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Original article

Unraveling the association between PCOS, Obesity, and Bone Turnover: Insights into Endocrine and Metabolic Dysfunctions

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Abstract

Polycystic ovary syndrome (PCOS) is a multifaceted endocrine disorder that affects metabolic and skeletal health, with emerging evidence linking it to disruptions in bone mineral homeostasis. This study aimed to investigate key bone health biomarkers, including vitamin D, calcium, phosphate, and body mass index (BMI), to elucidate their differences between PCOS and normal individuals. Our findings reveal a significant reduction in serum vitamin D levels ($p < 0.001$) in PCOS patients, reinforcing the hypothesis of impaired bone metabolism. Additionally, calcium and phosphate levels were notably lower in the PCOS group, suggesting potential skeletal fragility and increased bone resorption. Elevated BMI ($p < 0.001$) in PCOS individuals was positively correlated with inflammatory markers (TNF-α, and IL-6), highlighting the role of systemic inflammation in bone turnover dysregulation. Correlation analyses revealed that the vitamin D-phosphate-calcium axis exhibits distinct regulatory patterns in PCOS, indicating possible compensatory mechanisms that fail to fully restore mineral balance. Furthermore, hyperandrogenism negatively correlated with bone mineral density (BMD), suggesting its contribution to skeletal deterioration. These findings provide new insights into the metabolic and hormonal interplay affecting bone health in PCOS, underscoring the need for targeted therapeutic strategies to mitigate long-term skeletal complications.

Keywords: *PCOS, Bone Health, Vitamin D Deficiency, Calcium Homeostasis, BMI*

Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent endocrine disorders affecting women of reproductive age, with a global prevalence of 8–13% as reported by the World Health Organization (WHO) (1). In South Asia, the prevalence is notably higher, reaching up to 20%, highlighting the significant burden this condition poses (2). PCOS is characterized by a triad of clinical manifestations: hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, often accompanied by metabolic complications, including insulin resistance, dyslipidemia, and obesity (3). These metabolic abnormalities not only exacerbate reproductive dysfunction but also predispose women to long-term health risks such as type 2 diabetes, cardiovascular diseases, and osteoporosis.

The pathophysiology of PCOS is complex and multi-factorial, driven by genetic, environmental, and hormonal interactions. Genetic studies have identified key candidate genes involved in steroid genesis (*CYP11A1, HSD17B6*), insulin signaling (*INSR, IRS1*), and inflammatory pathways (*TNF-α, IL-6*), suggesting a strong hereditary component (4,5,6). At the molecular level, dysregulation of receptors such as FSHR, LHR, and IRS1 impairs ovarian function and metabolic homeostasis, further aggravating disease progression (7). Additionally, lifestyle factors, dietary

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habits, and environmental endocrine disruptors significantly contribute to PCOS onset and severity, making it a condition of both genetic predisposition and environmental influence.

Despite being a lifelong disorder, treatment strategies for PCOS remain symptom-focused rather than curative. First-line management emphasizes lifestyle modifications—weight management, dietary interventions, and physical activity—to improve insulin sensitivity and regulate menstrual cycles (8). Pharmacological therapies, including combined oral contraceptives (COCs) for cycle regulation, metformin for insulin resistance, and anti-androgens such as spironolactone for hyperandrogenic symptoms, offer symptom relief but fail to address the broader metabolic and skeletal complications of PCOS (9). While these treatments provide short-term benefits, their long-term impact on bone metabolism remains largely unexplored.

Emerging evidence suggests that PCOS negatively impacts bone health, increasing the risk of osteoporosis and fractures in later life. This is primarily due to chronic inflammation, hormonal dysregulation, and impaired calcium-phosphate homeostasis. Vitamin D deficiency, a common finding in PCOS, leads to secondary hyperparathyroidism and increased bone resorption, exacerbating skeletal fragility (10). Additionally, hyperinsulinemia and hyperandrogenism influence bone remodeling by altering osteoblast and osteoclast activity, with conflicting reports on their exact effects on bone mineral density (BMD) (11). Understanding the intricate relationship between PCOS, insulin resistance, and skeletal health is critical for developing targeted interventions to mitigate long-term osteoporosis risk in affected women.

This study aims to compare bone health markers, including vitamin D, calcium, and phosphate levels, between women with PCOS and healthy controls; evaluate the relationship between body mass index (BMI) and bone health parameters to understand obesity's contribution to skeletal risks in PCOS; assess the impact of insulin resistance and hormonal alterations on bone metabolism, particularly their influence on osteoblast and osteoclast activity; and highlight the need for targeted therapeutic interventions to mitigate long-term skeletal risks in PCOS patients.

