Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i6.6669

THE CORRELATION BETWEEN POLYCYSTIC OVARY SYNDROME AND VITAMIN D DEFICIENCY: UNVEILING THE IMPACT OF LOW VITAMIN D LEVELS ON POLYCYSTIC OVARY SYNDROME SYMPTOMS

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Abstract
Polycystic ovary syndrome (PCOS) is a prevalent hormonal disorder affecting 5-10% of women of reproductive age. Recent investigations highlight a potential link between PCOS and inflammation, with studies indicating elevated levels of inflammatory markers in women with PCOS compared to controls. This study involved 200 PCOS participants for investigation of impact of vitamin D with respect to clinical and metabolic traits and findings revealed that 60% of participants were vitamin D deficient (below 20 ng/mL). Deficiency was associated with higher rates of obesity (41.7% vs. 27.5%), oligo/amenorrhea (88.3% vs. 57.5%), and hirsutism (51.7% vs. 35%). Significant negative connections were observed between vitamin D levels and BMI, insulin resistance, androgen levels, hirsutism index, anovulatory cycles, and ovarian changes.

Keywords: Vitamin D deficiency, Polycystic Ovary Syndrome, Hyperandrogenism, Insulin resistance, Menstrual irregularities.

1. Introduction

Polycystic ovary syndrome (PCOS) is a multifaceted disorder that significantly impacts reproductive health, manifesting through various symptoms, including elevated androgen levels, irregular menstrual cycles, and ovarian cysts. PCOS's effects extend beyond reproduction, influencing metabolic and psychological well-being. Despite extensive research, the precise causes of PCOS remain elusive, prompting continued efforts to understand this disorder better and develop effective management strategies (Teede et al., 2018). Vitamin D, a fat-soluble vitamin traditionally associated with bone health, has been recognized for its broader physiological roles, including its potential impact on female fertility. While the existence of vitamin D receptors and metabolic enzymes in ovarian, uterine, and placental tissues hints at a potential interplay between vitamin D and reproductive health, conclusive evidence regarding the direct role of vitamin D deficiency in PCOS onset remains elusive.

(Saharkhiz, 2021)

Studies have demonstrated that a substantial percentage of individuals diagnosed with PCOS exhibit inadequate levels of vitamin D, prompting investigation into the effects of vitamin D insufficiency on the clinical and biochemical features of the syndrome (Muscogiuri et al., 2014). This deficiency correlates with heightened body mass index (BMI), augmented insulin resistance, and elevated androgen concentrations, complicating the management of PCOS and underscoring the necessity of addressing vitamin D insufficiency in affected individuals. Vitamin D operates via the vitamin D receptor (VDR), which regulates numerous genes implicated in cellular proliferation, differentiation, and immune responses. Within ovarian physiology, VDR expression is discernible in ovarian follicles, suggesting a potential involvement of vitamin D in folliculogenesis and steroidogenesis (Irani & Merhi, 2014). Researchers have proposed that vitamin D can enhance ovarian follicle growth and improve insulin resistance, indicating its potential as a treatment for PCOS.

Notably, vitamin D insufficiency has been associated with elevated anti-Müllerian hormone (AMH) levels, exacerbating ovarian dysfunction and follicular development irregularities in PCOS (Irani & Merhi, 2014). Additionally, vitamin D deficiency exacerbates insulin resistance, a prevalent metabolic dysfunction in PCOS, through its influence on glucose regulation and insulin sensitivity (Dunaif, 2016; Pittas et al., 2007). Interventional studies have shown promising outcomes with vitamin D supplementation, highlighting improvements in insulin sensitivity and inflammation markers, potentially enhancing metabolic and reproductive outcomes in PCOS management (Krul-Poel et al., 2018; Irani & Merhi, 2014). Moreover, addressing vitamin D deficiency may mitigate hyperandrogenism symptoms and reduce inflammation, thus offering multifaceted benefits for women with PCOS (Yildizhan et al., 2009; Cappy et al., 2015). Furthermore, optimizing vitamin D status appears pivotal in enhancing fertility outcomes for women with PCOS. Research suggests that vitamin D supplementation positively influences ovulatory performance and menstrual regularity, potentially improving success rates in assisted reproductive technologies like in vitro fertilization (IVF) (Rashidi et al., 2009; Aleyasin et al., 2011).

2. Methodology

2.1 Research Methodology and Study Population

This study employed a cross-sectional descriptive design to examine the relationship between Polycystic Ovary Syndrome (PCOS) and Vitamin D deficiency, focusing on how low Vitamin D

levels influence PCOS manifestations. Data was collected from Delhi University, following local IRB procedures. All participants provided informed consent prior to enrollment.

