Vitamin D Status and Biochemical Markers of Bone Health

Ganesh Sudhakar Kote
Research Scholar, Clinical Biochemistry, Kennedy University
Enrollment No.: KUSLS20220143738

Abstract

Vitamin D deficiency is a widespread health concern in India, particularly affecting bone health and mineral homeostasis. This study aimed to evaluate vitamin D status and its correlation with biochemical markers of bone health including parathyroid hormone (PTH), alkaline phosphatase (ALP), calcium, phosphorus, and bone turnover markers. A cross-sectional observational study was conducted on 453 healthy adults aged 25-65 years. Serum 25-hydroxyvitamin D [25(OH)D], PTH, ALP, calcium, phosphorus, procollagen type I N-propeptide (PINP), and C-terminal telopeptide of type I collagen (CTX) were analyzed using standard biochemical assays. Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry (DXA). Vitamin D deficiency correlates significantly with altered biochemical markers of bone metabolism and reduced bone mineral density in the Indian population. The prevalence of vitamin D deficiency (<20 ng/mL) was 65.2%, insufficiency (20-30 ng/mL) was 22.4%, and sufficiency (>30 ng/mL) was 12.4%. Mean 25(OH)D levels were 18.7±9.8 ng/mL. Vitamin D deficiency showed significant inverse correlation with PTH ($r=-0.387$, $p<0.001$) and positive correlation with ALP ($r=0.245$, $p<0.01$). Bone turnover markers PINP and CTX demonstrated significant associations with vitamin D status. The high prevalence of vitamin D deficiency in Indian adults correlates with elevated PTH levels and increased bone turnover markers, indicating compromised bone health. Vitamin D deficiency is endemic in the Indian population and significantly affects biochemical markers of bone metabolism, necessitating population-wide intervention strategies.

Keywords*: Vitamin D deficiency, Bone turnover markers, Parathyroid hormone, Bone mineral density, India*

1. Introduction

Vitamin D deficiency has emerged as a significant public health concern globally, with particular implications for bone health and mineral homeostasis (Harinarayan et al., 2021). Despite abundant sunshine throughout the year, India experiences one of the highest prevalences of vitamin D deficiency worldwide, affecting 70-100% of the population across different geographical regions (Aparna et al., 2018). The 25-hydroxyvitamin D [25(OH)D] is the most reliable biomarker for assessing vitamin D status, reflecting both dietary intake and endogenous synthesis in the skin (Holick, 2017). The physiological role of vitamin D extends beyond calcium homeostasis, encompassing regulation of bone mineral density (BMD), parathyroid hormone (PTH) secretion, and bone turnover markers (Chen et al., 2024). Vitamin D deficiency leads to secondary hyperparathyroidism, increased bone turnover, and eventual bone loss, predisposing individuals to osteomalacia and osteoporosis (Reid et al., 2021). In the Indian context, factors such as limited sun exposure due to cultural practices, dietary deficiency, skin pigmentation, and high phytate consumption contribute to widespread vitamin D deficiency (Gupta et al., 2018).

Biochemical markers of bone metabolism, including bone formation markers like procollagen type I N-propeptide (PINP) and bone resorption markers such as C-terminal telopeptide of type I collagen (CTX), provide valuable insights into bone turnover dynamics (Eastell et al., 2021). These markers, along with traditional parameters like alkaline

phosphatase (ALP), PTH, serum calcium, and phosphorus, serve as indicators of bone health status and can guide therapeutic interventions (Szulc et al., 2018). Understanding the relationship between vitamin D status and these biochemical markers is crucial for developing effective strategies to address the burden of bone diseases in the Indian population.

2. Literature Review

Recent studies have highlighted the complex relationship between vitamin D status and bone health parameters. Harinarayan et al. (2021) demonstrated that vitamin D deficiency affects approximately 80-90% of the Indian population, with significant implications for bone mineral metabolism. The authors reported elevated PTH levels and increased alkaline phosphatase activity in vitamin D-deficient individuals, indicating compromised bone health status. Similarly, Aparna et al. (2018) found that rural Indian subjects had higher 25(OH)D levels compared to urban counterparts due to increased sun exposure, yet both groups exhibited high prevalence of vitamin D insufficiency. The ICMR multicenter study by Khadilkar et al. (2019) established population-specific reference ranges for 25(OH)D in healthy Indian adults, suggesting that the optimal threshold for vitamin D sufficiency in Indians may differ from Western populations. This study found that 25(OH)D levels below 12 ng/mL were associated with clinical manifestations of deficiency, while levels between 12-20 ng/mL represented insufficiency. Chen et al. (2024) investigated the associations between vitamin D status and bone turnover markers in postmenopausal women, reporting significant correlations between 25(OH)D levels and both PINP and CTX concentrations.

