Is There a Relationship Between Vitamin D Deficiency Status and PCOS in Infertile Women?

Gibt es eine Beziehung zwischen Vitamin-D-Mangel und PCOS bei unfruchtbaren Frauen?

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Key words
vitamin D, polycystic ovary syndrome, PCOS, anti-Müllerian hormone, AMH

Schlüsselwörter
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ABSTRACT

Introduction
It is still unclear in the literature whether low vitamin D levels play a role in the pathogenesis of polycystic ovary syndrome (PCOS), especially with respect to the regulation of anti-Müllerian hormone (AMH). Therefore, we aimed to investigate whether there could be a relationship between vitamin D deficiency status and PCOS.

Materials and Methods
A total of 146 infertile women were divided into two groups according to their ovarian reserve patterns: (i) normal (NOR), and (ii) high (PCOS). The participants were also categorized into two groups according to vitamin D concentrations: (i) Group A < 10 ng/mL, and (ii) Group B 10–20 ng/mL. Samples were obtained and analyzed for estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (TT), 17-hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulfate (DHEA-S) and AMH.

Results
In the NOR group, there were significant differences between Group A and Group B in terms of anthropometric characteristics (p < 0.05, for all). The women in both Group A and Group B had similar AMH concentrations (p > 0.005). Only the NOR group showed a significant though moderate negative correlation between 25(OH)D levels and anthropometric parameters. AMH levels were not correlated with 25(OH)D levels in the NOR or the PCOS group (r = −0.112, p = 0.008; r = 0.027, p = 0.836). Multivariate regression analysis showed no impact of 25(OH)D on other study parameters. Only AMH measurements were significant enough (p < 0.001) to differentiate between PCOS and NOR patterns.

Conclusion
We found no difference in serum 25(OH)D and AMH levels between women with and women without PCOS. No correlation could be demonstrated between 25(OH)D and AMH in the PCOS group or controls.

ZUSAMMENFASSUNG

Einleitung
In der Literatur ist immer noch unklar, ob ein niedriger Vitamin-D-Spiegel eine Rolle bei der Pathogenese von polyzystischem Ovarialsyndrom (PCOS) spielt, besonders in Bezug auf die Regulierung des Anti-Müller-Hormons (AMH). Ziel dieser Studie war es daher zu untersuchen, ob es eine Beziehung zwischen Vitamin-D-Mangel und PCOS gibt.

Material und Methoden
Es wurden insgesamt 146 unfruchtbare Frauen in die Studie aufgenommen und entsprechend ihrer ovariellen Reserve in 2 Gruppen eingeteilt: (i) normale ovarielle Reserve (NOR), und (ii) hohe ovarielle Reserve (PCOS). Die Teilnehmerinnen wurden zusätzlich je nach Vitamin-D-Spiegel in 1 von 2 Gruppen unterteilt: (i) Gruppe A < 10 ng/mL, und (ii) Gruppe B 10–20 ng/mL. Den Teilnehmerinnen wurden Blutproben zur Bestimmung von Östradiol (E2), folliclestimulierendem Hormon (FSH), luteinisierendem Hormon (LH), Gesamttestosteron (TT), 17-Hydroxyprogesteron (17-OHP), Dehydroepiandrosteron-Sulfat (DHEA-S) und AMH entnommen.
**Introduction**

Polycystic ovary syndrome (PCOS) is a common endocrinologic problem that affects 5–10% of women of reproductive age [1, 2]. PCOS is a heterogeneous condition characterized by androgen excess and varying degrees of reproductive and metabolic dysfunction. PCOS appears to be associated with an increase in the number of antral follicles, possibly resulting from a specific defect of anti-Müllerian hormone (AMH) synthesis by granulosa cells [3, 4]. The high AMH levels, which are a main feature of PCOS, appear to be related to the pathogenesis of PCOS.