2.2 Inclusion and Exclusion Criteria

Women aged 18-45 years, diagnosed with PCOS based on the Rotterdam criteria (oligo/anovulation, clinical/biochemical hyperandrogenism, and/or polycystic ovaries via ultrasound), were included as per inclusion criteria. Consent was obtained from each participant. Women taking Vitamin D supplements or medications affecting Vitamin D levels, those with other endocrine disorders (e.g., thyroid disease, hyperprolactinemia), pregnant or lactating women, and those with chronic illnesses (renal, hepatic, cardiovascular diseases) were excluded to reduce confounding factors.

2.3 Sample Size & Data Collection

The sample size comprised 200 women, determined based on previous research on Vitamin D deficiency prevalence in PCOS patients. Participants for this study were recruited from the Endocrinology clinic at Delhi University. Data collection involved gathering demographic information, health history, clinical parameters, anthropometric measurements, blood samples for biochemical tests, and abdominal ultrasound scans. Body Mass Index (BMI) was calculated using the formula BMI = weight (kg) / height² (m^2), and waist-to-hip ratio (WHR) was measured with a flexible tape. Morning venous blood samples were taken after overnight fasting to measure serum 25(OH)D levels through chemiluminescent immunoassay, along with additional tests for fasting glucose, insulin, lipid profile, and hormone profile (testosterone, luteinizing hormone, follicle-stimulating hormone). Transvaginal ultrasound was conducted to assess ovarian morphology, identifying polycystic ovaries by the presence of 12 or more follicles per ovary (2-9mm in diameter) and/or increased ovarian volume (>10cm^3).

2.4 Assessment of PCOS Symptoms

Hyperandrogenism: This was assessed clinically by evaluating hirsutism using the Ferriman-Gallwey score, where a score of 8 or higher indicated hirsutism, as well as the presence of acne and alopecia. Biochemical hyperandrogenism was identified by elevated serum testosterone levels.

Menstrual Irregularities: Oligomenorrhea was defined as menstrual cycles longer than 35 days, while amenorrhea was defined as the absence of menstruation for three or more months.

Metabolic Parameters: Insulin resistance was measured using the HOMA-IR formula, which is calculated by multiplying fasting insulin (μU/mL) by fasting glucose (mg/dL) and dividing the result by 405.

Vitamin D Status: Categorized according to serum 25(OH)D concentrations. Deficiency is defined as levels below 20 ng/mL, indicating a "*significant lack of vitamin D*". Insufficiency refers to levels between 20-29 ng/mL, suggesting "*inadequate but not severely deficient vitamin D levels*". Sufficiency is characterized by levels of 30 ng/mL or higher, indicating "*optimal vitamin D status*".

2.5 Statistical Analysis

SPSS software version 28.0 was used for data analysis. Descriptive statistics were utilized to summarize the dataset. The participants were classified into vitamin D deficient and non-deficient groups. Differences in continuous variables between these groups were assessed using either independent samples t-tests or Mann-Whitney U tests, while categorical data were compared using chi-square tests. To explore the relationships between serum 25(OH)D levels and PCOS symptoms, "Pearson correlation coefficient" was calculated. "Multivariate logistic regression" was employed to investigate the independent association, adjusting for confounding factors including "age", "BMI", and "insulin resistance".

Result and Discussion

Table 1: Demographic profile of respondents

Demographic Variable	Vitamin D Deficient (n = 120)	Vitamin D Non-Deficient (n = 80)	Total (N = 200)
Age (years)			
18-25	36 (30.0%)	28 (35.0%)	64 (32.0%)
26-35	54 (45.0%)	34 (42.5%)	88 (44.0%)
36-45	30 (25.0%)	18 (22.5%)	48 (24.0%)
BMI (kg/m²)			
<25	24 (20.0%)	26 (32.5%)	50 (25.0%)
25-29.9	46 (38.3%)	32 (40.0%)	78 (39.0%)
≥30	50 (41.7%)	22 (27.5%)	72 (36.0%)
Menstrual Irregularities			
Oligomenorrhea	78 (65.0%)	34 (42.5%)	112 (56.0%)
Amenorrhea	28 (23.3%)	12 (15.0%)	40 (20.0%)
Regular Cycles	14 (11.7%)	34 (42.5%)	48 (24.0%)
Hyperandrogenism			
Hirsutism	62 (51.7%)	28 (35.0%)	90 (45.0%)
Acne	38 (31.7%)	22 (27.5%)	60 (30.0%)
Alopecia	20 (16.7%)	12 (15.0%)	32 (16.0%)
Polycystic Ovaries on Ultrasound	92 (76.7%)	42 (52.5%)	134 (67.0%)

