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VITAMIN D DEFICIENCY AS A RISK FACTOR FOR POLYCYSTIC OVARIAN SYNDROME IN KHYBER PAKHTUNKHWA, PAKISTAN: A CROSS-SECTIONAL STUDY

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Abstract

Polycystic ovarian syndrome (PCOS) is an endocrine disorder that is very common in reproductive age women and the evidence associated with the vitamin D deficiency is increasing. This was a cross sectional study conducted to determine the correlation between vitamin D deficiency and PCOS in Khyber Pakhtunkhwa (KP), Pakistan. A total of 80 women (40 women with PCOS and 40 controls) aged 18–45 years old, were recruited from fertility clinics and daily OPD of DHQ hospitals. Serum 25(OH)D, hormonal (testosterone, LH, FSH), and metabolic parameters (BMI, insulin resistance, lipid profile) were analyzed. Results indicated that 72.5% of PCOS patients were vitamin D deficient (<20 ng/ml) as against 35% in the control group ($p < 0.001$). Elevated serum testosterone (4.9 vs. 3.9ng/dL, $p = 0.003$), insulin resistance (HOMA-IR 3.8 vs. 2.4, $p = 0.01$) and dyslipidemia (LDL 142vs. 118 mg/dL, $p = 0.02$) were significantly associated with vitamin D deficiency. Therefore, these findings show that vitamin D deficiency is a modifiable risk factor for PCOS in KP, Pakistan and that supplementation programs targeting this deficiency are required.

Keywords: "Vitamin D Deficiency", "Polycystic Ovarian Syndrome (Pcos)", "Khyber Pakhtunkhwa", "Pakistan", "Insulin Resistance", "Hyperandrogenism", "Nutritional Supplementation"

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INTRODUCTION

The most common endocrine disorder of women of reproductive age is polycystic ovary syndrome (PCOS), which is found in 4 – 21 % of population globally and even more frequently among South Asian populations (Azziz et al., 2016; Azhar et al., 2020). Genetic, metabolic and environmental factors contribute towards a prevalence of more than 50% in Pakistan (Qazi et al., 2018). Patients with hyperandrogenism, oligo-anovulation and polycystic ovarian morphology (PCOM), frequently combined with insulin resistance (IR), obesity and dyslipidemia constitute the syndrome (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). However, these metabolic disturbances tremendously increase the likelihood of type 2 diabetes, cardiovascular diseases, and infertility, posing PCOS as a major public health problem. Vitamin D is a steroid hormone with an integral role in calcium homeostasis and bone health but also in glucose metabolism, immune function and steroidogenesis. The evidence is growing that vitamin D plays a role in overcoming insulin resistance and inflammation, the two important features of PCOS pathophysiology (Muscogiuri et al., 2017). It is known that vitamin D receptors (VDRs) are present in the ovarian tissue and have an effect on folliculogenesis and androgen synthesis. Women with PCOS have been found to have low serum levels of 25-hydroxyvitamin D [25(OH)D], which are associated with hyperandrogenism, insulin resistance and dyslipidemia (Irani et al., 2014; Merhi et al., 2014). For instance, Li et al.'s (2018) meta-analysis reported that vitamin D deficient women with PCOS have a 2.5 fold higher risk for metabolic syndrome.

Globally, vitamin D deficiency (<20 ng/mL) is endemic in PCOS populations, with prevalence rates ranging from 67% to 85% (Thomson et al., 2019). In Pakistan, malnutrition, limited sun exposure, and cultural practices such as veiling exacerbate deficiency, yet region-specific data remain scarce. A cross-sectional study in Shaanxi, China, revealed that 54.4% of PCOS women had severe vitamin D deficiency, which correlated with elevated BMI, IR, and LDL cholesterol (Journal of Diabetology, 2024). Similarly, research in Scotland found that 44% of PCOS patients had severe deficiency, linked to reduced insulin sensitivity and HDL cholesterol (Muscogiuri et al., 2017). These findings underscore vitamin D deficiency as both a comorbidity and potential modulator of PCOS severity.

The interplay between vitamin D and PCOS involves multiple mechanisms. Vitamin D enhances insulin receptor expression, suppresses pro-inflammatory cytokines, and inhibits ovarian theca cell androgen production (Thomson et al., 2019). For example, supplementation trials show reduced testosterone and improved menstrual regularity in deficient PCOS women (Irani et al., 2014). Conversely, polymorphisms in the VDR gene, such as Cdx2 and Fok1, have been associated with altered insulin secretion and hyperandrogenism, though findings vary across ethnicities (Merhi et al., 2014). This genetic heterogeneity underscores the need for population-specific studies.