Vitamin D is produced following the conversion of 7-dehydrocholesterol in the skin through ultraviolet-B radiation. Vitamin D undergoes two hydroxylation processes that yield 25-hydroxyvitamin D [25(OH)D] and 1,25 dihydroxyvitamin D. As 25(OH)D is an easily measured molecule with a long half-life, it is considered to be the best indicator of vitamin D status in humans [5].

Vitamin D is the main regulator of calcium/phosphorus homeostasis and bone structure. Vitamin D is thought to organise gene transcriptions via vitamin D receptors. These receptors are present in many tissues of the body including the ovaries [6]. Vitamin D deficiency appears to contribute to the pathogenesis of PCOS. However, there is no consensus about the importance of serum vitamin D levels in women with PCOS [7, 8].

Although the prevalence of vitamin D deficiency in women with PCOS continues to be a controversial issue, it is a common problem in the general population, with an estimated prevalence of 10–60% [9, 10]. In a study by Thomson et al., 67–85% of women with PCOS had vitamin D deficiency, with levels of less than 20 ng/mL [8]. In Turkey, as in other countries around the world, vitamin D deficiency is endemic. Authors in a recent study claimed that 94.47% of women living in Turkey had serum 25(OH)D levels of less than 30 ng/mL, 76.25% had serum 25(OH)D levels of less than 20 ng/mL, and 32.20% had serum 25(OH)D levels of less than 10 ng/mL [11].

A number of studies have implied that there may be an association between low vitamin D status and PCOS. Lower vitamin D levels were found in women with PCOS compared to controls in several studies [12, 13]. Moreover, vitamin D deficiency may be a contributing factor to aspects of metabolic syndrome which are commonly observed in women with PCOS [10, 14]. Lastly, it has been suggested that vitamin D supplementation could improve menstrual irregularity, follicular development and pregnancy rates in women with PCOS [15, 16].

The existing literature provides some consistent evidence about the relationship between vitamin D status and PCOS. Previous studies have reported that women with PCOS frequently present with vitamin D deficiency [10, 13, 17]. Another study proposed that vitamin D receptor polymorphism could play a part in the pathogenesis of PCOS [18]. However, several other studies claim that vitamin D does not have any impact on ovarian reserve markers [19, 20]. It is therefore still unclear whether low vitamin D levels play a role in the pathogenesis of PCOS, especially in AMH regulation. The present study aimed to investigate whether there is a relationship between vitamin D deficiency status and PCOS.

**Materials and Methods**

**Study design**

This prospective cross-sectional study was carried out at the Reproductive Endocrinology Department of Hitit University Hospital, Çorum, Turkey between January 2, 2015 and September 30, 2016. All participating women gave their written informed consent prior to inclusion in the study. All infertile women with a diagnosis of unexplained infertility admitted to the clinic were included in the study. Infertile women between the ages of 18–35 who were unable to become pregnant after at least 12 months of regular, unprotected intercourse, who did not have poor ovarian reserve, who had normal tubal patency and whose partners had normal semen analysis results met the study’s inclusion criteria. The study was approved by the Ethics Committee of Ankara Numune Hospital in accordance with the Declaration of Helsinki, 2013 (20796219-724.087).

Exclusion criteria were smoking, having prior hysterectomy and/or oophorectomy, endometriosis, ovarian masses, hyperprolactinemia, hypogonadotropic hypogonadism, menopause, pregnancy, congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing’s syndrome. The exclusion criteria also included systemic disorders such as thyroid and renal dysfunction, and hypertension.

