition using four library databases of PsychINFO, MedLine, PubMed and Cochrane online library. Search approaches for the different databases can be obtained from the researchers. All databases were searched from inception to October 2017, with eligible papers limited to English language and human subjects.

Eligible Studies
Inclusion Criteria
1. Publication in English and Arabic languages.
2. Prospective, retrospective cohort and cross-sectional, case–control studies.
3. Studies enrolling women with PCOS whether with or without a control group
4. Studies including vitamin D status or VDR polymorphisms or polymorphisms related to vitamin D metabolism.

Exclusion Criteria
1. Studies of different endpoint or selected languages (English and Arabic).
2. letters, abstracts, and conference proceedings that were not published in fully peer-reviewed journals.
3. Studies were not excluded on their methodological quality as the entire evidence base was required to address the aims of this research.
4. Publications with overlapping patient populations in the regression models.

PCOS was defined by the presence of a combination of oligo- or anovulation, PCO morphology, and hyperandrogenism, according to the National Institutes of Health (NIH) criteria or the Rotterdam criteria [11].

Decision-Making
Relevant publications were identified from title, abstract and study descriptors by one researcher; the decision to include was independently validated by a second and disagreements were referred to third for an independent ruling.

Data Extraction and Quality Assessment
Authors screened titles and abstracts of all the articles and extracted data from those reporting frequencies of PCOS and related traits in adolescent and adult women.

Valid international definitions included 1990 National Institutes of Health (NIH) [12] and 2006 Androgen Excess and PCOS Society (AE-PCOS)[13].

Independence
Independent researchers investigated the library databases to reduce errors/bias in accessing evidence.

Data Synthesis and statistical analysis:
Statistical method used: SPSS Software (version 20.0, SPSS, Inc.)

Univariate analyses and subsequently multivariate analyses with HOMA-IR (independent variable) and serum 25OHD and BMI (dependent variables) were carried out. A P value <0.05 was considered statistically significant.

We reported Mean values of serum 25OHD, HOMA-IR, and BMI were employed when available. These data were weighted by the number of participants included in the study. However, in case the mean values were not reported, the median was used . Linear regression models of the weighted means were used to assess the independent relationships between serum vitamin D, BMI, and IR in women affected by PCOS and controls.

The study was done after approval of ethical board of Umm Al-qura university.

RESULTS
The initial search was broad; accepting any article related to the attribution of Vitamin D to PCOSso as to ensure a fully comprehensive view of available work, and generated 612 articles. Preliminary application of study criteria identified 327 potential studies for inclusion that met one or more criteria. Further review of these investigations by independent reviewers yielded 96 RCTs that fully met all inclusion criteria. No individual authors were contacted for information. No further review of methodological quality of the studies was conducted beyond that it appeared in a peer review journal and comprised an RCT. The 96 eligible articles were again closely examined and data extracted using a standard protocol regarding target population, sample size, program provider, program content, intervention components, processes, and outcomes. Comparison among provider type was computation of differences between percent of successful program to number attempted. No further statistical analyses were employed.