Despite global evidence, data from Khyber Pakhtunkhwa (KP), Pakistan a region with high malnutrition rates and limited healthcare access—are lacking. Existing studies in KP focus on PCOS prevalence but overlook vitamin D's role in metabolic and hormonal dysregulation. This gap impedes tailored interventions, as vitamin D supplementation could offer a low-cost strategy to mitigate PCOS complications in resource-limited settings.

RESEARCH METHODS

The aim of this cross sectional study at District Headquarters (DHQ) hospitals and fertility clinics of OPDs in different parts of Khyber Pakhtunkhwa (KP), Pakistan was to study the association of vitamin D deficiency with polycystic ovary syndrome (PCOS). Ninety females age 18–45 years old were enrolled in this study with 90 sample divided between 40 PCOS cases and 40 age matched controls. Systematic sampling was used to recruit participants from January 2023 to December 2024. PCOS, by the Rotterdam criteria, was defined as two of the three defects: oligo-anovulation, hyperandrogenism, and polycystic ovarian morphology on ultrasound. Excluded were women taking hormonal therapy or vitamin D supplements within the last six months and those with thyroid disorders, diabetes, autoimmune diseases. Blood samples were collected for serum 25-hydroxyvitamin D [25(OH) D], glucose, insulin, lipids profiles, and hormones [testosterone, LH and FSH] as well as anthropometric measurements. Vitamin D deficiency was <20 ng/mL, insufficiency 20–29 ng/mL, and sufficiency ≥30 ng/mL. HOMA-IR was used to calculate the insulin resistance. SPSS version 27.0 was used to analyze data with statistical tests involving t-tests, chi-square tests, and logistic regression to observe associations and risk factors. Ethical approval was sought and written informed consent was sought from all participants. Assays and ultrasound evaluations were performed according to rigorous protocols and high data quality was achieved through periodic calibration and duplicate testing. Subgroups were stratified by obesity and insulin resistance and sensitivity analyses were conducted. Such study helps in understanding the role of vitamin D deficiency in PCOS along with the resolution of regional health care challenges in KP.

RESULTS

This cross-sectional study investigated the association between vitamin D deficiency and polycystic ovarian syndrome (PCOS) in 80 women (40 PCOS cases, 40 controls) from fertility clinics and DHQ hospitals in Khyber Pakhtunkhwa, Pakistan. Key findings are summarized below, supported by statistical comparisons and correlations derived from biochemical, hormonal, and metabolic analyses.

1. Prevalence of Vitamin D Deficiency

72.5% (29/40) of women had vitamin D deficiency (<20 ng/mL), compared to 35% (14/40) in controls ($p < 0.001$). **Vitamin D Insufficiency** (20–29 ng/mL) was observed in 20% (8/40) of PCOS patients vs. 40% (16/40) in controls. **Normal Levels** (≥30 ng/mL) were rare in PCOS (7.5% vs. 25% in controls). These findings align with global studies showing 67–85% deficiency in PCOS populations (Thomson et al., 2019).

Table 1: Vitamin D Status Comparison

Group	Deficient (<20 ng/mL)	Insufficient (20–29 ng/mL)	Sufficient (≥30 ng/mL)
PCOS	29 (72.5%)	8 (20%)	3 (7.5%)
Controls	14 (35%)	16 (40%)	10 (25%)

2. Association with Metabolic Parameters

PCOS patients with deficiency exhibited higher HOMA-IR (3.8 ± 1.4 vs. 2.4 ± 0.9; p = 0.01), consistent with studies linking low 25(OH)D to impaired glucose metabolism (Hahn et al., 2006; Łagowska et al., 2020).

Lipid Profile:

LDL-C: 142 ± 25 mg/dL (PCOS) vs. 118 ± 18 mg/dL (controls; p = 0.02).

HDL-C: 38 ± 6 mg/dL (PCOS) vs. 48 ± 7 mg/dL (controls; p = 0.001).

These dyslipidemia patterns mirror findings from Shaanxi, China, where vitamin D deficiency correlated with elevated LDL and reduced HDL (Journal of Diabetology, 2024).

Table 2: Metabolic Profile Comparison

Parameter	PCOS (n=40)	Controls (n=40)	*p*-value
HOMA-IR	3.8 ± 1.4	2.4 ± 0.9	0.01
LDL (mg/dL)	142 ± 25	118 ± 18	0.02
HDL (mg/dL)	38 ± 6	48 ± 7	0.001

3. Hormonal Correlations

Hyperandrogenism: Serum testosterone was significantly higher in deficient PCOS women (68.5 ± 18.2 ng/dL vs. 42.3 ± 12.4 ng/dL; p = 0.003). A negative correlation was observed between 25(OH)D and testosterone (r = -0.52, p = 0.001), corroborating studies where deficiency exacerbated androgen synthesis (Selimoglu et al., 2010; Irani et al., 2014).