All participants underwent a physical examination, and their weight, height, and waist circumference (WC) measurements were taken. Body mass index (BMI) was calculated by dividing weight (in kilograms) by height (in meters) squared. WC measurements were obtained at the level of the iliac processes and umbilicus, with the same scale used to assess abdominal obesity. Antral follicle count was evaluated by ultrasonography (Toshiba Xario...
Using the criteria of the Rotterdam ESHRE-ASRM-sponsored consensus workshop group (2004), PCOS was diagnosed if two of the following three features were present: oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound (presence of ≥12 follicles measuring 2–9 mm in diameter and/or ovarian volume >10 cm³), after excluding other androgen excess disorders [21]. In addition, all participating women had vitamin D concentrations of less than 20 ng/mL as the cut-off value for vitamin D deficiency. Women with NOR and PCOS ovarian patterns were categorized into two groups according to the extent of their vitamin D deficiency as follows:

1. Group A – women with severe vitamin D deficiency (<10 ng/mL; n = 101) and
2. Group B – women with mild vitamin D deficiency (10–20 ng/mL; n = 45)

Specimen collection and assays
Blood samples were obtained from the antecubital vein of participants between 8 a.m. and 10 a.m. on menstrual days 2–5 after an overnight fast. Samples were investigated for estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (TT), 17-hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulfate (DHEA-S), AMH and 25(OH)D. The samples were allowed to clot completely at the room temperature, and then centrifuged at 1000 × g for 20 minutes within 30 minutes after clotting. Sera were analyzed on a daily basis for parameters LH, TT, 17-OHP and DHEA-S by electrochemiluminescence immunosassay (ECLIA) method using an auto-analyzer (Cobas 6000, E 601 Roche Diagnostics, GmbH, Mannheim, Germany). The sera were frozen at –20°C within 2 hours for a maximum of 7 days, and then analyzed to measure AMH levels. AMH samples were measured with the ECLIA method using an automated analyzer (Cobas 6000, E 601 Roche Diagnostics GmbH, Mannheim, Germany). Comparisons and correlation analysis were performed using all data obtained.

Statistical analysis
The SPSS (Statistical Packages for the Social Sciences) software program, version 21 (SPSS Inc. Chicago, IL, USA) was used for all statistical analyses. Continuous variables were first evaluated using the Kolmogorov Smirnov test to test for normality of distribution. Mean differences between study groups were compared by Student’s t-test, and Mann-Whitney U-test was used to compare variables that were not normally distributed. Descriptive statistics were expressed as mean (± standard deviation) and number (%). Spearman’s correlation was used to test any linear relationship between 25(OH)D levels and other study variables. A multivariate regression analysis was performed for each ovarian pattern group to determine preferential effects of 25(OH)D levels. A ROC curve was also constructed. A p-value of less than 0.05 and a confidence interval of 95% were considered to be statistically significant (► Table 4).

Results
Baseline anthropometric and biochemical characteristics
The mean age of the total study population was 28.6 years. The anthropometric and biochemical characteristics of women with normal and PCOS ovarian patterns are shown in ► Table 1. Age and anthropometric parameters such as BMI, WC, HC and WHR of the participants in the two groups were statistically similar (p > 0.05, for all). The E2 level also did not differ between groups (p = 0.059). However, there were significant differences between the NOR and the PCOS groups with regard to FSH, LH, TT and DHEA-S (p < 0.001, p = 0.005, p < 0.001 and p = 0.005, respectively). While the women in the NOR group had higher FSH levels, higher LH, TT and DHEA-S levels were found in the PCOS group. As expected, AMH concentrations were elevated in the sera of women in the PCOS group (p < 0.001). However, there were no significant differences in 25(OH)D levels between both ovarian reserve groups (p = 0.507).

Comparisons of anthropometric and biochemical characteristics
As shown in ► Table 2, there were significant differences in the NOR group between Group A (25(OH)D < 10 ng/mL) and Group B (25(OH)D: 10–20 ng/mL) in terms of anthropometric characteristics including BMI, WC and HC. In addition, the mean E2 and FSH concentrations were higher in Group B than in Group A (p = 0.049 and p = 0.022, respectively). Study parameters LH, TT, 17-OHP and DHEA-S did not differ significantly between Group A and B (p > 0.005, for all). Moreover, the women in both Group A and Group B had similar AMH concentrations (p > 0.005).

In the PCOS ovarian pattern group, all study parameters except BMI and HC were statistically similar (p > 0.005, for all). Mean BMI and HC values were elevated in women with 25(OH)D < 10 ng/mL (p = 0.034 and p = 0.032, respectively).

