Original Article

Serum 25(OH) vitamin D deficiency among young adults in the East Khasi Hills district of Meghalaya and its influence on bone mineral density: Investigating the involvement of the RANKL/RANK/OPG system

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Abstract

Introduction: Vitamin D's precise role in bone mineral density regulation remains elusive. Nevertheless, its deficiency is linked to increased bone turnover through the upregulation of RANK ligands by osteoblasts. This study aimed to (i) evaluate vitamin D status in young adults and (ii) assess the association between vitamin D deficiency and bone turnover markers receptor activator of nuclear factor-κB ligand (RANKL), RANK, and the osteoprotegerin (OPG) in determining bone mineral density. **Materials and Methods:** This cross-sectional study involved 474 participants from the East Khasi Hills district, Meghalaya. Vitamin D levels were measured using the UniCel DxI 800 system, while OPG, RANK, and RANKL were assessed through enzyme-linked immunosorbent assay (ELISA). Additionally, a whole-body dual X-ray absorptiometry (DEXA) scan determined bone mineral density. Vitamin D deficiency was categorised as <20 ng/ml, insufficiency as 20–29 ng/ml, and sufficiency as ≥30 ng/ml. **Results:** Findings indicated 54.6% vitamin D deficiency and 35.4% insufficiency in young adults. Osteoporosis affected 26%, and 67% exhibited osteopenia. A weak positive correlation was found between vitamin 25(OH) D and bone mineral density T score ($r = 0.16$, $r^2 = 0.02$, $P = 0.44$). Additionally, moderately weak correlations were observed between serum vitamin D and OPG ($r = -0.42$, $r^2 = 0.18$, $P < 0.001$) and between vitamin D and RANKL ($r = -0.13$, $r^2 = 0.01$, $P = 0.18$). **Conclusion:** The study suggests that vitamin D deficiency diminishes bone mineral density by promoting RANKL-RANK osteoclastogenesis and upregulating OPG expression. As young adults form a significant workforce, creating awareness is crucial for maintaining optimal health.

Keywords: Bone mineral density, osteoprotegerin, receptor activator of nuclear factor (RANK), receptor activator of nuclear factor-κB ligand, serum 25(OH) vitamin D, young adult population

Introduction

Despite abundant sunshine in India, vitamin D deficiency affects 70–100% of the population,[1] with regions like Meghalaya facing exacerbated challenges due to limited sun exposure. The lack of awareness and low dietary intake significantly impact bone health, correlating with the receptor activator of nuclear factor-κB ligand (RANKL)/RANK/osteoprotegerin (OPG) system, which is crucial for bone remodelling and density. This study conducted in Meghalaya's East Khasi Hills district aims to evaluate the prevalence of vitamin D deficiency in young adults and its subsequent impact on bone mineral density. The findings will aid health professionals in identifying high-risk individuals, particularly young adults, who form the primary workforce, as low

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peak bone mass increases the risk of fracture and osteoporosis later in life.

Materials and Methods

Study setting and design

This was a community-based, observational, cross-sectional study conducted among young adults aged 18–35 years who were long-term residents of Meghalaya's East Khasi Hills District. Ethical clearance was obtained from an institutional ethical review. Approval for conducting the study was secured from the District Medical and Health Officer, East Khasi Hills. Subsequently, authorization was obtained from the primary health centre (PHC) medical officer and block development manager in several blocks, who facilitated contact with the ASHA employees and the village headman. Consequently, the participants were invited for screening at an integrated child development services (ICDS) centre, community hall, or sub-centre. The study participants were selected from 34 clusters (16 clusters in five blocks of rural areas and 18 clusters in two blocks in East Khasi Hills), resulting in a total sample size of 474 (with a target of 400). For the selection of houses in the villages, we employed systematic random sampling.

After selecting the participants based on the screening questionnaire, written and informed consent would be obtained from all subjects in a language best understood by them.

Sampling technique and size

With the prevalence of vitamin D deficiency estimated at 80% and using the formula $4pq/d^2$ with a 5% allowable error, the sample size has been calculated to be 400. To compensate for the study design effect, a sample size of 474 was targeted. A 30-multi-stage cluster sampling method was followed.

Inclusion and exclusion criteria

The study included young adults between the ages of 18 and 35 years who appeared healthy. The inclusion criteria involved being a permanent resident of the area and being willing to participate in the research. The study excluded pregnant or nursing women, participants on medication (e.g., oral contraceptive pills, calcium and vitamin D supplements, steroids), and those with a history of confirmed systemic illness (e.g., kidney disease, primary hyperparathyroidism, liver disease, diabetes mellitus, gastrointestinal disease, tuberculosis, bone disease, and cancer).