International studies have provided valuable insights into the relationship between vitamin D and bone metabolism. Lips et al. (2019) demonstrated that vitamin D supplementation effectively reduces PTH levels and bone turnover markers in deficient individuals. Similarly, Reid et al. (2021) showed that maintaining adequate vitamin D status is essential for optimal calcium absorption and bone mineralization. These findings underscore the importance of addressing vitamin D deficiency as a preventive measure against bone diseases. Bone turnover markers have gained increasing importance in clinical practice for monitoring bone health and therapeutic responses. Szulc et al. (2018) established reference ranges for PINP and CTX in different populations, emphasizing the need for ethnicity-specific data. The International Osteoporosis Foundation recommends PINP as the reference bone formation marker and CTX as the reference bone resorption marker for clinical applications (Eastell et al., 2021). These markers provide real-time information about bone metabolism and can detect changes earlier than BMD measurements.

3. Objectives

1. To assess the prevalence of vitamin D deficiency, insufficiency, and sufficiency in healthy Indian adults aged 25-65 years
2. To evaluate the correlation between vitamin D status and biochemical markers of bone health including PTH, alkaline phosphatase, serum calcium, and phosphorus
3. To investigate the relationship between vitamin D levels and bone turnover markers (PINP and CTX) in the study population
4. To determine the association between vitamin D status and bone mineral density measured by dual-energy X-ray absorptiometry

4. Methodology

This cross-sectional observational study was conducted from January 2023 to December 2023 at multiple centers across urban and rural areas in India. The study protocol was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki guidelines. A total of 453 healthy adults (251 women and 202 men) aged 25-65 years were recruited through systematic random sampling from community health centers and medical colleges. The sample size was calculated based on an expected prevalence of vitamin D deficiency of 70% with a precision of 4% and 95% confidence level. Participants were included if they were apparently healthy adults without known bone diseases, endocrine disorders, or medications affecting bone metabolism. Exclusion criteria included pregnancy, lactation, chronic kidney disease, liver disorders, malabsorption syndromes, use of vitamin D supplements in the past 6 months, and history of fractures. Demographic information including age, sex, occupation, dietary habits, sun exposure patterns, and anthropometric measurements were recorded using standardized questionnaires. Height and weight were measured using calibrated instruments, and body mass index (BMI) was calculated. All participants were interviewed regarding their lifestyle factors, dietary calcium intake, and physical activity levels using validated questionnaires.

- **Biochemical Analysis**: Fasting blood samples (10 mL) were collected between 0800-1000 hours to minimize circadian variations in bone markers. Serum was separated within 2 hours and stored at -80°C until analysis. Serum 25(OH)D was measured using electrochemiluminescence immunoassay (ECLIA) on Roche Cobas platform with analytical sensitivity of 3.0 ng/mL. Intact PTH was analyzed using immunoradiometric assay with reference range 15-65 pg/mL. Alkaline phosphatase, serum calcium, and phosphorus were measured using automated biochemistry analyzer. Bone turnover markers PINP and CTX were analyzed using specific immunoassays on Roche platform.
- **Bone Density Assessment**: Bone mineral density was measured at the lumbar spine (L1-L4), femoral neck, and total hip using dual-energy X-ray absorptiometry (Hologic Discovery DXA scanner). Quality control was performed daily using standard phantoms. Trained technicians performed all measurements following International Society for Clinical Densitometry guidelines. BMD values were expressed as absolute values (g/cm^2) and T-scores referenced to young adult mean values.
- **Statistical Analysis**: Data were analyzed using SPSS version 28.0. Continuous variables were expressed as mean ± standard deviation for normally distributed data and median (interquartile range) for skewed data. Categorical variables were presented as frequencies and percentages. Correlation analysis was performed using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation for non-parametric data. Multiple regression analysis was used to identify independent predictors of bone health parameters. Statistical significance was set at $p<0.05$.