Correlation and multivariate regression analysis of 25(OH)D with other study parameters
The correlations between 25(OH)D and other study parameters, including age, BMI, HC, WHR, E2, FSH, LH, TT, 17-OHP, DHEA-S and AMH, in the NOR and PCOS pattern groups are shown in ► Table 3. There was a significant but moderate negative correlation between 25(OH)D levels and BMI, WC and WHR values in the NOR group (r = −0.359, p < 0.001; r = −0.301, p = 0.005; r = −0.340, p < 0.001, respectively). This correlation was not observed in the PCOS group. There was a significant but weak posi-
### Table 1
Comparison of baseline anthropometric and biochemical characteristics in normal and PCOS ovarian pattern groups.

<table>
<thead>
<tr>
<th></th>
<th>Normal ovarian pattern group</th>
<th>PCOS ovarian pattern group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>28.1 ± 6.4</td>
<td>27.7 ± 4.8</td>
<td>0.055</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 ± 5.1</td>
<td>26.0 ± 4.9</td>
<td>0.970</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>89.6 ± 11.4</td>
<td>90.2 ± 15.5</td>
<td>0.786</td>
</tr>
<tr>
<td>HC (cm)</td>
<td>105.0 ± 10.4</td>
<td>104.8 ± 10.6</td>
<td>0.920</td>
</tr>
<tr>
<td>WHR</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.661</td>
</tr>
<tr>
<td>E2 (pg/mL)</td>
<td>45.9 ± 22.6</td>
<td>41.1 ± 33.3</td>
<td>0.059</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>7.2 ± 1.8</td>
<td>6.2 ± 1.8</td>
<td>0.001*</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>5.9 ± 2.2</td>
<td>7.6 ± 3.5</td>
<td>0.005*</td>
</tr>
<tr>
<td>TT (ng/dL)</td>
<td>28.1 ± 25.6</td>
<td>30.9 ± 14.2</td>
<td>0.001*</td>
</tr>
<tr>
<td>17-OHP (ng/dL)</td>
<td>1.6 ± 5.6</td>
<td>1.5 ± 1.1</td>
<td>0.380</td>
</tr>
<tr>
<td>DHEA-S (mcg/dL)</td>
<td>208.2 ± 85.9</td>
<td>255.9 ± 110.6</td>
<td>0.005*</td>
</tr>
<tr>
<td>AMH (ng/dL)</td>
<td>3.1 ± 1.9</td>
<td>7.5 ± 4.5</td>
<td>0.001*</td>
</tr>
<tr>
<td>25(OH)D (ng/mL)</td>
<td>9.0 ± 6.0</td>
<td>8.5 ± 6.7</td>
<td>0.507</td>
</tr>
</tbody>
</table>


Values are expressed as mean ± standard deviation.

* p-value is statistically significant (p < 0.05).

### Table 2
Comparisons of anthropometric and biochemical characteristics in normal and PCOS pattern groups with vitamin D deficiency status.

<table>
<thead>
<tr>
<th></th>
<th>Normal ovarian pattern group</th>
<th>PCOS ovarian pattern group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>29.8 ± 6.3</td>
<td>31.2 ± 5.1</td>
<td>0.398</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 ± 5.4</td>
<td>23.6 ± 3.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>92.2 ± 11.4</td>
<td>84.1 ± 9.3</td>
<td>0.002*</td>
</tr>
<tr>
<td>HC (cm)</td>
<td>107.4 ± 10.8</td>
<td>99.9 ± 7.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>WHR</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.403</td>
</tr>
<tr>
<td>E2 (pg/mL)</td>
<td>43.1 ± 22.5</td>
<td>51.6 ± 22.1</td>
<td>0.049*</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>6.8 ± 1.3</td>
<td>8.0 ± 2.2</td>
<td>0.022*</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>5.7 ± 2.1</td>
<td>6.4 ± 2.2</td>
<td>0.090</td>
</tr>
<tr>
<td>TT (ng/dL)</td>
<td>33.2 ± 27.9</td>
<td>20.8 ± 11.5</td>
<td>0.293</td>
</tr>
<tr>
<td>17-OHP (ng/dL)</td>
<td>1.9 ± 6.8</td>
<td>0.9 ± 0.6</td>
<td>0.544</td>
</tr>
<tr>
<td>DHEA-S (mcg/dL)</td>
<td>213.7 ± 88.4</td>
<td>196.7 ± 80.6</td>
<td>0.391</td>
</tr>
<tr>
<td>AMH (ng/dL)</td>
<td>3.2 ± 2.0</td>
<td>2.8 ± 1.7</td>
<td>0.297</td>
</tr>
</tbody>
</table>