Data collection instruments

The screening was performed using a predesigned, simple screening questionnaire after obtaining written informed consent from the participants.

The consumption and food frequency pattern of various foods were noted.

A clinical assessment including anthropometry and a brief systemic examination with special reference to the musculoskeletal system was undertaken.

Operational definition

Reference value and cut-off limit were determined using the US Endocrine Society Guidelines, 2011. Vitamin D deficiency was defined as a serum level of 25(OH) D below 20 ng/ml, insufficiency between 20–29 ng/ml and sufficiency above 30 ng/ml.[2]

T score of −1.0 or above was considered normal bone density, a T-score between −1.0 and −2.5 indicates osteopenia and a T score of −2.5 and above was diagnosed as osteoporosis (World Health Organisation [WHO]).

Data analysis and procedure

The statistical analysis was performed using MS Excel. Descriptive statistics were used for all variables, including mean, standard deviation, and errors. For analytical statistics, an unpaired *t*-test was employed to compare the means and assess significance. For categorical data, the Chi-square test was conducted and expressed as a percentage. The correlation of serum 25(OH) vitamin D with RANK L, RANK, OPG, and bone mineral density was assessed using Pearson rank correlation. A P value of < 0.05 was considered statistically significant.

With all aseptic and antiseptic measures, 5cc of venous blood was collected from the participants in the field and transferred into a properly labelled plain red vacutainer and ethylene diamine tetra acetic acid (EDTA) vacutainer. Serum 25-hydroxy vitamin D and parathyroid hormone (PTH) were estimated in a chemiluminescent immunoassay using the UniCel DxI 800 system (Beckman Coulter, USA). Serum total calcium and phosphorus were estimated in AU 2700 and AU480 clinical chemistry auto analyzer (Beckman Coulter, USA). Serum-ionized calcium was estimated in an ion-sensitive electrolyte analyzer (Caretium). RANK and OPG assays were conducted by enzyme-linked immunosorbent assay (ELISA) technique using a RAY Biotech Inc. USA kit. Soluble RANKL was estimated using the Elbascience USA ELISA kit. Quality control of the test parameters analysed was ensured by using internal quality control samples from Bio-Rad and external quality control samples of ACBI CMC, Vellore. Whole-body dual X-ray absorptiometry (DEXA) scan was performed using Hologic DEXA scan to calculate the bone mineral density. A T-score of −1.0 or above was considered normal bone density, a T-score between −1.0 and −2.5 indicates osteopenia, and a T-score of −2.5 and above was diagnosed as osteoporosis (WHO).

Results

The total study population was screened from 34 clusters (16 clusters in five blocks of rural and 18 clusters of urban areas in East Khasi Hills) giving a total sample size of 474 (target being 400).

Demographic details

The demographic analysis of the study revealed that 30.6% of participants belonged to the age group of 30–35 years. The majority of the study population identified as Christians (78.8%), with a predominant affiliation with the Khasi ethnic group (92.3%).

Regarding educational status, 52.3% of participants had completed high school. In terms of occupation, 65.5% of participants engaged in physical work, exposing them to sunlight for more than 30 minutes. A significant portion of the study participants (85.9%) had no knowledge about vitamin D [Table 1].

Anthropometric parameters

Female participants exhibited a mean BMI of 20.5 ± 3.05, while males had a mean BMI of 19.9 ± 2.26 [Table 2]. Based on BMI status, 24.3% of males and 26.1% of females in the East Khasi Hills district of Meghalaya were found to be underweight. The majority of study participants (70% males and 61.9% females) had a normal weight. Overweight individuals constituted 5.6% of males and 10% of females, while 2% of females were classified as obese [Table 3].

Food consumption pattern

Analysis of the food frequency questionnaire revealed that 60.4% of the study population did not consume milk. Egg consumption varied, with 69.8% of participants consuming 1–4 pieces of egg per week or per month. Daily consumption of 1–2 pieces of red meat with rice, the staple food habit, was observed in 43.5% of the population [Table 4].

Clinical manifestation and associated comorbidities

Approximately 54.8% of the study population reported muscle pain, while 17.2% reported bone pain [Table 5].

Vitamin D status

Vitamin D deficiency was prevalent in 54.6% of participants, with 35.4% showing insufficiency. Only 10% of the participants were found to be vitamin D-sufficient [Table 6].