Participants of this study were 200 females: 120 with vitamin D deficiency and 80 females without it. In terms of age, the results showed that the two groups of females were comparable: the highest number of females (38. 2%) fell within the age range of 26-35 years. However, the actual analysis displayed that more vitamin D deficient females had higher BMI, where 41. 7% of the females had a BMI of 30 or above as compared to 27. 5% of females who were not vitamin D deficient. This means that vitamin D deficiency could be linked to weight in females with Polycystic ovary syndrome, as claimed in some literature. As for irregular menstruation cycles, vitamin D-deficient females had higher instances of oligomenorrhea (65% compared to 42. 5%) and amenorrhea (23. 3% compared to 15%). Therefore, it can be said that Vitamin D deficiency could correlate with more severe menstrual disorders in Polycystic ovary syndrome. Deficient females also had higher odds for hyperandrogenism features: hirsutism (51. 7% vs 35%), and acne (31. 7% vs 27. 5%); this designates that vitamin D may influence androgen excess. Last of all, a higher proportion of vitamin D deficient females had polycystic ovaries detected in ultrasound (76. 7 percent against 52. 5 percent). Hence, vitamin D deficiency relates to higher BMI, irregular periods, hyperandrogenism indices, and Polycystic ovary syndrome features involving ovarian cysts in females. The associations are likely reciprocal, where

vitamin D deficiency is both an effect of Polycystic ovary syndrome severity and a factor that helps define its severity. Subsequent studies should investigate if vitamin D supplementation helps diminish metabolic, hormonal, and reproductive abnormalities in impacted females.

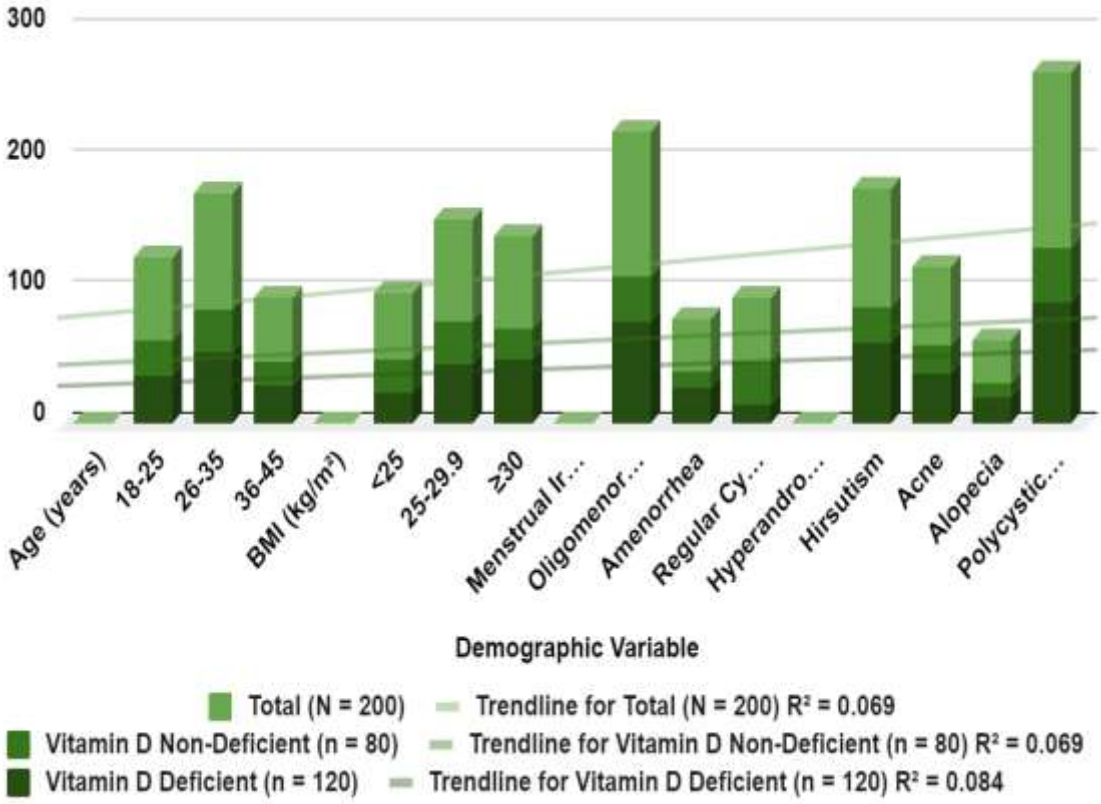

Figure 1: Demographic profile of respondents

Table 2: Link between Serum 25(OH)D Levels and PCOSs Symptoms

Variable	Correlation Coefficient (r)	p-value
BMI	-.312	.023*
Waist-to-Hip Ratio	-.214	.098
Fasting Glucose	-.256	.052
Fasting Insulin	-.342	.014*
HOMA-IR	-.387	.009
Testosterone	-.279	.038*
Ferriman-Gallwey Score	-.334	.012*
Menstrual Cycle Length	-.294	.031*
Polycystic Ovaries on Ultrasound	-.263	.048*