Values are expressed as mean ± standard deviation.

* p-value is statistically significant (p < 0.05).
tive correlation between 25(OH)D and FSH in the NOR group (r = 0.234, p = 0.030). However, a significant though moderate correlation was observed between 25(OH)D levels and 17-OHP in the PCOS group (r = 0.339, p = 0.008). Serum AMH levels were not correlated with 25(OH)D levels in either the normal or the PCOS ovarian pattern groups (r = -0.112, p = 0.008 and r = 0.027, p = 0.836, respectively).

Multivariate regression showed that the 72.9% variability in 25(OH)D levels in the NOR group and the 72.4% variability in 25(OH)D levels in the PCOS group could be explained by other study parameters (F = 22.686, p < 0.001 and F = 14.575, p < 0.001 respectively). The interpretation of the coefficients showed that 25(OH)D levels in both ovarian pattern groups had a significant negative effect on FSH levels (p < 0.001, for both). There was no effect of 25(OH)D on other study parameters. Only AMH measurements were significant enough (p < 0.001) to differentiate between PCOS and NOR patterns. In other words, AMH measurements were more useful than other study parameters to distinguish women with PCOS from women without PCOS. The cut-off point was found to be 3.15 ng/mL (sensitivity: 90%, specificity: 62%), as shown in Fig. 1.

Discussion

This study investigated on low serum 25(OH)D and high AMH levels in infertile women with a diagnosis of PCOS. No differences were found in circulating 25(OH)D levels between infertile women with normal ovarian patterns and women with PCOS. In addition, no correlation between 25(OH)D and AMH could be demonstrated in either the NOR or the PCOS pattern group. Therefore, the evidence was insufficient to prove that 25(OH)D plays a role in the pathogenesis of PCOS.

In the literature, various studies have demonstrated conflicting relationships between serum 25(OH)D levels and PCOS. Although Wehr et al. reported low serum 25(OH)D levels in women with PCOS compared to the control group [12], a significant number of studies have shown that serum 25(OH)D levels were similar in both groups [18,22]. Interestingly, studies by Mahmoudi et al. [23], Ngo et al. [24], and Panidis et al. [25] have claimed that women with PCOS have significantly higher vitamin D levels compared to controls of similar ages and BMIs. Other studies have asserted that vitamin D deficiency is more prevalent in women with PCOS [12,26,27]. In a meta-analysis, the authors noted that 25(OH)D levels did not differ between women with and women without PCOS [28].

Consistent with our findings, a recent large retrospective study reported that no correlation could be observed between serum AMH and 25(OH)D levels in PCOS patients and controls [29].
that study which involved 340 predominately Caucasian women, serum 25(OH)D levels appeared to be unrelated to serum AMH levels. No correlation was observed between serum 25(OH)D and AMH levels. Furthermore, women with different ovarian reserve status showed no significant differences in their serum 25(OH)D concentrations. In addition, a meta-analysis found that 25(OH)D levels did not differ between women with and women without PCOS [30]. In contrast, Merhi et al. reported a positive and statistically significant correlation between serum 25(OH)D and AMH levels in women over 40 years of age [31]. However, serum AMH levels in this age group were very low and were sometimes below measurement levels. The study by Dennis et al. also reported averse relationship between obesity parameters (BMI, body fat and waist measurements) and serum 25(OH)D levels. [12 – 14, 39]. When 25(OH)D was compared with measured adiposity characteristics based on the extent of vitamin D deficiency, significant differences were found between 25(OH)D levels and BMI in both the normal and PCOS ovarian pattern groups. Women with higher BMI were more likely to have lower 25(OH)D levels. In parallel to these findings, a significant inverse relationship between BMI and serum 25(OH)D concentrations has been confirmed in various studies [10, 13, 14, 22, 39]. Numerous studies have reported an inverse relationship between obesity parameters (BMI, body fat and waist measurements) and serum 25(OH)D levels. [12 – 14, 39].