The prevalence of serum vitamin 25(OH) D deficiency was higher in urban participants compared to rural participants [Table 7]. The prevalence of serum vitamin 25(OH) D deficiency was higher in urban participants compared to rural participants [Table 7]. Among the study participants, the mean vitamin D level was 20.2 ± 7.55 ng/ml [Table 8]. A significant difference was observed in the mean PTH and OPG levels between the vitamin D-sufficient and vitamin D-deficient participants ($P = 0.001$) [Table 9].

Vitamin D and bone mineral density

Among the 30 ($n = 30$) vitamin D-deficient participants, 67% exhibited osteopenia, 26% showed osteoporosis and 7% had normal bone density [Table 10].

Using the cut-off of 20 ng/ml, vitamin 25(OH) D was weakly positively correlated with the T-score of bone mineral density, $r = (-0.16)$, $r^2 = 0.02$, $P = 0.44$ [Figure 1].

Vitamin D and markers of bone turnover

Serum vitamin D was moderately negatively correlated with osteoprotegerin ($r = (-0.42)$, $R^2 = 0.18$, $P < 0.001$) [Figure 2]. A weak, negative non-significant correlation was found between vitamin D level and RANK L ($R = -0.13$), $R^2 = 0.01$, $P = 0.18$) [Figure 3]. No correlation was found between vitamin D and RANK [Figure 4].

Table 1: Demographic details of study participants

Demographic details	Total no. of participants	Percentage of participants
Age in years		
18–20	69	14.5%
21–25	131	27.6%
26–30	129	27.3%
30–35	145	30.6%
Khasi	437	92.3%
Garo	4	0.8%
Jaintia	2	0.4%
Others	31	6.5%
Physical activity		
Sedentary	2	0.4%
Moderate	315	66.5%
Heavy	157	33.1%
Duration of sun exposure		
>15 min	35	7.38%
15–30 min	129	27.2%
<30 min	310	65.5%
Use of sunscreen		
No	411	86.8%
Yes	67	14.2%
Knowledge about Vit D		
No	407	85.9%
Yes	67	14.1%

Table 2: Anthropometric details of the male and female participants

Measurements	Male (n=87)	Female (n=130)
Weight (kg)	49.39±6.16	44.8±7.32
Height (cm)	157.4±6.45	147.7±6.59
Body mass index (kg/m^2)	19.9±2.26	20.5±3.05
Waist circumference (cm)	27.4±2.73	27.4±3.09
Hip circumference (cm)	31.6±2.19	32.3±2.36

Table 3: Nutritional status of the participants based on body mass index (BMI)

Status	Number of participants	Percentage
Underweight <18.5	124	26.0%
Normal weight 18.5–24.9	307	64.7%
Overweight 25–29.9	38	7.98%
Obese 30 and above	5	1.05%
Total	474	100%

Discussion

Our study uncovers a notable prevalence of serum 25(OH) vitamin D deficiencies in 54.6% and insufficiency in 35.4% of young adult participants. This trend correlates with findings

Table 4: Consumption and frequency pattern of the various foods in the study participants

Diet	Total no. of participants	Percentage of participants
Milk		
Does not consume	286	60.4%
Weekly	149	31.4%
Monthly	2	0.4%
Daily	37	7.8%
Egg		
Does not consume	75	15.8%
Weekly	331	69.8%
Monthly	0	0
Daily	68	14.4%
Dairy products		
Does not consume	226	47.8%
Weekly	243	51.2%
Monthly	0	0
Daily	5	1.0%
Red meat		
Does not consume	24	5.0%
Weekly	244	51.5%
Monthly	0	0
Daily	206	43.5%
Mushroom		
Does not consume	399	84.2%
Weekly	0	
Monthly	75	15.8%

Table 5: Clinical manifestation and associated comorbidities in the participants

Clinical manifestations	Total no. of participants	Percentage of participants
Bone pain	82	17.2%
Muscle pain	260	54.8%
Muscle weakness	4	0.8%
Fracture	1	0.21%
Gastritis	13	2.7%
Tuberculosis	4	0.84%
Rheumatism	4	0.84%
Thyroid disorder	4	0.84%
Malaria	3	0.63%
Renal stones	1	0.21%