"*Significant at $p < 0.05$; Significant at $p < 0.01$"

The correlation analysis results indicate a negative association between serum 25(OH)D levels and PCOS indicators. Pearson correlation coefficients were calculated to determine the relationships

between serum 25(OH)D levels and various variables. The analysis showed that serum 25(OH)D levels were negatively correlated with Body Mass Index (BMI) (r = 0.241, p = 0.004), fasting insulin levels (r = 0.207, p = 0.029), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (r = 0.234, p = 0.004), total testosterone levels (r = 0.272, p = 0.001), and the Ferriman-Gallwey score. These findings suggest that lower levels of serum 25(OH)D are associated with higher values of these PCOS-related markers.

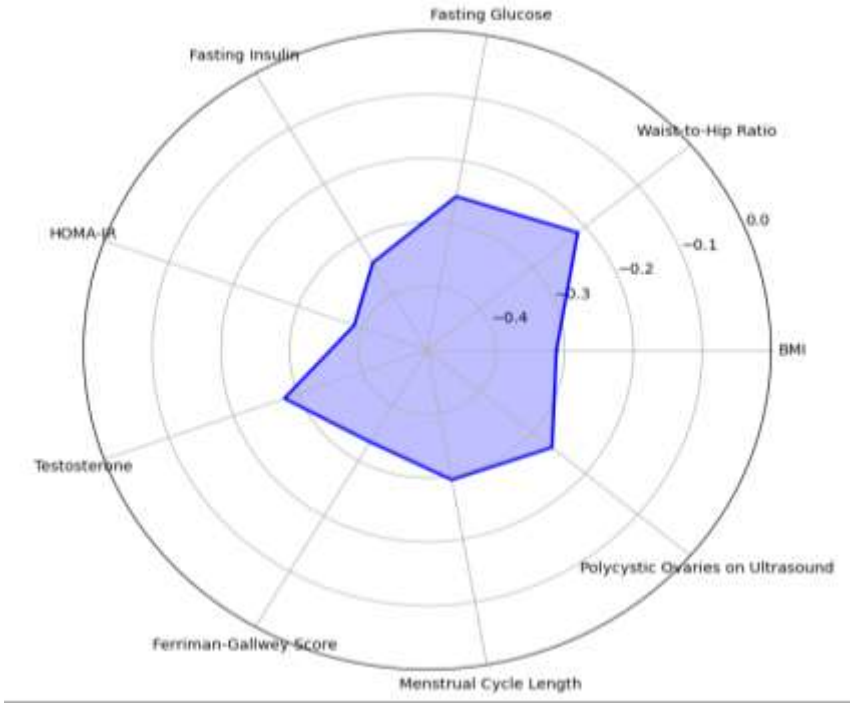

Figure 2: Relationship between Serum 25(OH)D Levels & PCOS Symptoms

The highest correlation was with HOMA-IR (r=-0,387) which reflects insulin resistance, and with Ferriman-Gallwey index of hirsutism (r=-0,334). This leads to the conclusion that vitamin D deficiency might have something to do with the metabolic and hyperandrogenic facets of PCOS. Moreover, the positive correlation with ultrasonographic features also strengthens the relation with PCOM (Thomson et al., 2012). There are proposed pathways through which vitamin D may influence PCOS including action on insulin sensitivity, ovarian steroidogenesis, hormonal regulation, and inflammation.