Finally, 8 studies were included and detailed as the focus for the present study.
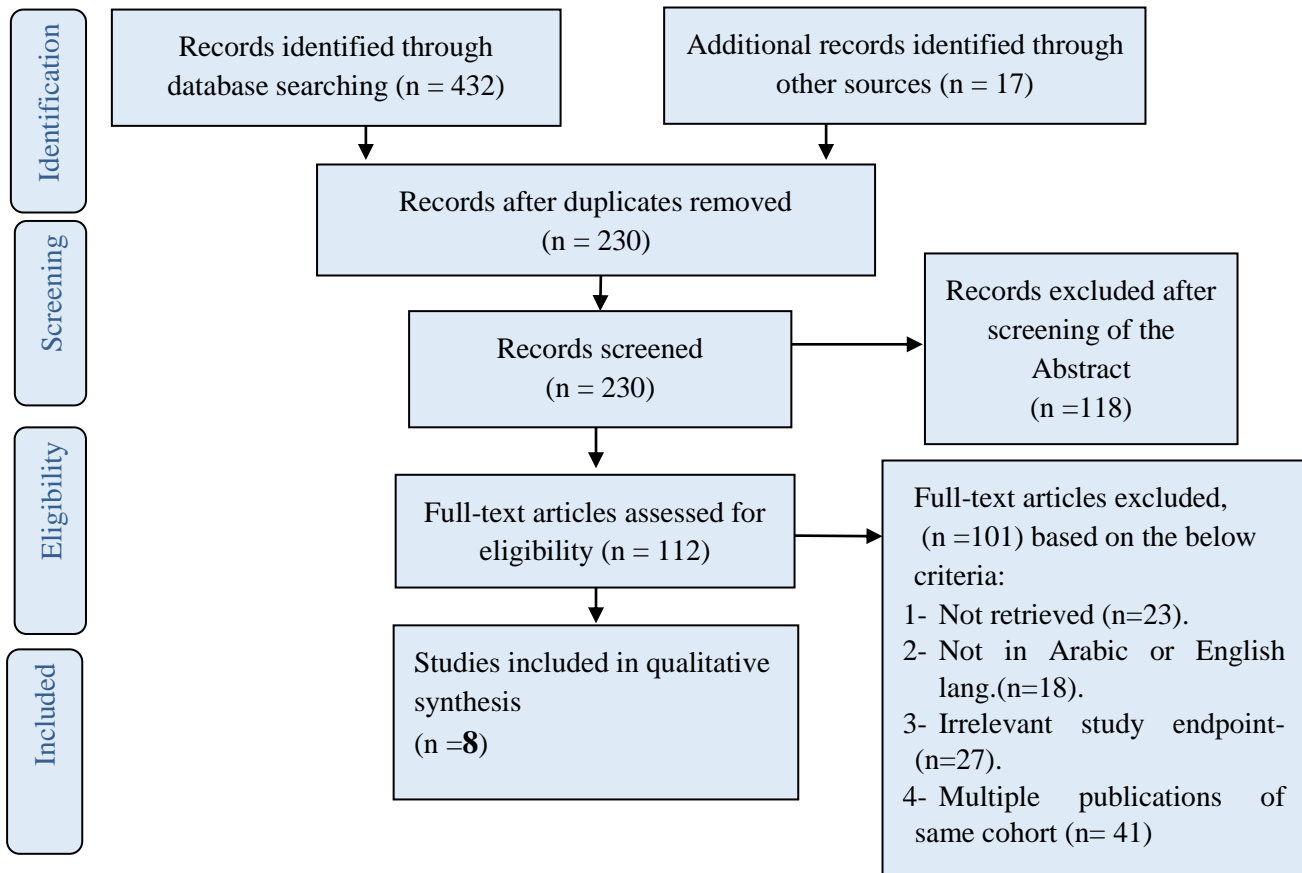
Figure 1: PRISMA flow diagram showing the selection criteria of the assessed studies[14].

Assessment of Correlation between vitamin D status and metabolic disturbances in PCOS in the included studies:

Twelve observational studies were included, adopting a cross-sectional or case–control design, having vitamin D status as one of the primary outcomes.

Characteristics of the studies are detailed in Table 1.

In average, the studies included premenopausal women (16–48 years) of various ethnicities, with the number of participants ranging from 30 to 291. Different stratifications were used: six studies compared PCOS women with controls [15,17,18,20,21,22], whilstfour studies compared lean vs obese PCOS women [16,19,20,22].

It was also observed that big differences were found in the prevalence of vitamin D deficiency (defined as serum 25OHD levels <50 nmol/l), ranging from 37% in a study carried out in Italy [22] to 67.5% in a study carried out in Germany[16].

Seven of all the included observational studies investigated the correlation between vitamin D status and IR [15-22], majority of these studies used HOMA-IR as an indicator of IR.

Three studies reported insulin sensitivity using the quantitative insulin-sensitivity check index [16,18,20]. In one study carried out by Muscogiuri *et al*. [22] in 23 obese and 15 lean PCOS women, IR was evaluated using the hyperinsulinemic–euglycemic clamp (HEC) method, the gold standard for the determination of IR. They found a positive correlation between serum 25OHD levels and glucose uptake during HEC ($r=0.33$; $P=0.03$). Additionally, Serum 25OHD levels were inversely correlated with BMI ($r=-0.49$; $P=0.04$), waist circumference ($r=-0.41$; $P=0.008$), and total fat mass ($r=-0.47$; $P=0.02$). In a multivariate analysis, the authors reported that only total fat mass was an independent predictor of serum 25OHD[22].