Table 6: Vitamin D status in the study participants

Status	Total no. of participants	Percentage of participants
Deficient <20 ng/ml	259	54.6%
Insufficient 20–29 ng/ml	168	35.4%
Normal 30 ng/ml and above	47	10%
Total no. of cases	474	100

from other community-based Indian studies, which reported a prevalence of 17% in adolescents (12–17 years) and 32% in young adults (18–24 years).[3] In research involving free-living healthy young adults, findings revealed that by the end of winter, 36% of individuals aged 18 to 29 years exhibited a deficiency in vitamin D.[4] Globally, numerous countries have reported a significant prevalence of low vitamin D levels, with over 20% of the population having 25(OH) D levels <30 nmol/L in nations like India, Tunisia, Pakistan, and Afghanistan.[5] In South Asian adults, the most significant occurrence of vitamin D deficiency was identified in Pakistan (73%; 95% confidence interval [CI]: 63 to 83%), trailed by Bangladesh (67%; 95% CI: 50 to 83%), India (67%; 95% CI: 61 to 73%), Nepal (57%; 95% CI: 53 to 60%), and Sri Lanka (48%; 95% CI: 41 to 55%), respectively.[6]

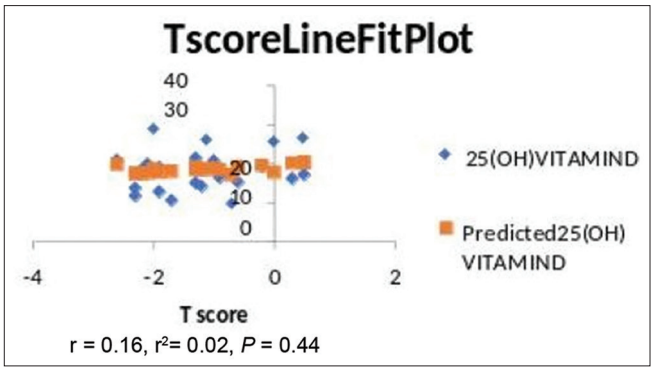

Figure 1: Linear association of serum 25(OH) vitamin D (ng/ml) with T-score of bone mineral density

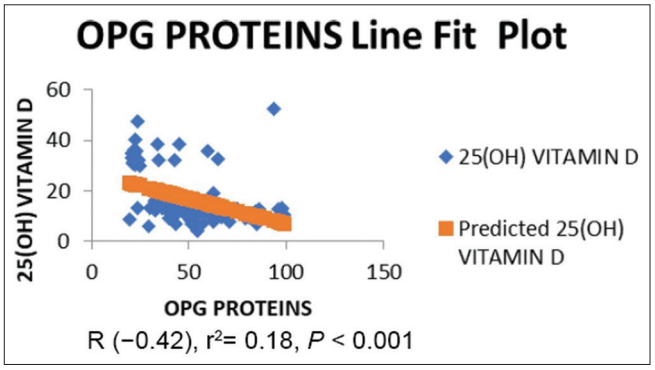

Figure 2: Linear association of serum 25(OH) vitamin D (ng/ml) with osteoprotegerin (OPG) (pg/ml)

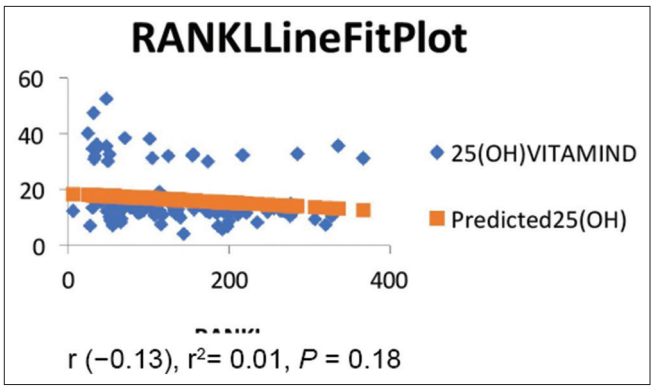

Figure 3: Linear association of serum 25(OH) vitamin D (ng/ml) with RANKL (pg/ml)

Table 7: Status of serum 25 hydroxy vitamin D level in the rural and urban population

Area	Total no. of sample size	Serum 25 hydroxy vitamin D level (mean±SD) (ng/ml)	Deficient	Insufficient	Sufficient
Rural	219	21.0±7.8	50.7 (*n*=111)	35.6% (*n*=78)	13.7% (*n*=30)
Urban	255	19.4±7.2	58.8% (*n*=150)	34.5% (*n*=88)	6.7% (*n*=17)
		P=0.019			

