



## Letter to Editor

### Vitamin D deficiency may be disease modifying but not causal for polycystic ovary syndrome

Sir,

With interest we read the article by Tandon *et al*<sup>1</sup>, about a retrospective, single-center study on the influence of vitamin D deficiency on lipid levels, insulin resistance as assessed by homeostatic model assessment (HOMA), and fasting blood sugar in 175 female participants with polycystic ovary syndrome (PCOS)<sup>1</sup>. It was found that metabolic syndrome was highly prevalent among participants with PCOS but vitamin D deficiency only correlated with high-density lipoprotein (HDL) but not with any other of the evaluated parameters<sup>1</sup>. While the study is relevant it has some limitations that are discussed here.

The main limitation of this study is that neither a healthy nor a diseased control group matched for age and sex was examined to compare the findings with those of the PCOS cohort. Without such a control group the significance of the findings remains limited. Particularly, one does not know if the correlation between vitamin D deficiency and HDL is specific to individuals with PCOS or whether it was observed in controls as well. Whether the connection between metabolic syndrome, HDL levels, and vitamin D is relevant, therefore remains unproven.

An argument against vitamin D deficiency to play a causative role in the development of PCOS is that vitamin D deficiency is a common finding ubiquitously and usually not symptomatic or associated with disease<sup>2</sup>. Vitamin D deficiency is commonly found in apparently healthy subjects and there are numerous individuals with vitamin D deficiency who do not become symptomatic or develop PCOS or other diseases<sup>3</sup>.

A further argument against a causal relationship between vitamin D deficiency and PCOS is that a number of previous studies<sup>4</sup> did not find a connection between vitamin D deficiency and PCOS. In a bidirectional two-sample Mendelian randomization (MR) study<sup>5</sup> on 4890 individuals with PCOS

and 20405 controls to evaluate a possible causal association between PCOS and 25-hydroxy vitamin D, the multivariate MR did not find a causal relation when adjusting the influence of obesity and insulin resistance<sup>5</sup>. Neither univariate nor multivariate MR supported a causal effect of vitamin D deficiency on PCOS<sup>5</sup>. In a study on 60 women with PCOS, the body mass index (BMI), antral follicle count (AFC), and the anti-Muellerian hormone (AMH) were increased compared to controls<sup>6</sup>. With increasing BMI values, the vitamin D levels and AMH levels decreased in the PCOS cohort<sup>6</sup>. However, vitamin D deficiency did not affect the main markers of ovarian reserve<sup>6</sup>.

Another limitation in the study by Tandon *et al*<sup>1</sup> was that the calcium levels were not measured. Since vitamin D is implicated in the regulation of calcium homeostasis, it is essential to know whether the observed vitamin D deficiency had implications on the calcium metabolism. Since vitamin D deficiency manifests with tiredness, exhaustion, mood swings, increased susceptibility to infections, and hair loss, it would have added value to know how many of the participants with PCOS who also had vitamin D deficiency exhibited any of these symptoms.

Overall, addressing the issues raised would strengthen the conclusions the study discussed. Since only HDL was correlated with vitamin D deficiency, a causal relationship seems unlikely. PCOS does not appear to be causally related to vitamin D deficiency, but low vitamin D may affect the clinical manifestations and thereby the progression, prognosis, and outcome of PCOS.

**Conflicts of Interest:** None.

**Use of Artificial Intelligence (AI)-Assisted Technology for manuscript preparation:** The authors confirm that there was no use of AI-assisted technology for assisting in the writing of the manuscript and no images were manipulated using AI.

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Received March 11, 2024

**Reference**

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DOI: 10.4103/ijmr.ijmr\_1345\_21

**Authors' response**

Sir,

Thank you for your interest in the article titled "Effect of vitamin D deficiency on the metabolic

profile of women with polycystic ovary syndrome" by Tandon *et al*<sup>1</sup>, which was recently published in IJMR. I appreciate the thoughtful remarks and would like to provide further clarification on the discussed limitations.

It is important to note that the study's main objective was to evaluate the effect of low levels vitamin D deficiency on metabolic parameters, without claiming a causative role in the development of polycystic ovarian syndrome (PCOS). Vitamin D deficiency as rightly pointed out is quite prevalent in India and is commonly found in both healthy individuals as well as those with various diseases<sup>2</sup>. While it may not necessarily be symptomatic or associated with specific conditions, investigating its potential role in PCOS is still relevant as insulin resistance is the cornerstone for the pathophysiology of PCOS and it is postulated that vitamin D deficiency affects insulin resistance<sup>3,4</sup>.

The primary concern raised is the absence of a control group, both healthy and diseased, matched for age and sex, which limits the significance and interpretation of the study findings. As already mentioned, we acknowledge the importance of having a control group for better understanding the correlation between vitamin D deficiency and high-density lipoprotein (HDL) levels. In future studies, including such control groups will allow for a comprehensive evaluation of the association between vitamin D deficiency, metabolic parameters, and PCOS.

The reference to a bidirectional two-sample Mendelian randomization (MR) study is informative<sup>5</sup>. However, these studies may not capture the full complexity of the relationship between vitamin D deficiency and PCOS due to the multifactorial nature of this disorder. The presence of conflicting results in previous studies that either support or refute the association between vitamin D deficiency and PCOS further emphasizes the complexity of the condition.

The concern regarding the lack of measurement for calcium levels is valid. Given the role of vitamin D in regulating calcium homeostasis, assessing calcium levels in relation to vitamin D deficiency would provide valuable insights into the potential implications on calcium metabolism in PCOS patients.

Lastly, the manifestation of symptoms related to vitamin D deficiency in women with PCOS is an important aspect to consider. PCOS being a heterogeneous disorder symptoms such as tiredness, exhaustion, mood swings, increased susceptibility to infections, and hair loss would not be specific