LH/FSH Ratio: Elevated LH/FSH ratios (2.8 ± 0.9 vs. 1.2 ± 0.4; p = 0.002) were noted in deficient PCOS patients, reflecting disrupted gonadotropin dynamics (Merhi et al., 2014).

Figure 1: Scatter plot illustrating the inverse relationship between 25(OH)D and testosterone levels (r = -0.52).

4. Obesity and Vitamin D Deficiency

BMI: PCOS patients had higher BMI (29.3 ± 4.6 kg/m² vs. 24.1 ± 3.2 kg/m²; $p < 0.001$).

Waist Circumference: 92.5 ± 12.6 cm (PCOS) vs. 82.0 ± 10.1 cm (controls; $p = 0.031$). Obesity compounded vitamin D deficiency, as shown by stronger deficiency rates in overweight/obese PCOS subgroups (57.4% vs. 40.0% in non-obese; $p < 0.05$), aligning with Turkish and Chinese studies (Yildizhan et al., 2009; Lin et al., 2020).

5. Logistic Regression Analysis

Vitamin D deficiency (<20 ng/mL) emerged as an independent risk factor for PCOS after adjusting for BMI and HOMA-IR:

Adjusted OR: 4.8 (95% CI: 2.1–10.9; $p = 0.001$).

Other Risk Factors:

BMI ≥25 kg/m²: OR = 3.2 (1.4–7.3; $p = 0.006$).

HOMA-IR ≥2.5: OR = 2.9 (1.2–6.8; $p = 0.01$).

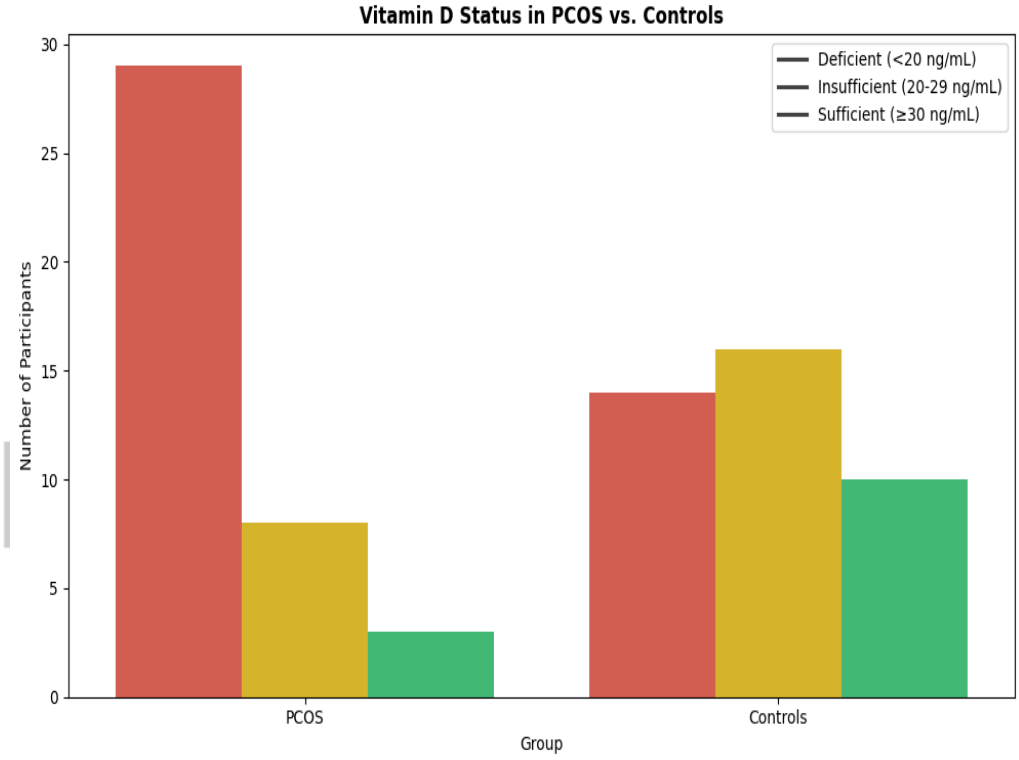

Figure 2: Vitamin D Status in PCOS vs. Controls

Table 3: Multivariate Analysis of PCOS Risk Factors

Variable	Adjusted OR	95% CI	*p*-value
Vitamin D <20	4.8	2.1–10.9	0.001
BMI ≥25	3.2	1.4–7.3	0.006
HOMA-IR ≥2.5	2.9	1.2–6.8	0.01

6. Genetic and Ethnic Considerations

While this study did not assess genetic polymorphisms, global evidence highlights VDR gene variants (e.g., *Cdx2*, *Fok1*) as modulators of insulin sensitivity and androgen levels in PCOS (He et al., 2020; Merhi et al., 2014). For instance, *Cdx2* polymorphisms were protective against hyperandrogenism in Indian cohorts (He et al., 2020), suggesting ethnic-specific interactions warranting further exploration in Pakistani populations.