SD=Standard deviation

Table 8: Mean±SD of serum biochemical parameters in the study participants

Serum parameters	Mean±SD
Vitamin D (ng/ml)	20.2±7.55
PTH (pg/ml)	41.9±25.2
Total Calcium (mg/dl)	1.33±0,17
Ionised calcium (mmol/L)	2.60±0.32
Phosphorus (mg/dl)	3.41±4.48
OPG (pg/ml)	51.84±21.6
RANK (ng/ml)	0.81±0.22
sRANKL (pg/ml)	128.3±84.6

SD=Standard deviation

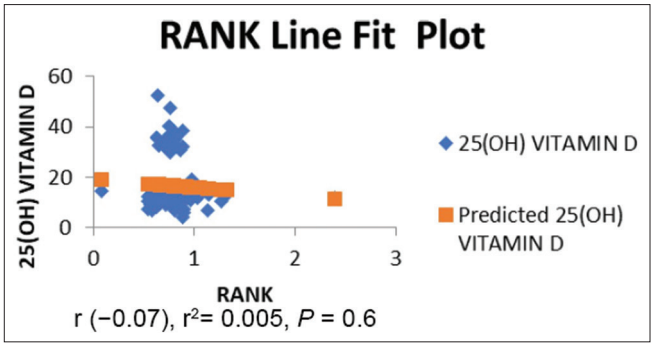

Figure 4: Linear association of serum 25(OH) vitamin D (ng/ml) with RANK (ng/ml)

A survey conducted between October 2017 and March 2018 in the Delhi-National Capital Region (NCR) region revealed that most people were unaware of their vitamin D deficiency, with individuals aged 21–35 showing the highest insufficiency.[7] Probable reasons for deficiency in our study may include the consumption of a smaller amount of a vitamin D-rich diet, insufficient exposure to sunlight, and environmental factors. The staple diet for participants consisted mainly of rice with one or two pieces of red meat. A majority (67%) belonged to a low-income group earning less than Rs. 5000 per month, limiting their ability to consume quality vitamin D-rich food.

Regarding BMI status, 24.3% of male and 26.1% of female participants in the East Khasi Hills district of Meghalaya were found to be underweight. The majority (70% of males and 61.9% of females) had a normal weight, while 5.6% of males and 10% of females were overweight, and 2% of females were obese. Interestingly, our study found no correlation between body mass index and serum vitamin 25(OH) D level (r(−0.08), $r^2 = 0.007$, $P = 0.06$), possibly due to the predominant normal or underweight distribution. Obesity could contribute to the rising levels of vitamin D deficiency, given its fat-soluble nature.[8]

A significant difference ($P = 0.019$) was found in the mean level of vitamin D between the urban and rural populations. Vitamin D deficiency was more prevalent in urban areas (50.7%) than in rural areas (58.8%), contradicting various studies that observed a higher prevalence in rural areas. This aligns with research indicating the prevalence of severe deficiency, deficiency, and insufficiency of vitamin D in urban areas of the NCR of Delhi, India, at 71%, 27%, and 2%, respectively. Conversely, in rural areas, the corresponding prevalence was 20%, 47%, and 25%.[9] In our study, rural participants were involved in moderate-to-heavy outdoor physical activity, exposing them to sun rays for a longer duration. Conversely, urban participants, with indoor lifestyles, sunscreen use, and concerns about tanning and skin cancers, had higher vitamin D inadequacy.

In our study, vitamin D deficiency was most prevalent in Jatah village in the Mawkynrew block of the rural area in the East Khasi Hills. This aligns with the experience of health and medical officers who have encountered many cases of rickets among children. In a study conducted near Delhi in 2008, it was observed that men and women living in rural areas had vitamin D levels six to three times higher than those in urban areas. The deficiency in urban areas was attributed to pollution, which restricted sunlight exposure.[10] A weak positive correlation was found between the duration of sun exposure and serum vitamin D level (r = 0.256). Vitamin D synthesis depends on exposure to UV-B radiation (290–320 nm). A study in New Delhi recommended sunlight exposure between 10 a.m. and 2 p.m. for 10 minutes to half an hour twice a week for adequate vitamin D production in Indian skin type.[11] Shockingly, 86.9% of our participants had no knowledge that sun rays were the major source of vitamin D, highlighting a significant gap in awareness.