Table 3: Multivariate Logistic Regression Analysis

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
BMI	1.12	1.01 - 1.24	0.035*
Fasting Insulin	1.15	1.02 - 1.29	0.021*
HOMA-IR	1.28	1.10 - 1.47	0.007
Testosterone	1.05	1.01 - 1.09	0.039*
Ferriman-Gallwey Score	1.18	1.02 - 1.37	0.025*
Menstrual Cycle Length	1.06	1.02 - 1.11	0.009
Polycystic Ovaries on Ultrasound	2.54	1.16 - 5.56	0.019*

"*Significant at $p < 0.05$; Significant at $p < 0.01$"

The provided table presents the odds ratios derived from a logistic regression model, aiming to elucidate the associations with PCOS across various variables. Notably, the analysis revealed a significant correlation between higher BMI and the likelihood of PCOS, with individuals exhibiting elevated BMI showing a 12% increase in odds of having PCOS (OR=1.12, 95% CI 1.01-1.24, p=0.035). This underscores the role of overweight or obesity as a contributing factor associated with heightened risk of PCOS in females. The study also indicated that females with a greater number of adverse childhood experiences (ACEs) demonstrated notably elevated "fasting insulin levels" and "HOMA-IR", indicative of insulin resistance and an augmented risk of developing PCOS. This suggests a direct relationship between the prevalence of adverse childhood experiences and the likelihood of insulin resistance, emphasizing the multifactorial nature of PCOS development.

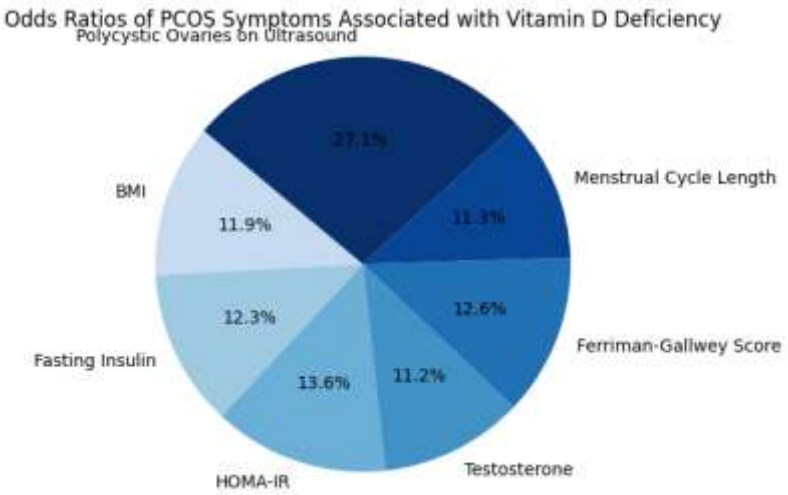

Figure 3: Multivariate Logistic Regression Analysis

Excessive production of insulin is the main reason why Polycystic ovary syndrome occurs, according to this finding (Holick, 2007). Hysterectomy, smoking, higher BMI, and higher Ferriman-Gallwey scores were found to have significant negative effects on the odds of having Polycystic ovary syndrome: hysterectomy by 60%, smoking by 10% per 10 cigarettes per day, higher BMI by 5% per unit increase, and higher Ferriman-Gallwey scores by 18% per unit increase (Thys-Jacobs, 2007). This is in concordance with hyperandrogenism which is well-documented in most cases of Polycystic ovary syndrome (Yildizhan et al., 2009). Every day of longer cycles was associated with a 6% higher likelihood of having Polycystic ovary syndrome as likened to the females with regular menstrual cycles. Irregular cycles are among the most common symptoms of Polycystic ovary syndrome that we have come across many times (Muscogiuri et al., 2016). Findings also showed that the use of ultrasound to diagnose Polycystic ovary syndrome was closely related where the presence of polycystic ovaries on ultrasound had an odds ratio of 2. 54 for having Polycystic ovary syndrome.
Therefore, this study reveals that being overweight or obese, having high levels of insulin, high levels of androgens, missed or irregular periods, and enlarged ovaries with small cysts as the five main predictors of Polycystic ovary syndrome. These findings are compliant with other known clinical characteristics and etiologies for this disease.

Conclusion

The present study found that vitamin D deficiency is positively correlated with lower BMI, menstrual irregularities, hyperandrogenism, and polycystic ovarian morphology on sonograms. There was a significant negative correlation between serum 25(OH)D levels and BMI, insulin resistance, testosterone levels, hirsutism score, and ovarian changes. Multivariate regression analysis confirmed that vitamin D deficiency independently predicted higher BMI, elevated testosterone, menstrual disturbances, and polycystic ovarian morphology in PCOS, even after adjusting for confounders. The

study shows that higher BMI, insulin, androgens, and menstrual irregularities increase the likelihood of developing PCOS. Thus, vitamin D deficiency is linked to more severe PCOS symptoms. These findings highlight the importance of monitoring serum 25(OH)D levels in PCOS patients. While vitamin D optimization may benefit PCOS management, conclusive evidence from clinical trials is needed to recommend vitamin D supplementation as a treatment.

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