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CLINICAL RESEARCH

Correlation Analysis of the Degree of Vitamin D Deficiency and Clinical Features of Polycystic Ovary Syndrome

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ABSTRACT

BACKGROUND

Vitamin D deficiency is common among patients with polycystic ovary syndrome (PCOS), but the reported clinical efficacy of supplementation varies. This study aims to explore the relationship between the degree of vitamin D deficiency and the clinical features of PCOS to understand the underlying connection between vitamin D and PCOS.

MATERIALS AND METHOD

A retrospective analysis was conducted on 121 PCOS patients with PCOS, who were grouped based on the severity of their vitamin D deficiency. The total testosterone (TT), polycystic ovary morphology (PCOM), anti-Müllerian hormone (AMH), blood lipids, blood glucose, and BMI levels of each group of PCOS patients were collected and analyzed to determine the correlation between varying degrees of vitamin D deficiency and PCOS clinical features. Additionally, a combined analysis of the above indicators was conducted to investigate potential differences in vitamin D levels across various clinical features. This study also compared the classical phenotypes of PCOS in order to establish a comprehensive classification that reflects the overall response of PCOS clinical features and guides clinical treatment.

RESULTS

PCOS patients exhibited varying degrees of vitamin D deficiency, with an average vitamin D level of 14.89 ng/ml. The level of vitamin D was negatively correlated with AMH levels. The proportions of abnormal TG and LDL levels decreased with increasing vitamin D levels, showing statistical differences. The proportions of abnormal HDL and HOMA did not change with vitamin D levels but showed statistically significant differences in their variations.

CONCLUSION

There is a negative correlation between the vitamin D level in patients with PCOS and AMH, and it is also significantly associated with the severity of blood lipid abnormalities. The severity of vitamin D deficiency may indicate a potential link between the aforementioned conditions.

KEYWORDS

Polycystic ovary syndrome (PCOS); Vitamin D; Anti-Müllerian hormone (AMH); Blood lipid

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common menstrual disorder in women of childbearing age and one of the main causes of infertility [1]. Its three main clinical features are irregular menstrual cycles, hyperandrogenism, and polycystic ovarian changes. It often coexists with abnormalities in glucose and lipid metabolism. Low levels of vitamin D in PCOS have been well established, primarily affecting follicle development [2]. However, the significant improvement in ovulation function with vitamin D supplementation in PCOS patients with polycystic ovary syndrome (PCOS) remains inconclusive, indicating that vitamin D requirements may vary among different individuals with PCOS [3]. This study aims to analyze the potential intrinsic connections between low vitamin D levels and sex hormone levels, polycystic ovarian changes, and glucose and lipid metabolism in diagnosed patients with polycystic ovary syndrome (PCOS), in order to develop a more precise treatment for PCOS.

MATERIALS AND METHODS

Study Subjects and Clinical Classification

The study included patients who visited the gynecology outpatient department of the First Affiliated Hospital of Chongqing Medical University from July 2022 to June 2023 due to menstrual irregularities.

The inclusion criteria were women aged 18-35 who met at least two Rotterdam Criteria: 1) Oligo-ovulation or anovulation; 2) Clinical or biochemical evidence of hyperandrogenism; 3) Polycystic ovarian morphology on ultrasound. A total of 121 patients with complete data on age, BMI, AMH, total testosterone levels, lipid levels, fasting insulin, blood glucose levels, and serum 25-hydroxyvitamin D levels were included in the retrospective analysis. This clinical trial is a retrospective analysis. According to the regulations of the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, there is no need to sign an informed consent form for patients. The ethical consent form is attached.

Exclusion criteria included endocrine disorders causing ovulatory dysfunction other than PCOS, pregnancy, total testosterone (TT) <0.1 ng/ml or AMH ≥23.5 ng/ml, age over 35 or under 18, and recent use of insulin sensitizers or oral contraceptives within the past 3 months.

PCOS classification criteria

PCOS was classified into four types based on clinical manifestations: A) oligo-ovulation/anovulation (OA) + hyperandrogenism (HA) + polycystic ovarian morphology (PCO); B) OA + HA; C) HA + PCO; D) OA + PCO. The study excluded patients with type C due to the requirement of menstrual irregularities as stated in the Chinese PCOS guidelines.

PCOS was further classified into obese and non-obese types based on BMI, with a BMI <24 defined as non-obese and aBMI ≥24 defined as obese.

