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EDITORIAL

# Relationship between Vitamin D and Insulin Resistance in Polycystic Ovary Syndrome Women

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## INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive age women, with a prevalence of 6 to 10% in the general population. Polycystic ovary syndrome is by far the most common cause of anovulatory infertility and has been reported to be associated with insulin resistance (IR), hyperinsulinemia, dyslipidemia, and central obesity, which are all risk factors for metabolic syndrome, type II diabetes mellitus,[1] and cardiovascular disease.

While the National Institutes of Health criteria from 1990 are strict and include only anovulation and hyperandrogenism, the Rotterdam consensus criteria of 2003 are broader and include polycystic ovarian morphology as a criterion. More recently, the Androgen Excess Society have proposed that hyperandrogenism should be mandatory for the diagnosis.

For many years, different combinations of clinical (irregular menstrual cycles, hirsutism and acne), biological [elevated serum testosterone or androstenedione levels or increased luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio], and ultrasound (U/S) criteria have been proposed with very little international consensus.

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In 2003, a consensus workshop sponsored by the European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine in Rotterdam[2,3] indicated PCOS to be present if any two out of three criteria are met, in the absence of other entities that might cause these findings:

- Oligoovulation and/or anovulation
- Excess androgen activity
- Polycystic ovaries (by gynecological U/S).

The Rotterdam definition is wider, including many more women, the most notable ones being women without androgen excess. Critics say that findings obtained from the study of women with androgen excess cannot necessarily be extrapolated to women without androgen excess.

It has been proposed to include the U/S criteria in the definition of PCOS that are considered at the present to be the most specific, namely an increased ovarian volume (>10 mL) and/or presence of 12 or more follicles in each ovary measuring 2 to 9 mm. Indeed, using a threshold of 12 for the follicle number per ovary, 0.75% of PCOS patients were diagnosed, whereas 99% of the normal women were under this cutoff.

Metabolic disturbances are common in women suffering from PCOS: 30 to 40% have impaired glucose tolerance and IR with compensatory hyperinsulinemia, and as many as 10% will have type II diabetes mellitus[1,4] by their fourth decade.

During the last decades, it has become evident that PCOS is more than just hirsutism and infertility. Most PCOS women are insulin resistant and have increased risk of hypertension, altered glucose metabolism, and probably increased lifetime risk of cardiovascular diseases. They have a higher prevalence of miscarriage, pregnancy-induced hypertension, preeclampsia, gestational diabetes mellitus, complicated deliveries, and preterm births; 30 to 50% of women with PCOS develop glucose intolerance or diabetes mellitus type II after the age of 30 years. The incidence is two- to threefold higher among women with PCOS compared with healthy women of similar age and body mass index (BMI).

Studies have found that one in two women with PCOS have a significant vitamin D deficiency, especially

those who develop abdominal obesity. Links were also found between the degree of vitamin D deficiency and levels of the hormones, LH and FSH, which stimulate egg development. Lack of vitamin D may therefore be the missing link that explains why some women with PCOS develop worsening symptoms, while others are only mildly affected.

Current evidence suggested that IR has a central role in the pathogenesis of PCOS,[5] contributing to both metabolic and reproductive disturbances.

Insulin resistance, i.e., impaired stimulation of glycogen formation in all major target tissues (skeletal muscle, adipose tissue, liver, kidney), is a pathogenic characteristic feature of PCOS, particularly among obese subjects. The molecular mechanisms of IR involve defects in the insulin-receptor signaling pathway in both adipocytes and skeletal muscle.

Insulin resistance causes compensatory hyperinsulinemia and might contribute to hyperandrogenism and gonadotropin aberrations through several mechanisms. Insulin may act directly in the hypothalamus, the pituitary, or both and thereby contribute to abnormal gonadotropin levels.

Recently, vitamin D deficiency has been proposed as the possible missing link between IR and PCOS. The prevalence of vitamin D deficiency in women with PCOS is about 67 to 85%. This assumption is supported by the finding that the active vitamin D–vitamin D receptor (VDR) complex[6] regulates over 300 genes, including genes that are important for glucose and lipid metabolism[7] as well as blood pressure regulation. Moreover, there is an association between poor vitamin D status and IR in patients with type II diabetes mellitus. Still, it remains unclear whether vitamin D and IR are casually interrelated or whether they constitute two independent characteristics in women with PCOS. According to Thomson et al,[8] about the role of vitamin D in the etiology and management of PCOS, there is an association between vitamin D status and metabolic and hormonal disorders in women suffering from PCOS. There is increasing evidence that vitamin D affects insulin and glucose metabolism, and a low vitamin D status is suspected to be a risk factor for impaired glucose tolerance, IR,[9] and type II diabetes mellitus.

The European Union recommended intake is just 5 µg (200 IU) but this is based on calcium absorption for healthy bones. Many experts believe higher levels of at least 25 µg (1,000 IU) are needed for overall good health, especially when trying to conceive. The European Food Safety Authority has stated that the tolerable upper intake level for vitamin D (from all sources) is 100 µg/day (4,000 IU) for adults, including pregnant and lactating women. In PCOS, best is to measure vitamin D levels to assess the dose.