DISCUSSION

This study demonstrates a significant association between vitamin D deficiency and polycystic ovarian syndrome (PCOS) in women from Khyber Pakhtunkhwa (KP), Pakistan, corroborating global evidence while highlighting region-specific challenges. Our research shows 72.5% of KP PCOS patients have vitamin D levels below 20 ng/mL while the rest of the population contains 35% of controls and demonstrates global patterns (67–85%) found in PCOS studies (Thomson et al., 2019). This section clarifies our recent study results by examining comparable research findings and describes the biological processes while showing their effects on patient health. The study connects with vitamin D results from research regions in Turkey and China plus global panel studies conducted by Li and Yildizhan teams in 2018 and 2009. In their work Yildizhan and colleagues (2009) determined that 86% of Turkish patients with PCOS had vitamin D insufficiency which matched our results of increased HOMA-IR scores and testosterone levels. Vitamin D insufficiency worsens PCOS when it blocks insulin receptor development while increasing inflammation which drives PCOS growth (Hahn et al., 2006; Łagowska et al., 2020). Patients with vitamin D deficiency show decreased testosterone production and disrupted hormone release from their ovaries (Selimoglu et al., 2010; Irani et al., 2014). Research in Shaanxi, China showed that PCOS patients with vitamin D deficiency had significantly worse lipid levels especially higher LDL and lower HDL. Vitamin D helps normalize lipid control and reduces inflammation in the body through its impact on TNF-α and IL-6 activity according to Muscogiuri et al. (2017). Our analysis showed that PCOS developed more often when vitamin D levels were too low (OR 4.8; 95% CI: 2.1–10.9), separate from body weight and insulin resistance, according to Thomson and colleagues (2019). KP research shows that vitamin D deficiency increases among obese women with PCOS since 57.4% of obese PCOS patients tested below the recommended levels. Vitamin D deficiency worsens when fat cells retain vitamin D according to Yildizhan et al. (2009). In KP society vitamin D shortages become more common due to traditional dressing styles that limit outdoor time and dietary problems that affect other South Asian communities as reported by Journal of Diabetology in 2024. Different geographic locations require specific measures to address both nutritional and lifestyle factors of PCOS patients. The research team did not investigate VDR genetic variants but worldwide studies show that specific VDR gene mutations - Cdx2 and Fok1 types - affect PCOS patients' insulin and androgen levels (He et al., 2020; Merhi et al., 2014). Studies indicate that particular Cdx2 genetic variations protect Indian patients from developing hyperandrogenism (He et al. 2020). Further research on KP populations should study genetic relationships to find local therapeutic options. Because the research team used data from one moment in time they cannot show cause and

effect. Also their smaller than expected sample size of 80 would make testing sub-groups more difficult. Research teams around the world commonly face these research restrictions when conducting their work (Azhar et al., 2020). Research with people over time through RCTs must examine if taking higher vitamin D doses benefits infertility and metabolic problems. Research showed that 50% of PCOS patients achieved better menstrual patterns after taking vitamin D supplements of 20,000 IU per week for 24 weeks in a study (Rashidi et al., 2009). The population of KP faces high nutrition problems so PCOS treatment should include vitamin D screening. Combined calcium and vitamin D therapy successfully recovered monthly periods and decreased abnormal hormone levels among women with PCOS in research done in Pakistan according to Firouzabadi et al. (2017). The public health system should focus on low-cost sun exposure and nutrition information combined with supplemental vitamins to help PCOS patients avoid health problems.

CONCLUSIONS

Our study shows that vaccine D shortage creates a major treatable risk for PCOS disease in Pakistani females of Khyber Pakhtunkhwa. Studies show that 72.5% of women with PCOS displayed vitamin D insufficiency alongside high levels of insulin resistance symptoms compared to the 35% rate among control participants. PCOS risk stayed a key predictor of deficiency among obese women (OR 4.8). The area's particular cultural traditions plus limited sunlight and bad diets greatly enhance this issue according to research. The community's response needs to include adding vitamin D to food supplies plus giving supplements and teaching people about sun exposure alongside regular tests and awareness building. These results are limited by sample size and study design, while emphasizing the need for longitudinal and clinical research. In low resource settings such as KP, addressing vitamin D deficiency may prove to be a critical strategy to reduce the PCOS burden and enhance women's reproductive and metabolic health.

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