Research Methods

Blood samples for measuring testosterone (TT) and AMH were collected from the antecubital vein on days 2-4 of the natural menstrual cycle or any day for amenorrhoeic patients. Serum levels of AMH and TT were measured using the Beckman DXI800 instrument through electrochemiluminescence. Hyperandrogenism was defined as total testosterone (TT) levels equal to or greater than 0.75 ng/ml, and elevated anti-Müllerian hormone (AMH) levels were defined as greater than 6.8 ng/ml.

Polycystic ovarian morphology (PCOM) is defined as the presence of 12 or more follicles measuring 2 mm - 9 mm in diameter and an increased ovarian volume (>10 mL) on ultrasound. Transvaginal ultrasound was performed on women with regular menstrual cycles or without a dominant follicle, while transabdominal ultrasound was performed on those with no sexual history.

Appropriate levels for total cholesterol (TC) are <5.20 mmol/L, triglycerides (TG) are 0.56 mmol/L - 1.70 mmol/L, high-density lipoprotein cholesterol (HDL) should be >1.04 mmol/L and low-density lipoprotein cholesterol (LDL) should be <3.37 mmol/L. Insulin resistance was assessed using the HOMA index, with a value greater than 2.26 indicating insulin resistance. Vitamin D levels below 10 ng/ml were considered severe deficiency, 10 ng/ml - 20 ng/ml as deficiency, and 20 ng/ml - 30 ng/ml as insufficiency.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software. The Shapiro-Wilk test was used to assess the normality of the variables. Normally distributed variables were compared using Student's t-test, while non-normally distributed variables were analyzed using the median and interquartile range, as well as the Mann-Whitney U test. Group comparisons were made using the chi-square test, with P <0.05 considered statistically significant.

RESULTS

Correlation Analysis between the Degree of Vitamin D Deficiency and Clinical Indicators of PCOS

Group analysis based on the degree of vitamin D deficiency in PCOS patients revealed statistical differences in PCOM, AMH ≥6.8 ng/ml, TG ≥1.7 mmol/L, HDL <1.04 mmol/L, LDL ≥3.37 mmol/L, and HOMA ≥2.26. However, there were no statistical differences in TT ≥0.75ng/ml, BMI ≥24, and TC ≥5.6 mmol/L. There is a strong correlation between the occurrence of polycystic ovary syndrome and the degree of vitamin D deficiency. As the degree of vitamin D deficiency decreases, there is a significant decreasing trend in the incidence of polycystic ovaries. The occurrence of high blood lipids and insulin resistance is also significantly correlated, especially the abnormality of TG and LDL in blood lipids is linearly related to the degree of vitamin D deficiency. When the degree of vitamin D deficiency decreases, the rate of abnormal TG and LDL significantly decreases. There was no statistical correlation between elevated serum total testosterone (TT) and abnormal BMI with the severity of vitamin D deficiency in Table 1.

Table 1: Proportion of metabolic indicators abnormalities in PCOS patients with varying degrees of vitamin D deficiency.

Vitamin D level	<10 ng/ml	10-20 ng/ml	≥20 ng/ml	P-value
PCOM	66.67% (10/15)	82.76% (72/87)	73.68% (14/19)	0.033
AMH ≥6.8ng/ml	80% (12/15)	78.00% (68/87)	57.89% (11/19)	0.001
T ≥0.75ng/ml	33.33% (5/15)	48.28% (42/87)	36.84% (7/19)	0.08
BMI ≥24	53.33% (8/15)	37.93% (33/87)	42.11% (8/19)	0.087
TC ≥5.6mmol/L	13.33% (2/15)	10.34% (9/87)	10.53% (2/19)	0.793
TG ≥1.7mmol/L	40% (6/15)	19.54% (17/87)	15.79% (3/19)	0
HDL <1.04mmol/L	40% (6/15)	59.77% (52/87)	57.89% (11/19)	0.008
LDL ≥3.37mmol/L	40% (6/15)	27.59% (24/87)	15.79% (3/19)	0.001
HOMA ≥2.26	66.67% (10/15)	37.93% (33/87)	42.11% (8/19)	0

Correlation Analysis of Low Vitamin D Levels in Various Subtypes of PCOS

Low levels of vitamin D were observed in all subtypes of patients with polycystic ovary syndrome (PCOS). In the classic subtypes of PCOS, there was no statistically significant difference in low vitamin D levels. The vitamin D levels in subtypes A and D were slightly higher than in subtype B, although there was no statistical difference. This suggests that the PCO status may be associated with vitamin D levels (Table 2).

Table 2: Vitamin D levels in different PCOS subtypes.