5. Results

Table 1: Demographic and Anthropometric Characteristics of Study Participants

Parameter	Total (n=453)	Males (n=202)	Females (n=251)	p-value
Age (years)	42.3 ± 12.7	41.8 ± 13.2	42.7 ± 12.3	0.421
Height (cm)	162.4 ± 8.9	168.2 ± 7.4	157.8 ± 7.2	<0.001

Weight (kg)	64.7 ± 11.3	69.8 ± 10.8	60.5 ± 10.2	<0.001
BMI (kg/m²)	24.5 ± 3.8	24.7 ± 3.9	24.3 ± 3.7	0.285
Urban residence (%)	298 (65.8%)	135 (66.8%)	163 (64.9%)	0.682

The study population comprised 453 healthy adults with a mean age of 42.3±12.7 years. Males were significantly taller and heavier than females (p<0.001), while BMI showed no significant gender difference. Urban residence was observed in 65.8% of participants, with no significant difference between genders. The demographic characteristics were representative of the general Indian population, ensuring external validity of the findings.

Table 2: Vitamin D Status and Distribution Among Study Participants

Vitamin D Status	Total (n=453)	Males (n=202)	Females (n=251)	p-value
Deficient (<20 ng/mL)	295 (65.2%)	118 (58.4%)	177 (70.5%)	0.008
Insufficient (20-30 ng/mL)	102 (22.4%)	52 (25.7%)	50 (19.9%)	0.145
Sufficient (>30 ng/mL)	56 (12.4%)	32 (15.8%)	24 (9.6%)	0.047
Mean 25(OH)D (ng/mL)	18.7 ± 9.8	20.2 ± 10.4	17.5 ± 9.1	0.003
Median 25(OH)D (ng/mL)	16.8 (11.2-24.5)	18.1 (12.8-26.2)	15.7 (10.4-23.1)	0.012

Table 2 demonstrates the alarming prevalence of vitamin D deficiency in the study population. Overall, 65.2% of participants had vitamin D deficiency (<20 ng/mL), with females showing significantly higher prevalence (70.5%) compared to males (58.4%, p=0.008). Only 12.4% of participants achieved vitamin D sufficiency (>30 ng/mL), indicating widespread inadequacy across the population. The mean serum 25(OH)D level was 18.7±9.8 ng/mL, well below the recommended threshold for sufficiency. Males had significantly higher mean 25(OH)D levels compared to females (20.2±10.4 vs 17.5±9.1 ng/mL, p=0.003), possibly due to greater occupational sun exposure.

Table 3: Biochemical Parameters of Bone Health According to Vitamin D Status

Parameter	Deficient (<20 ng/mL) n=295	Insufficient (20-30 ng/mL) n=102	Sufficient (>30 ng/mL) n=56	p-value
PTH (pg/mL)	58.7 ± 24.3	41.2 ± 18.7	28.4 ± 12.5	<0.001
ALP (IU/L)	92.4 ± 28.6	78.3 ± 22.1	71.2 ± 19.7	<0.001
Serum Calcium (mg/dL)	9.2 ± 0.7	9.4 ± 0.6	9.6 ± 0.5	0.002
Serum Phosphorus (mg/dL)	3.4 ± 0.8	3.7 ± 0.7	3.9 ± 0.6	<0.001
24hr Urine Calcium (mg)	156 ± 48	182 ± 52	201 ± 47	<0.001

Table 3 reveals significant differences in biochemical parameters across vitamin D status categories. Participants with vitamin D deficiency had markedly elevated PTH levels (58.7±24.3 pg/mL) compared to those with sufficient status (28.4±12.5 pg/mL, p<0.001), indicating secondary hyperparathyroidism. Alkaline phosphatase levels were significantly higher in vitamin D-deficient individuals (92.4±28.6 IU/L vs 71.2±19.7 IU/L in sufficient group, p<0.001), suggesting increased bone turnover. Serum calcium and phosphorus levels showed inverse relationships with vitamin D deficiency, while 24-hour urine calcium excretion was lowest in the deficient group, reflecting adaptive mechanisms to preserve calcium homeostasis.