Table 1: Baseline characteristics of the included study

Authors	Location	Year of Publication	Groups	Sample size	Mean BMI(kg/m2)	Mean HOMA-IR
Panidis et al. [15]	Greece	2005	PCOS	291	25.5	2.8
			Control	84	26.2	2.6
Hahn et al. [16]	Germany	2006	PCOS	120		
			Obese	98	37.1	5.7
			Lean	32	22.2	1.7
Savastano S et al. [17]	India	2011	PCOS	60	27.1	5.5
			Control	109		
Ngo et al. [18]	Australia	2011	PCOS	27	26.9	2.1
			Control	20	26.3	1.4
Yildizhan R et al. [19]	Turkey	2009	PCOS	100		
			Obese	57	32.8	4.6
			Lean	43	22.1	2.2
Hassan et al. [20]	Egypt	2012	PCOS	30		
			Obese		29.3	7.9
			Control	15	25.8	2.1
Mazloomi et al. [21]	Iran	2012	PCOS	103	27.7	2.3
			Control	115	26.2	1.5
Muscogiuri et al. [22]	Italy	2012	PCOS	38	25.1 (all)	NR
			Obese	23		
			Lean	15		
			Control	103		

The studies that compared serum 25OHD levels between PCOS and control women yielded conflicting results. In detail, three studies demonstrated a significantly lower serum 25OHD level in PCOS women: 32.4 vs 73.7 nmol/l in 90 PCOS women and 47 control women (24), 30.0 vs 43.7 nmol/l among 103 PCOS women and their controls (28), and 17.7 vs 79.2 nmol/l in 30 PCOS women and 15 control women (27). By contrast, another study among 291 PCOS women and 109 control women demonstrated a lower serum 25OHD level in control women than in PCOS women (53.5 vs 73.7 nmol/l) (23).

Table 2: Clinical outcome of patients enrolled in the included studies

Authors	25OHD assay	Groups	Mean BMI(kg/m2)	Mean HOMA-IR	Mean serum 25OHD(nmol/l)	Prevalence of 25OHD deficiency b(%)	Main results regarding vitamin D and metabolic disturbances
Panidis et al. [15]	Immunoassay (BioSource Europe)	PCOS	25.5	2.8	73.7		25OHD was inversely correlated with BMI, insulin levels, and HOMA-IR; however, all were BMI dependent
		Control	26.2	2.6	53.5		
Hahn et al. [16]	Immunoassay (DiaSorin)	PCOS				67.5	25OHD was inversely correlated with BMI, body fat, HOMA-IR, and insulin levels. There was a positive association between 25OHD and QUICKI
		Obese	37.1	5.7	37.4		
		Lean	22.2	1.7	53.2		
Savastan et al. [17]	ELISA (immundiagnostik)	PCOS	27.1	5.5	52.3		25OHD was inversely correlated with HOMA-IR and fasting plasma glucose levels
		Control	NR	NR	NR		
Ngo et al. [18]	Immunoassay (IDS)	PCOS	26.9	2.1	79.3		25OHD was positively correlated with QUICKI in the PCOS group
		Control	26.3	1.4	60.5		
Yildizha et al. [19]	HPLC	PCOS				67	25OHD was inversely correlated with BMI, WHR, HOMA-IR, and TG levels
		Obese	32.8	4.6	31.9		
		Lean	22.1	2.2	73.1		
Hassan et al. [20]	Immunoassay (IDS)	PCOS					25OHD was inversely correlated with BMI, HOMA-IR, QUICKI, and fasting insulin levels
		Obese	29.3	7.9	17.7		
		Control	25.8	2.1	79.2		
Mazloom et al. [21]	ELISA (DRG)	PCOS	27.7	2.3	30		PCOS women had significantly lower 25OHD and adiponectin levels. 25OHD was inversely correlated with BMI. 25OHD was positively correlated with adiponectin levels. There was no association between 25OHD and HOMA-IR
		Control	26.2	1.5	43.7		
Muscogiuri et al. [22]	Immunoassay (DiaSorin)	PCOS	25.1 (all)	NR		37	25OHD was inversely correlated with BMI, waist:hip ratio, and total fat mass. There was a positive association between 25OHD and glucose uptake during HEC
		Obese			51.9		
		Lean			75.4		
		Control					

DISCUSSION

The objective of the present study was to investigate the correlation between Vit D and PCOS mainly through observing polymorphisms in metabolic disturbances; especially Insulin resistance.