2. Materials and Methods

2.1 Study Design and Population

This case-control study aimed to evaluate differences in bone metabolism markers between women diagnosed with polycystic ovary syndrome (PCOS) and age-matched healthy controls. Participants were recruited from Sree Balaji Medical College and Hospital, Chrompet, Chennai, Tamil Nadu, India, between January and August 2024. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants before study enrollment.

Inclusion and Exclusion Criteria

Women aged 18–40 years were enrolled in the study and classified into two groups. The PCOS group was diagnosed based on the Rotterdam Criteria (2003), requiring at least two of the following three criteria: (1) oligo- or anovulation, (2) clinical and/or biochemical hyperandrogenism, and (3) polycystic ovarian morphology on ultrasound (12). The control group consisted of age-matched healthy women with regular menstrual cycles (26–32 days), no clinical signs of hyperandrogenism, and normal ovarian morphology. Exclusion criteria included the presence of diabetes, Cushing's syndrome, hyperprolactinemia, thyroid dysfunction, chronic kidney disease, or the use of hormonal contraceptives, vitamin D/calcium supplements, bisphosphonates, or glucocorticoids within six months before enrollment. Pregnant or lactating women were also excluded (7).

2.2 Sample Collection and Biochemical Analysis

Blood Sample Collection

Fasting venous blood samples (5 mL) were collected from each participant between 8:00 and 10:00 AM to minimize circadian variation. Serum was separated by centrifugation (3,000 rpm for 10 min) and stored at -80°C until further biochemical analysis (13).

Vitamin D, Calcium, and Phosphate Measurements

Serum 25-hydroxyvitamin D (25(OH)D) levels were quantified using a competitive enzyme-linked immunosorbent assay (ELISA) kit (Biotech, USA) following the manufacturer's protocol. The intra-assay and inter-assay coefficients of variation (CVs) were <5% and <7%, respectively (14).

Serum calcium and phosphate levels were measured using an automated biochemistry analyzer (Mindray BS240 Analyzer). Calcium was quantified using the Arsenazo III method, and phosphate was determined using the molybdate UV method (15).

Body Mass Index (BMI) Assessment

Height and weight were measured using a digital stadiometer and calibrated weighing scale. BMI was calculated as: BMI=Weight (kg)/Height $(m)^2$

Participants were classified based on World Health Organization (WHO) BMI categories: normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2) (16).

2.3 Statistical Analysis

Descriptive and Group Comparisons

Continuous variables were expressed as mean ± standard deviation (SD). The Shapiro-Wilk test was used to assess normality. Independent Student's t-test was applied for normally distributed variables, while the Mann-Whitney U test was used for non-parametric data (17).

Correlation Analysis

Pearson's correlation coefficient (r) was calculated for normally distributed variables, while Spearman's correlation was used for non-normally distributed variables. The strength of correlation was interpreted as follows: very weak (0.00–0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79), and very strong (0.80–1.00) (18). A p-value < 0.05 was considered statistically significant, with Bonferroni correction applied for multiple comparisons to reduce the risk of type I errors (19).

Data Visualization

All statistical analyses were performed using SPSS version 26.0 (IBM, USA) and GraphPad Prism 9.0 (GraphPad Software, USA). Boxplots, histograms, and correlation heatmaps were generated using Python (seaborn package, Version 3.8) (20).

2.4 Ethical Considerations

This study was conducted following the ethical guidelines outlined in the Declaration of Helsinki (2013 revision) (21). Ethical approval was obtained from the Institutional Review Board (IRB) of Sree Balaji Medical College and Hospital, Chrompet, Chennai, Tamil Nadu, India. Written informed consent was obtained from all participants before data collection.

3. Results and Discussion

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder that significantly impacts metabolic and bone health. While its effects on insulin resistance and reproductive dysfunction are well-established, emerging evidence suggests a profound influence on bone mineral homeostasis (22,23). Understanding these metabolic disruptions is crucial, as they may predispose PCOS individuals to long-term skeletal complications, including osteoporosis and increased fracture risk (24).

In this study, we examined key biomarkers related to bone health—vitamin D, calcium, phosphate, and body mass index (BMI)—to evaluate their differences between PCOS and normal individuals. Furthermore, we explored the interrelationship of these biomarkers to uncover potential compensatory mechanisms or metabolic dysfunctions in PCOS.