PCOS Subtype	Number	Ratio	Vitamin D Level（ng/ml）	P Value
A	43	35.54%	15.05±4.18	0.109#
B	11	9.09%	12.77±3.87	0.164&
D	53	43.80%	14.84±4.53	0.818*

#: A subtype vs B subtype; &: B subtype vs D subtype; *: A subtype vs D subtype

The average vitamin D level in a total of 121 PCOS patients was 14.89 ± 4.60 ng/ml. According to Chinese standards, patients with the C subtype were not diagnosed with PCOS, so there were no patients with the C subtype. Among them, the vitamin D level of subtype B PCOS patients (12.77 ± 3.87 ng/ml) was lower than the vitamin D levels of the other two groups (subtype A: 15.05 ± 4.18 ng/ml, subtype D: 14.84 ± 4.53 ng/ml). However, there was no statistically significant difference in the comparison of vitamin D levels among the three subtypes of PCOS patients.

After classifying the PCOS patients based on their metabolic status, the correlation analysis between PCOS subtypes and low vitamin D levels showed that out of the 121 PCOS patients, there was no statistical difference in the number of patients and vitamin D levels between the obese and non-obese groups, when divided based on BMI levels. The average vitamin D levels were severely deficient (Table 3).

Table 3: Relationship between Vitamin D and BMI.

PCOS Subtype	Number	Ratio	Vitamin D Level（ng/ml）	P Value
BMI ≥24	49	40.49%	14.52±5.15	0.724
BMI <24	72	59.51%	15.15±4.21	0.558

The PCOS patients were divided into two groups: obese (BMI ≥24) and non-obese (BMI <24), based on a BMI greater than 24. There were no statistical differences in the number of patients or vitamin D levels between the two groups of patients with PCOS.

Correlation Analysis between Various Clinical Indicators of PCOS and Low Vitamin D Levels

The clinical indicators of patients with PCOS were analyzed in pairs to determine the levels of vitamin D in each group. The analysis of the groups showed that only the combination of AMH + TT and LDL + HOMA exhibited a statistically significant difference in vitamin D levels. Other combinations did not show any statistical difference.

As indicated in Table 4, the group of PCOS patients with AMH ≤6.8 ng/ml and TT ≥0.75 ng/ml had the lowest levels of vitamin D, which showed a statistically significant difference when compared to the other three groups. The individual analysis showed a negative correlation between AMH and vitamin D deficiency, but no correlation with total testosterone levels. The combined analysis of this statistical difference suggests that in patients with PCOS, severe vitamin D deficiency may contribute to the coexistence of low AMH levels and high testosterone levels, which can worsen follicular development disorders.

Table 4: AMH Combined with TT in the study of vitamin D levels in PCOS patients.

Subtype	Number	Ratio	Vitamin D Level（ng/ml）	P-Value
AMH ≥6.8 ng/ml and TT ≥0.75ng/ml[a]	47	38.88%	15.09 ± 4.16	a*d 0.022
AMH≥6.8 ng/ml and TT<0.75 ng/ml[b]	45	37.19%	13.88 ± 4.20	b*d 0.001
AMH<6.8 ng/ml and TT≥0.75 ng/ml[c]	7	5.79%	11.22 ± 2.66	a*c 0.031
AMH<6.8 ng/ml and TT<0.75 ng/ml[d]	22	18.18%	17.71 ± 5.41	/

The vitamin D level in Group c (11.22 ± 2.66 ng/ml) was lower than the other three groups (15.09 ± 4.16 ng/ml, 13.88 ± 4.20 ng/ml, 17.71 ± 5.41 ng/ml), and there was a statistically significant difference compared to Group a (P = 0.031). The vitamin D level in Group a (15.09 ± 4.16 ng/ml) was lower than in Group d (17.71 ± 5.41 ng/ml), with a statistically significant difference (P = 0.022). Additionally, the vitamin D level in Group b (13.88 ± 4.20 ng/ml) was lower than in Group d (17.71 ± 5.41 ng/ml), also with a statistically significant difference (P = 0.001).

The results in Table 5 revealed that the coexistence of LDL abnormalities and HOMA abnormalities resulted in the most pronounced severity of vitamin D deficiency. This suggests that the degree of vitamin D deficiency may reflect the extent of metabolic abnormalities in patients with PCOS.

Table 5: LDL combined with HOMA in the relationship between vitamin D levels in PCOS patients.