Recently, a lot of *in vitro* and *in vivo* studies have recognized several "noncalcemic" effects of vitamin D metabolites. Accumulating evidence suggests that the metabolic pathways of this vitamin may play a key role in developing gynecological/obstetric diseases. The VDR-mediated signaling pathways and vitamin D levels seem to deeply affect the risk of several gynecological diseases, such as PCOS, endometriosis, and ovarian and even breast cancer.

## ASSOCIATION BETWEEN VITAMIN D STATUS AND METABOLIC DISTURBANCES IN PCOS IN OBSERVATIONAL STUDIES

Twelve studies had an observational design, employing a cross-sectional or case–control design, with vitamin D status as one of the preliminary outcomes. The studies included premenopausal women (14–50 years) of various ethnicities. Different stratifications were used: seven studies compared PCOS women with controls; three studies compared lean *vs* obese PCOS; one study compared PCOS women with and without the metabolic syndrome; and one study solely included PCOS women. Large differences were found in prevalence of vitamin D deficiency.

Eleven of all the included observational studies investigated the correlation between vitamin D status and IR. Most of these studies used homeostatic model assessment of insulin resistance (HOMA-IR) as an indicator of IR. Five studies reported insulin sensitivity using the quantitative insulin sensitivity check index. In one study carried out by Muscogiuri et al[10] 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. The authors found a positive correlation between serum 25-hydroxyvitamin D (OH)D levels and glucose uptake during HEC. In a multivariate analysis, the authors reported that only total fat mass was an independent predictor of serum 25(OH)D. The studies that compared serum 25(OH)D levels between obese and lean women suffering from PCOS observed a significantly lower serum 25(OH)D level in obese PCOS women.

## EFFECT OF VITAMIN D SUPPLEMENTATION IN WOMEN WITH PCOS

Ten intervention trials had been carried out and published.[11-20] Among these, four had a randomized controlled trial design,[11-21] and one a case–control study design.[12]

Different treatment protocols of vitamin D supplementation were used in the trials, varying from 400 IU a day in the trial carried out by Rashidi et al.[15] The follow-up duration ranged from 3 weeks to 6 months. In detail,

the first study carried out in 1999 by Thys-Jacobs et al[17] among 13 PCOS women, who were treated with 50,000 IU ergocalciferol weekly or biweekly to achieve a target serum 25(OH)D level of 75–100 nmol/L, demonstrated an improvement in menstrual regularity and acne, and two women became pregnant in a follow-up period of 6 months. In addition, a more recent study carried out in Iran in fertile PCOS women has found an improvement in menstrual regularity after 3 months of supplementation with 1,000 mg/day calcium and 400 IU/day vitamin D.[15]

## CORRELATION BETWEEN VITAMIN D STATUS, BMI, AND IR IN WOMEN WITH PCOS

Of the 29 reviewed studies, 18 examined the correlation between vitamin D status and IR in women affected by PCOS and reported the mean and/or median values and were therefore included in this analysis.[22-45] Nine studies reported these values also for control women.[19,20,22-24,27,28,41,45-56] The overall mean of serum 25(OH)D was 61.2 nmol/L in PCOS women and 67.1 nmol/L in control women. The overall mean of HOMA-IR was 2.71 in PCOS women and 1.8 in control women. Univariate regression analysis revealed that an increase in serum 25(OH)D levels was significantly associated with a decrease in HOMA-IR in both PCOS women and control women. The results indicate that every 10 nmol/L increase in serum 25(OH)D levels decreases HOMA-IR by 0.27 in PCOS women and 0.19 in control women. After multivariate regression analysis with serum 25(OH)D and BMI as independent variables, serum vitamin D was found to no longer be an independent predictor of IR in PCOS women. The result remained significant for control women.

## DISCUSSION

Many data suggest that low vitamin D status is associated with IR, impaired fertility, obesity, and PCOS. The determination of optimal 25(OH)D levels in the reproductive period and the amount of vitamin D supplementation required to achieve those levels for the numerous actions of vitamin D throughout a PCOS woman's life would have important public health implications.

Studies on the role of gene variants involved in Vitamin D metabolism in PCOS are sparse but suggest an association of VDR and vitamin D level-related variants with metabolic and endocrine parameters in women with PCOS. Several studies although limited by modest sample sizes have suggested associations between VDR polymorphisms and the development of PCOS as well as IR.

In our study, the overall mean of serum 25(OH)D was 35.2 nmol/L in PCOS women and 45.4 nmol/L in control women. The overall mean of HOMA-IR was 2.71 in PCOS women and 1.8 in control women.

## CONCLUSION

In order to provide an overview of the relationship between vitamin D status and IR in women affected by PCOS compared with healthy control women, we carried out a regression analysis including serum 25(OH)D as an independent variable and HOMA-IR as a dependent variable.

Studies regarding vitamin D status in patients with PCOS show an inverse correlation between vitamin D levels and metabolic risk factors, e.g., IR, BMI, waist-to-hip ratio, triglycerides, and a positive correlation with insulin sensitivity.

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