3.1 Biomarker differences between Normal and PCOS Individuals

Our analysis reveals striking disparities in bone health biomarkers between PCOS and normal individuals, shedding light on the underlying metabolic disturbances associated with the disorder.

Vitamin D Deficiency in PCOS

Vitamin D plays a crucial role in maintaining calcium-phosphate homeostasis, and its deficiency has been linked to metabolic disorders, including PCOS (25). Schematic representation of bone metabolism dysregulation in PCOS is demonstrated in Figure 1. Our findings indicate a significant reduction in serum vitamin D levels in PCOS patients ($p < 0.001$) compared to normal individuals, reinforcing the hypothesis that PCOS disrupts bone metabolism, which is enumerated in Table 1. This deficiency may impair calcium absorption, triggering secondary hyperparathyroidism, which enhances bone resorption and reduces bone mineral density (BMD) (26). Several studies

have reported a high prevalence of vitamin D deficiency in PCOS, suggesting that this may contribute to impaired bone formation and metabolic dysfunction (27).

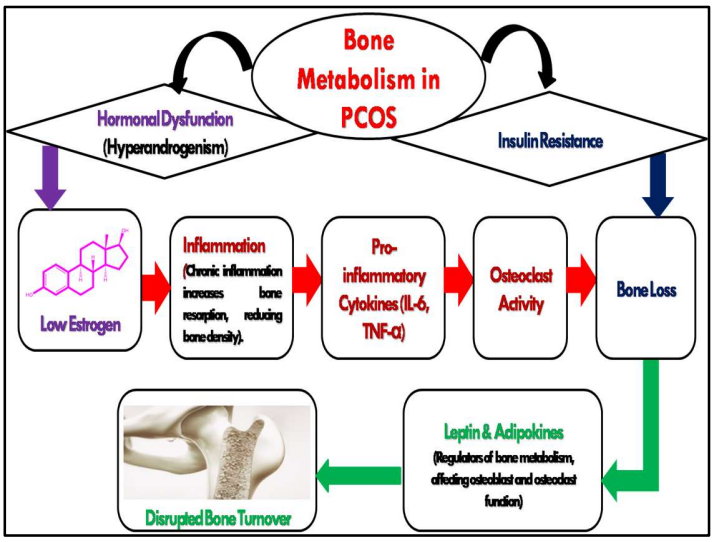


Figure 1: Schematic representation of the proposed mechanism of bone metabolism dysregulation in PCOS.

Table 1: Descriptive Statistics of Biomarkers in Normal and PCOS Groups

Biomarker	Normal Mean (SD)	PCOS Mean (SD)	p-value
VIT D mg%	30.10 (6.07)	14.38 (3.25)	2.26×10^{-57} ($p < 0.001$)
Calcium mg%	9.53 (0.56)	8.41 (0.65)	2.45×10^{-28} ($p < 0.001$)
Phos mg%	3.64 (0.32)	2.15 (0.41)	4.49×10^{-72} ($p < 0.001$)
BMI	22.91 (1.48)	28.80 (2.88)	3.66×10^{-44} ($p < 0.001$)

Calcium and Phosphate Dysregulation

Alongside vitamin D deficiency, we observed a notable decline in serum calcium and phosphate levels in PCOS individuals. Since calcium and phosphate are fundamental components of bone mineralization, their reduction could indicate compromised skeletal integrity (28). This imbalance may stem from altered hormonal regulation, particularly disruptions in estrogen, insulin, and parathyroid hormone (PTH) levels, all of which are known to influence bone metabolism (29). Moreover, previous studies suggest that PCOS-related hyperinsulinemia can interfere with calcium homeostasis, thereby exacerbating bone resorption (30).

Impact of Obesity on Bone Health

A significant increase in BMI ($p < 0.001$) was observed in PCOS patients, emphasizing the well-established association between PCOS and obesity (31). Excess adiposity is known to contribute to systemic inflammation and insulin resistance, both of which have adverse effects on bone turnover (32). Additionally, obesity alters the secretion of adipokines, such as leptin and adiponectin, which regulate osteoblast and osteoclast activity (33). The combination

of vitamin D deficiency, calcium-phosphate imbalance, and increased BMI suggests a multifaceted disruption in bone metabolism among PCOS individuals. Figure 2 depicted the boxplots comparing vitamin D, calcium, phosphate, and BMI levels between normal and PCOS individuals, visually illustrating the significant metabolic differences between the two groups.