Likewise, several recent studies explored the role of vitamin D and its metabolites in overall health and in specific reproductive disorders of women. VDR mRNA and protein are detected in the human endometrium, myometrium, ovarian, cervical and breast tissues[23]. Vitamin D deficiency is hypothesized to contribute to the pathophysiology of a spectrum of gynecological disorders, of which polycystic ovary syndrome (PCOS) appears to be most well studied.

Another major factor predisposing PCOS is Obesity , while an increased adiposity has been consistently associated with reduced serum 25 (OH)D concentrations [24].Some intervention studies have reported significant improvements in HOMA-IR scores and/or insulin secretion after vitamin D supplementation in obese or overweight subjects [25]. Moreover, vitamin D supplementation seemed to induce an effect on losing weight, but it is suggested that energy balance should be controlled for a better result [26].Evidences suggested that physical activity (especially cardiorespiratory fitness)and normal vitamin D levels, reduce insulin resistance and help maintenance of weight loss, decreasing thus the risk of chronic diseases, including type 2 diabetes [27].

In our study, the physical activity levels of the subjects in the insulin-resistant group were reported as lower.Nevertheless, a study conducted by Muscogiuri *et al.*[22]that used glucose clamp technique for measuring insulin sensitivity, the authors suggested that there was no cause-effect relationship between the vitamin D concentrations and insulin sensitivity in obese subjects, emphasizing that both low serum 25 (OH)D concentration and insulin resistance appear to be dependent on the increased body size [22].

In the current study, we provided an overview of the correlation between these variables by carrying out a linear regression analysis. The univariate linear regression analysis revealed both serum vitamin D and BMI to be independent predictors of IR. However, in the multivariate analysis, serum 25OHD was no longer an independent predictor of IR in PCOS women. A strong independent relationship was observed between BMI as an explanatory variable and serum 25OHD as an outcome variable.

The demonstrated inverse relationship between BMI and vitamin D status has been established in earlier reports [28].It has been shown that in obese individuals a higher proportion of vitamin D, which is fat soluble, is sequestered in adipose tissue and thereby the bioavailability of vitamin D is low.

A small number of observational studies identified an inverse association between serum 25(OH)D levels with insulin resistance, features of hyperandrogenism and circulating androgens in women with PCOS [9,16,18]. In an observational study, Thys-Jacobs et al. [29]described normalization of menstrual cyclicity in 7 out of 9 oligomenorrheic women with PCOS who underwent supplementation with vitamin D and calcium over a 6 month period; the authors implied therapeutic efficacy of vitamin D for women with PCOS. Others reported that dietary supplementation with vitamin D or an analog improves insulin sensitivity [30], circulating testosterone and parameters of ovarian folliculogenesis and ovulation. Another small scale study on 12 overweight and vitamin D deficient women with PCOS, revealed a significant lowering effect in circulating androgens (total testosterone and androstenedione) following three month intervention with vitamin D and calcium [31].

Another important note is that the inconsistent results in the reviewed articles may be explained by the hypothesis that vitamin D supplementation may only be effective on IR in case a significant IR exists. As the majority of the reviewed studies did not include diabetic PCOS women, this could be a possible explanation why an effect of vitamin D supplementation on IR was not evident in all

studies. However, the RCT carried out by Ardabili *et al*. did not report an effect of vitamin D supplementation, despite HOMA-IR of 3.17 in PCOS women [18].

Recently, the Institute of Medicine, reviewing all the evidence, has set the required serum 25OHD levels at 50nmol/l [32],but expert opinions remain divided. In addition, no optimal treatment regimen has been established yet for the treatment of vitamin D deficiency in different populations. In this regard, this may influence the study results, as all the reviewed intervention studies used different amounts and durations of vitamin D supplementation.

CONCLUSION

There is a growing body of evidence suggesting an inverse association between vitamin D status and metabolic disturbances in PCOS in the current literature yet heterogeneity of the conducted studies made it difficult to come out with a solid conclusion. Nevertheless, normalization of vitamin D levels is recommended generally and especially for PCOS patients.

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