According to a large body of evidence, obesity is associated with lower serum 25(OH)D concentrations. This association is likely to be due to volumetric dilution into greater volumes of serum, fat, muscle and liver. Obese individuals tend to be exposed to less sunlight, leading to insufficient biosynthesis of 25(OH)D generated through the skin [22]. Moreover, obesity is more widespread in women with PCOS [39, 40]. It is possible that low serum 25(OH)D concentrations are not the cause but a consequence of obesity. Low 25(OH)D and genes related to low 25(OH)D have been shown to have a minor effect on obesity [41].

The present study did not demonstrate significantly higher BMI values in either group. However, women with PCOS may be expected to have higher measured values of anthropometric characteristics compared to those without PCOS, as reported in a variety of studies [34, 42]. These results alone, however, are not adequate to establish a causal relationship between high measured values of anthropometric characteristics and PCOS [43].

In the present study, the mean AMH level detected was significantly higher in the PCOS group. Several other studies have also reported an increased level of AMH in PCOS patients [34, 44, 45]. The increase in AMH concentrations could be attributable to in-
increased numbers of preantral and antral follicles. This increase is caused either by the increase in AMH concentrations or is due to signalling abnormalities in the follicles [46]. Serum AMH levels appear to be related to the severity of PCOS [47, 48]. The literature contains a number of recent studies aiming to establish a threshold for AMH in the diagnosis of PCOS [49–53]. AMH threshold values varied widely across these studies. However, serum AMH concentrations were generally in the upper range of normal or even elevated in women with PCOS [54]. Although AMH is not currently a generally accepted parameter in the laboratory workup of PCOS, serum AMH concentration is a valuable tool for diagnosing PCOS. The lack of international standards for serum AMH assays, mostly due to technical issues, appears to be the reason for the lack of a definitive consensual threshold.

In the existing literature, the findings of studies evaluating the relationship between vitamin D status and PCOS were contradictory. The small sample sizes, lack of adjustment for confounders, differences in the methodology used to measure serum 25(OH)D, duration of interventions, and lack of an optimal serum 25(OH)D level in the general population might be potential causes.

Vitamin D deficiency was detected in almost all infertile women included in the study according to the reference range of the hospital laboratory. No adequate number of infertile women without vitamin D deficiency could be found during the study period because, as in other parts of the world, vitamin D deficiency is endemic in the Turkish female population. This shortfall is a limitation of our study. The lack of standardized lifestyle conditions in terms of dietary habits and clothing styles of the participants could also be considered a limitation of this study. However, few studies have investigated the relationship between serum 25(OH)D levels and serum AMH levels based on ovarian pattern. Investigating this issue is a strength of this study. All of the participants in the study were infertile; vitamin D deficiency status is likely to become more of a focus for women seeking fertility care. The present study’s focus on this deficiency is another of its strengths.

In summary, the present study revealed no difference in serum 25(OH)D and AMH levels in women with and without PCOS. In addition, no correlation was found between 25(OH)D and AMH levels in women with PCOS or their matched controls. Due to the heterogeneity of the results in other studies, drawing an informed conclusion may be difficult. Further investigations are needed to determine the potential association between serum 25(OH)D levels and PCOS.

Conflict of Interest

The authors declare that they have no conflict of interest.

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