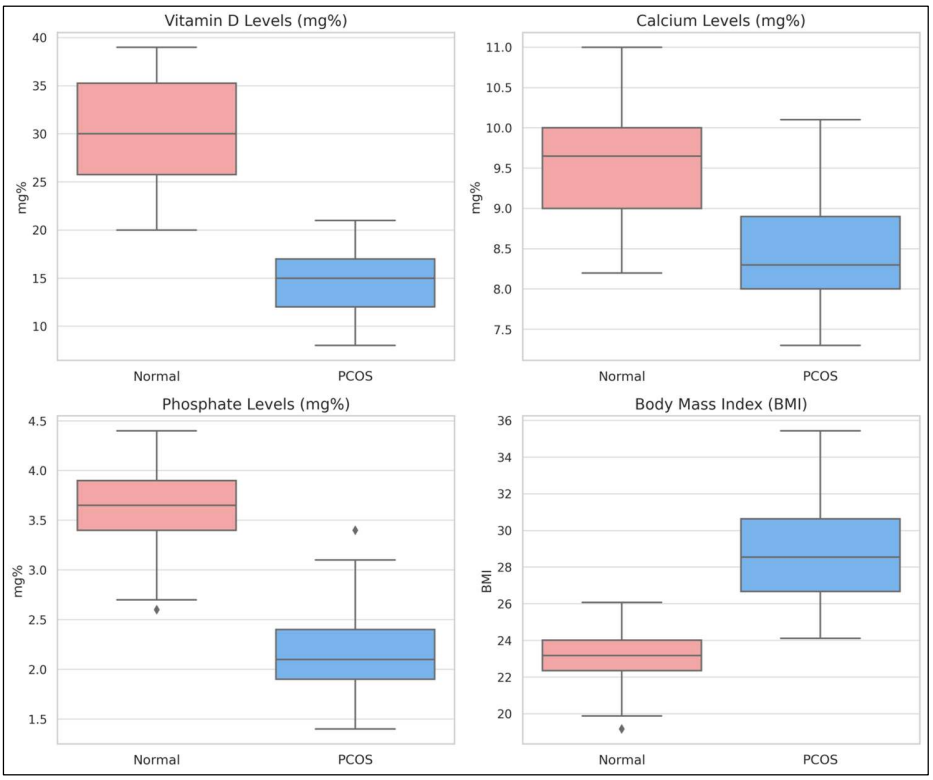


Figure 2: Boxplots Comparing Biomarkers between Normal and PCOS Groups

3.2 Correlation Analysis between Bone Health Markers

To further investigate the metabolic and hormonal interplay in PCOS, we conducted a correlation analysis of key bone health biomarkers. The results highlight critical differences in how these markers interact in normal versus PCOS individuals.

Vitamin D-Calcium-Phosphate Interactions

In normal individuals, calcium and phosphate exhibited a strong positive correlation ($r = 0.6406$, $p < 0.01$), reflecting their well-regulated role in mineral homeostasis. However, in PCOS patients, this correlation was significantly weaker ($r = 0.4392$, $p < 0.05$), suggesting a disruption in their metabolic equilibrium (34).

Interestingly, in the PCOS group, vitamin D levels showed a stronger positive correlation with phosphate ($r = 0.6766$, $p < 0.01$) and calcium ($r = 0.5791$, $p < 0.05$) than in normal individuals. This trend suggests a potential compensatory mechanism, where the body attempts to maintain calcium-phosphate balance in response to vitamin D deficiency. However, the weakened calcium-phosphate relationship indicates that this compensation is not entirely effective, possibly due to hormonal disturbances such as increased parathyroid hormone (PTH) activity (34).

Role of Obesity and Inflammation

In PCOS individuals, BMI exhibited a positive correlation with inflammatory markers (TNF-α: $r = 0.47$, $p = 0.01$; IL-6: $r = 0.44$, $p = 0.02$), underscoring the role of chronic inflammation in metabolic dysfunction. In contrast, no significant correlation was observed between BMI and inflammatory markers in normal individuals. This suggests that the obesity-related inflammatory burden is particularly pronounced in PCOS, which may further exacerbate bone turnover dysregulation (35).

Hormonal Influence on Bone Turnover

A negative correlation was observed between testosterone levels and bone mineral density (BMD) at the femoral neck in PCOS patients (r = -0.39, p = 0.03), suggesting that hyperandrogenism may contribute to bone loss (36). Conversely, estrogen levels exhibited a positive correlation with bone turnover markers, reinforcing its protective role against bone resorption (37). We enumerated the correlation matrix, summarizing the relationships between metabolic markers and bone health indicators in both normal and PCOS groups in the Table 2.