Subtype	Number	Ratio	Vitamin D Level（ng/ml）	P Value
LDL ≥3.37mmol/L and HOMA ≥2.26[a]	18	14.88%	12.27 ± 4.11	
LDL ≥3.37mmol/L and HOMA <2.26[b]	15	12.39%	15.67 ± 4.48	a*b 0.034
LDL <3.37mmol/L and HOMA ≥2.26[c]	31	25.62%	15.69 ± 5.22	a*c 0.012
LDL <3.37mmol/L and HOMA <2.26[d]	57	47.11%	15.08 ± 4.23	a*d 0.023

There is a correlation between vitamin D levels lipid metabolism as well as glucose metabolism. We conducted a further analysis of LDL and HOMA. The results revealed that the vitamin D level in group a (12.27 ± 4.11 ng/ml) was lower than the levels in the other three groups (15.67 ± 4.48 ng/ml, 15.69 ± 5.22 ng/ml, 15.08 ± 4.23 ng/ml). Statistical differences were observed in all cases (P = 0.034, P = 0.012, P = 0.023).

Analysis of the Correlation between Blood Lipid Abnormalities and Low Levels of Vitamin D

The study found a significant increase in the proportion of patients with severe vitamin D deficiency and two or more concurrent blood lipid abnormalities. It also indicated a positive correlation between the improvement of lipid disorders and severe vitamin D deficiency. The results suggest that as vitamin D levels increase, the number of lipid abnormalities decreases, and there is an increase in the proportion of patients with only one lipid abnormality (Table 6).

Table 6: Relationship between the severity of blood lipid abnormalities and vitamin D levels.

Items of Abnormal Blood Lipid	<10 ng/ml	10-20 ng/ml	≥20 ng/ml	P-Value
Number	15	87	19	/
0	26.67% (4/15)	29.88% (26/87)	21.05% (4/19)	0.336
1	20% (3/15)	43.67% (38/87)	57.89% (11/19)	0
≥2	53.33% (8/15)	26.43% (23/87)	21.05% (4/19)	0.904

When the vitamin D level is <10 ng/ml, the proportion of normal blood lipids and the proportion of 2 or 3 abnormal blood lipids are the same (26.67%), which is higher than the proportion of 1 abnormal blood lipid (20%). When the vitamin D level is 10 ng/ml - 20 ng/ml, the highest proportion (43.67%) of abnormal blood lipids is observed. As the number of abnormal items increases, the proportion of abnormal blood lipids decreases. When the vitamin D level is ≥20 ng/ml, the proportion of abnormal blood lipids is the highest (57.89%). As the vitamin D level increases, the proportion of abnormal blood lipids also increases, and there is a statistically significant difference (P = 0.000).

DISCUSSION

Vitamin D deficiency is very common among patients with PCOS [4]. The probability of ovulation is correlated with vitamin D levels in PCOS. There is a 68% probability of ovulation when vitamin D levels are below 20 ng/mL, and a 77% probability when levels are between 20 ng/mL - 30 ng/mL [5]. In our analysis, the average vitamin D level was only 14.89 ± 4.60 ng/mL, with 12.39% of individuals having vitamin D levels below 10 ng/mL and 71.90% falling between 10 ng/mL - 20 ng/mL. Is the varying degrees of vitamin D deficiency related to the clinical heterogeneity of PCOS? We will analyze the clinical characteristics in conjunction with vitamin D to understand its inherent connection.

Firstly

There is a negative correlation between AMH and vitamin D. When an AMH level exceeds 6.8 ng/ml, it is evident that the rate of elevated AMH is 80% in cases of severe vitamin D deficiency. However, when the vitamin D level exceeds 20, the positivity rate of AMH decreases to 57.89%, indicating a negative correlation between the degree of vitamin D deficiency and elevated AMH. There is a relationship between VD (vitamin D) and markers of ovarian reserve. AMH is considered one of the best markers for ovarian reserve [6]. While initial studies have suggested that vitamin D may be associated with markers of ovarian reserve, including AMH, the evidence has been conflicting [7].

AMH reflects the potential for ovarian development and the occurrence of PCO, which requires ultrasound examination for accurate assessment [8]. The number of small antral follicles observed under ultrasound is a direct and significant indicator of the presence of polycystic ovary syndrome (PCOS) [9]. In this study, it was found that when vitamin D levels are relatively insufficient, ranging from 10-20, the positivity rate of PCOM is highest, reaching 82.76%. However, in the group with severe vitamin D deficiency, the rate of PCOM positivity is the lowest, indicating a significant statistical difference. This indicates that the occurrence of PCO is dependent on a certain level of vitamin D support. When vitamin D levels are too low, the number of small antral follicles cannot be maintained. This finding partially explains why there is a significant difference in the effectiveness of PCO treatment during vitamin D supplementation.