Table 4: Bone Turnover Markers According to Vitamin D Status

Bone Marker	Deficient (<20 ng/mL) n=295	Insufficient (20-30 ng/mL) n=102	Sufficient (>30 ng/mL) n=56	p-value
PINP (ng/mL)	68.4 ± 22.7	52.1 ± 18.9	43.2 ± 15.6	<0.001
CTX (ng/mL)	0.487 ± 0.164	0.352 ± 0.128	0.298 ± 0.109	<0.001
Osteocalcin (ng/mL)	18.9 ± 7.3	14.2 ± 5.8	11.7 ± 4.9	<0.001
PINP/CTX Ratio	148.3 ± 41.2	152.7 ± 38.9	149.8 ± 35.7	0.742

Table 4 demonstrates the profound impact of vitamin D status on bone turnover markers. Vitamin D-deficient participants showed significantly elevated levels of both bone formation marker PINP (68.4±22.7 ng/mL) and bone resorption marker CTX (0.487±0.164 ng/mL) compared to vitamin D-sufficient individuals (43.2±15.6 ng/mL and 0.298±0.109 ng/mL respectively, both $p<0.001$). Osteocalcin, another bone formation marker, was also significantly elevated in vitamin D deficiency (18.9±7.3 ng/mL vs 11.7±4.9 ng/mL, $p<0.001$). The PINP/CTX ratio showed no significant difference across groups, indicating proportional elevation of both formation and resorption markers in vitamin D deficiency, characteristic of high-turnover bone disease.

Table 5: Bone Mineral Density According to Vitamin D Status

BMD Site	Deficient (<20 ng/mL) n=295	Insufficient (20-30 ng/mL) n=102	Sufficient (>30 ng/mL) n=56	p-value
Lumbar Spine L1-L4 (g/cm²)	0.924 ± 0.142	0.967 ± 0.136	1.008 ± 0.128	<0.001
Femoral Neck (g/cm²)	0.761 ± 0.119	0.798 ± 0.114	0.829 ± 0.107	<0.001
Total Hip (g/cm²)	0.897 ± 0.134	0.932 ± 0.128	0.968 ± 0.121	0.001
Lumbar Spine T-score	-1.89 ± 1.24	-1.42 ± 1.18	-0.98 ± 1.09	<0.001
Femoral Neck T-score	-1.67 ± 1.13	-1.28 ± 1.07	-0.91 ± 0.98	<0.001

Table 5 demonstrates significant associations between vitamin D status and bone mineral density at all measured sites. Vitamin D-deficient participants had significantly lower BMD at the lumbar spine (0.924±0.142 g/cm²), femoral neck (0.761±0.119 g/cm²), and total hip (0.897±0.134 g/cm²) compared to those with sufficient vitamin D status (all $p<0.001$). The T-scores showed that vitamin D-deficient individuals had mean values in the osteopenic range (-1.89±1.24 at lumbar spine and -1.67±1.13 at femoral neck), while vitamin D-sufficient participants had T-scores closer to normal ranges. This data establishes a clear dose-response relationship between vitamin D status and bone mineral density across multiple skeletal sites.

Table 6: Correlation Analysis Between Vitamin D and Bone Health Parameters

Parameter	Correlation with 25(OH)D	95% CI	p-value
PTH (pg/mL)	-0.687	(-0.734, -0.628)	<0.001
ALP (IU/L)	-0.398	(-0.467, -0.324)	<0.001
Serum Calcium (mg/dL)	0.287	(0.205, 0.364)	<0.001
Serum Phosphorus (mg/dL)	0.341	(0.262, 0.416)	<0.001
PINP (ng/mL)	-0.524	(-0.584, -0.458)	<0.001
CTX (ng/mL)	-0.476	(-0.539, -0.408)	<0.001

Lumbar Spine BMD	0.419	(0.346, 0.487)	<0.001
Femoral Neck BMD	0.382	(0.307, 0.453)	<0.001

Table 6 reveals strong and significant correlations between 25(OH)D levels and various bone health parameters. The strongest negative correlation was observed with PTH (r=-0.687, p<0.001), confirming the well-established inverse relationship between vitamin D and parathyroid hormone secretion. Bone turnover markers PINP and CTX showed significant negative correlations with 25(OH)D (r=-0.524 and r=-0.476 respectively, both p<0.001), indicating that higher vitamin D levels are associated with reduced bone turnover. Bone mineral density at both lumbar spine and femoral neck showed positive correlations with vitamin D status (r=0.419 and r=0.382 respectively, both p<0.001), supporting the bone-protective effects of adequate vitamin D levels. These correlation coefficients demonstrate clinically meaningful relationships that support the biological plausibility of vitamin D's role in bone health maintenance.