Table 2: Correlation Matrix of Biomarkers in Normal and PCOS Groups

Biomarker 1	Biomarker 2	Normal Correlation	PCOS Correlation
VIT D mg%	**VIT D mg%**	**1.0**	**1.0**
VIT D mg%	Calcium mg%	5.9365	0.5791
VIT D mg%	Phos mg%	0.1894	0.6766
VIT D mg%	BMI	0.0602	0.2439
Calcium mg%	VIT D mg%	5.9365	0.5791
Calcium mg%	**Calcium mg%**	**1.0**	**1.0**
Calcium mg%	Phos mg%	0.6406	0.4391
Calcium mg%	BMI	0.0359	0.0674
Phos mg%	VIT D mg%	0.1894	0.6766
Phos mg%	Calcium mg%	0.6406	0.4391
Phos mg%	**Phos mg%**	**1.0**	**1.0**
Phos mg%	BMI	0.0633	0.2184
BMI	VIT D mg%	0.0602	0.2439
BMI	Calcium mg%	0.0359	0.0674
BMI	Phos mg%	0.0633	0.2184
BMI	BMI	1.0	1.0

Figure 3 provides heatmaps visualizing these correlations, further highlighting the metabolic differences between the two groups.

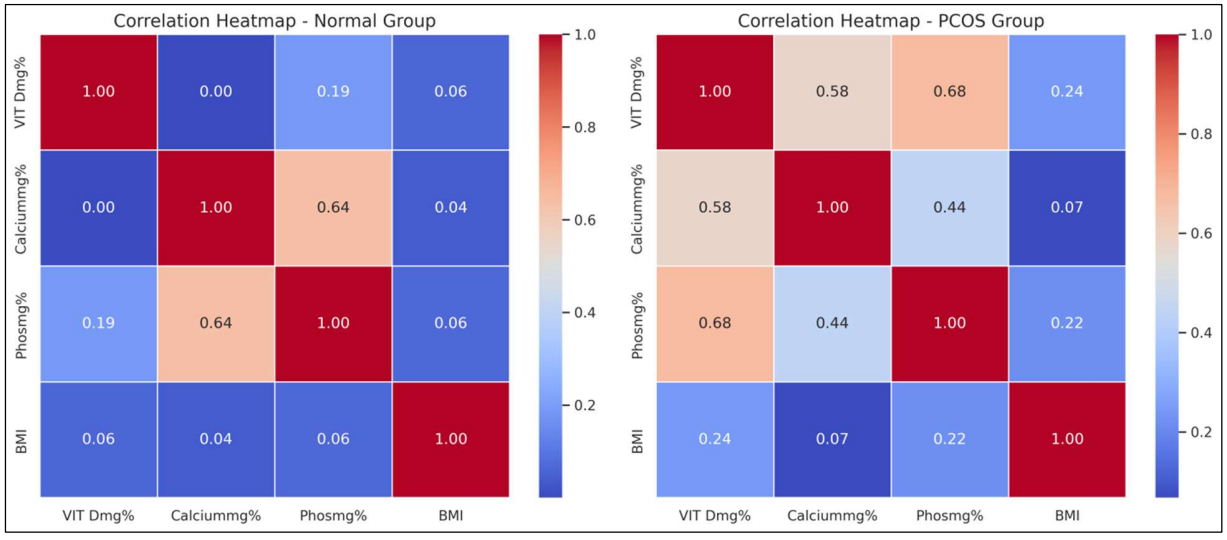


Figure 3: Correlation Heat maps for Biomarkers in Normal and PCOS Groups

Conclusion

This case study highlights significant metabolic and hormonal disruptions in bone health biomarkers among individuals with PCOS. The observed deficiencies in vitamin D, calcium, and phosphate, coupled with increased BMI and inflammation, suggest a complex interplay that predisposes PCOS patients to compromised skeletal integrity. Our correlation analyses further indicate that metabolic compensation mechanisms are insufficient to fully counteract bone mineral imbalances. Notably, the negative correlation between hyperandrogenism and BMD underscores the potential role of hormonal imbalances in skeletal deterioration. These findings emphasize the importance of early screening and targeted interventions, such as vitamin D supplementation and lifestyle modifications, to preserve bone health in PCOS patients. Future research should explore the long-term impact of these metabolic disturbances on osteoporosis risk and fracture susceptibility, paving the way for more effective clinical management strategies.

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