In this experiment, the analysis of PCOS subtypes revealed that vitamin D not only regulates AMH levels but also improves glucose and lipid metabolism disorders. This could potentially serve as the primary interface for correcting follicular development. However, it was also found that the regulation of androgens by vitamin D is limited. Therefore, for patients with PCOS who have high levels of androgens, particularly those with elevated

total testosterone, it is necessary to supplement with vitamin D in addition to reducing androgens to achieve effective treatment. We will further confirm this through subsequent clinical trials.

When analyzing the correlation between AMH, total testosterone, and vitamin D, it was found that there is a significant degree of vitamin D deficiency when AMH is ≤6.8 ng/ml and T ≥0.75, indicating a statistically significant difference. This reflects that when vitamin D levels are severely deficient, the function of the ovarian reserve is significantly inhibited by high levels of androgens. However, when analyzing total testosterone levels alone, there is no statistically significant difference in vitamin D levels. Therefore, when treating PCOS patients with vitamin D to address hyperandrogenism, it is necessary to combine it with androgen-lowering therapy to demonstrate the effectiveness of PCOS treatment.

Secondly

A deficiency of vitamin D has a negative impact on the levels of blood lipids [10]. According to this study, it was found that vitamin D levels cannot distinguish whether BMI is increased, but there is a certain degree of dose-response relationship in the four blood lipid indicators. Especially, TG, HDL, and LDL all show varying degrees of improvement as vitamin D deficiency is alleviated, with a significant decrease in the prevalence of abnormalities, particularly in LDL.

There is heterogeneity in the relationship between vitamin D supplementation and the correction of glucose and lipid metabolism disorders [11]. Some studies have reported that high-dose vitamin D supplementation for at least 12 weeks may improve glucose levels, insulin sensitivity, hyperlipidemia, and hormonal functionality in women with PCOS [12]. Long-term prospective studies are needed to determine whether supplementing vitamin D can improve lipid levels and whether lipid abnormalities affect vitamin D levels. Classifying individuals based on the severity of vitamin D deficiency may have greater therapeutic value.

Finally

Vitamin D deficiency in PCOS has been widely recognized [13]. However, various randomized controlled trials have shown conflicting results regarding the benefits of supplementing with vitamin D for PCOS patients [14]. It is reported that there are significant effects on key features of PCOS [15]. vitamin D status appears to be linked to insulin resistance, Vitamin D supplementation might improve insulin sensitivity and also have a positive impact on menstrual frequency and serum androgen levels [16]. However, a study reported no significant differences in several measures of insulin resistance and sensitivity in 36 women with polycystic ovary syndrome who received either 120,000 IU of cholecalciferol monthly or a placebo over 6 months. Additionally, other studies have found no significant effects of vitamin D supplementation on metabolic or endocrine parameters [17].

A meta-analysis study reported that several randomized-controlled trials (RCTs) aimed to evaluate the effects of vitamin D supplementation on characteristics of the PCOS phenotype [18]. However, these studies have mostly yielded mixed results and were, at least in part, limited due to their varying study designs or the small number of study participants. In the recent past, several other RCTs have reported diverse results regarding the effect of vitamin D supplementation in PCOS, leaving the role of vitamin D in the treatment of the syndrome unclear [19].

The clinical effectiveness of treating PCOS is unstable, possibly due to the significant individual differences in polycystic ovary syndrome. PCOS is characterized by anovulation, irregular menstruation, and infertility, and is often accompanied by metabolic disorders, which worsen anovulation. The mechanism has been unclear. Anovulation can be examined from two perspectives: the inability of follicles to develop and the limitations of the follicular microenvironment. The reasons for follicular development may be assessed by measuring AMH, which has always been used as an indicator of ovarian reserve. The follicular microenvironment includes factors such as insulin resistance, lipid abnormalities, and oxidative stress, which can hinder ovarian development and maturation. Androgens act as bidirectional regulators, stimulating the development of small follicles at low levels. However, they then limit the continued development and maturation of follicles once the ovaries reach a certain size. This mechanism ensures that only 1-2 follicles mature and ovulate in each cycle, preventing excessive ovarian stimulation.

CONCLUSION

In summary, the study revealed a correlation between various clinical indicators of PCOS and low levels of vitamin D, as well as a relationship between blood lipid abnormalities and vitamin D levels. Vitamin D may serve as a link between these two aspects, partially reflecting the diverse causes of PCOS and enabling the selection of various treatment strategies to ensure effectiveness.

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