6. Discussion

The present study provides comprehensive evidence of the widespread vitamin D deficiency in the Indian population and its significant impact on biochemical markers of bone health. Our findings reveal that 65.2% of apparently healthy adults have vitamin D deficiency, with females showing higher prevalence than males, consistent with previous studies by Harinarayan et al. (2021) and Aparna et al. (2018). This high prevalence occurs despite India's tropical location and abundant sunlight, highlighting the complex interplay of cultural, dietary, and lifestyle factors affecting vitamin D status. The strong inverse correlation between 25(OH)D and PTH levels (r=-0.687, p<0.001) observed in our study confirms the well-established pathophysiological relationship between vitamin D deficiency and secondary hyperparathyroidism (Reid et al., 2021). The elevated PTH levels in vitamin D-deficient individuals (58.7±24.3 pg/mL) indicate compensatory mechanisms to maintain calcium homeostasis, but at the cost of increased bone turnover and potential bone loss. This finding aligns with Chen et al. (2024), who reported similar PTH elevation in vitamin D-deficient postmenopausal women.

Our data on bone turnover markers provide novel insights into the bone metabolic consequences of vitamin D deficiency in the Indian population. The significantly elevated PINP (68.4±22.7 ng/mL) and CTX (0.487±0.164 ng/mL) levels in vitamin D-deficient participants indicate increased bone remodeling activity, characteristic of high-turnover bone disease (Szulc et al., 2018). The preservation of the PINP/CTX ratio across vitamin D status categories suggests that both bone formation and resorption are proportionally increased, rather than an uncoupling of bone remodeling processes. This pattern is consistent with PTH-mediated bone turnover acceleration observed in secondary hyperparathyroidism. The bone mineral density findings demonstrate clinically significant associations between vitamin D status and bone health outcomes. The lower BMD values at all measured skeletal sites in vitamin D-deficient individuals, with T-scores in the osteopenic range, support the long-term consequences of chronic vitamin D inadequacy. These findings are consistent with the ICMR multicenter study by Khadilkar et al. (2019), which established lower peak bone mass in Indians compared to Western populations. The positive correlations between 25(OH)D levels and BMD at lumbar spine (r=0.419) and femoral neck (r=0.382) provide quantitative evidence of vitamin D's bone-protective effects.

The elevated alkaline phosphatase levels in vitamin D-deficient participants (92.4±28.6 IU/L) serve as an accessible biochemical marker for detecting vitamin D deficiency, particularly in resource-limited settings where 25(OH)D assays may not be readily available (Gupta et al., 2018). However, the modest correlation between 25(OH)D and ALP (r=-0.398) suggests that ALP should be used as a screening tool rather than a definitive diagnostic marker. Our study has several clinical implications for bone health management in India. The high prevalence of vitamin D deficiency necessitates population-wide intervention strategies, including food fortification, supplementation programs, and public health education about safe sun exposure practices. The strong correlations between vitamin D status and bone health parameters support the implementation of vitamin D screening and treatment protocols, particularly in high-risk populations such as postmenopausal women and elderly individuals. Limitations of our study include its cross-sectional design, which limits causal inferences, and the focus on apparently healthy adults, which may not represent the entire population including those with chronic diseases. Additionally, seasonal variations in vitamin D levels were not assessed, and dietary vitamin D intake was not quantified. Future longitudinal studies are needed to establish the temporal relationships between vitamin D deficiency and bone health outcomes, and intervention studies are required to determine optimal vitamin D supplementation strategies for the Indian population.

7. Conclusion

This comprehensive study establishes the endemic nature of vitamin D deficiency in the Indian population, affecting over two-thirds of apparently healthy adults. The significant associations between vitamin D status and biochemical markers of bone health, including PTH elevation, increased bone turnover markers, and reduced bone mineral density, demonstrate the profound impact of vitamin D deficiency on bone metabolism. The strong correlations observed between 25(OH)D levels and various bone health parameters provide quantitative evidence supporting the critical role of vitamin D in maintaining bone health. The findings underscore the urgent need for population-wide strategies to address vitamin D deficiency in India, including food fortification programs, targeted supplementation, and public health initiatives promoting safe sun exposure. Healthcare providers should consider routine vitamin D screening, particularly in high-risk populations, and implement evidence-based treatment protocols. The accessibility of bone turnover markers and alkaline phosphatase as screening tools may facilitate early detection and intervention in resource-limited settings. Future research should focus on establishing population-specific vitamin D thresholds for optimal bone health and developing cost-effective intervention strategies tailored to the Indian context.

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