Excessive sunlight exposure can lead to the conversion of pre-vitamin D3 into lumisterol and tachysterol 3, which do not affect calcium metabolism. Factors such as latitude, season, and time of day impact the synthesis of pre-vitamin D3. Atmospheric pollution reduces solar radiation. Wearing protective clothing, skin pigmentation, and using sunscreen with SPF 15 can significantly decrease ultraviolet B (UVB) penetration into the skin, thus limiting pre-vitamin D3 production. The amount of UVB radiation reaching the Earth's surface depends on various factors including solar zenith angle, time of day, season, ozone levels, cloud cover, aerosols, and latitude and altitude, all of which influence the production of vitamin D3 in the skin.[12] Meghalaya, with its high altitude, cold winters, and cloud cover most of the year, has minimal UVB exposure, potentially leading

Table 9: Mean±SD of bone turnover markers among the Vitamin D deficient and vitamin D sufficient participants

Biochemical markers of bone turnover	Vitamin 25(OH) D cut-off <30 ng/ml	Vitamin 25(OH) D cut-off >30 ng/ml	*P*
Vitamin 25 (OH) D (ng/ml)	18.6±5.7	35.4±5.4	
PTH (pg/ml)	43.0±25.5	31.6±19.9	*P*=0.001
OPG (pg/ml)	56.8±19.5	35.0±22.4	*P*=0.0001
RANKL (pg/ml)	131.6±79.6	126.3±113	*P*=0.85
RANK (ng/ml)	0.82±0.25	0.77±0.07	*P*=0.10

SD=Standard deviation

Table 10: Bone mineral density of participants at the serum 25(OH) D cut-off <30 ng/ml

Whole-body DEXA scan T-score	No. of study participants (*n*=30)	Percentage of participants
–1.0 and above	2	7%
–1.0–-2.5	20	67%
≤−2.5 SD	8	26%
	n=30	

SD=Standard deviation

to hypovitaminosis D. Climatic conditions and lifestyle may contribute to vitamin D deficiency.

Among 30 (n = 30) vitamin D-deficient participants, 67% had osteopenia, 26% had osteoporosis, and 7% had normal bone density. Using the cut-off of 20 ng/ml, vitamin 25(OH) D was weakly positively correlated with the T-score of bone mineral density, r = (0.16), r^2 = 0.02, P = 0.44. A study in urban areas of Iran found an inverse correlation of 25(OH) D with bone mineral density (BMD) values at the total hip and spine.[13] The weak positive correlation observed in this study may be attributed to a lower number of participants willing to undergo DEXA scans for bone mineral density assessment. In a study involving postmenopausal women, comparable results were observed, revealing a substantial positive correlation between 25-hydroxy vitamin D levels and T-scores for bone mineral density (P < 0.000).[14]

In a study conducted on adolescents in Korea, it was found that the vitamin D-sufficient group had higher BMD Z-scores compared to the insufficient group, while the insufficient group had higher BMD Z-scores compared to the deficient group. Additionally, in linear regression analysis, 25(OH) D levels were positively correlated with BMD Z-scores, showing a particularly significant positive association.[15]

Our studies indicate that vitamin D deficiency increases the expression of RANKL and OPG. Serum vitamin D was moderately negatively correlated with OPG (R (−0.42), R^2 = 0.18, P < 0.001) and RANKL (r (−0.13), r^2 = 0.01, P = 0.18). This finding aligns with a study conducted on osteoporotic women, indicating a negative correlation between 25-hydroxyvitamin D and OPG (r = −0.171, P < 0.01), as well as a negative correlation between 25-hydroxyvitamin D and sRANK-l (r = −0.118, P < 0.05).[16] However, a study conducted on Egyptian children with acute lymphoblastic leukaemia observed a positive correlation between vitamin D and OPG levels.[17]

A study on serum vitamin D levels in knee osteoarthritis stages suggested that serum proteins, notably the RANKL/OPG ratio, could serve as early indicators for monitoring disease progression and may become crucial therapeutic targets for future OA treatment.[18]

RANKL binding to RANK triggers the activation of the NF-κB transcription factor on pre-osteoclasts. Acting as a decoy receptor, OPG, secreted by osteoblasts, binds to RANKL, thereby blocking its interaction with RANK. This intricate interplay among RANKL, RANK, and OPG plays a critical role in both immune regulation and maintaining bone health.[19]

Conclusion

The young adult population of East Khasi Hills shows a significant frequency of vitamin D insufficiency and deficiency, likely influenced by poor diet, environmental factors, and low income. This deficiency can reduce bone mineral density, as evidenced by negative correlations with bone turnover indicators. Adequate vitamin D levels are associated with better overall health, while deficiency increases the risk of spontaneous fractures and chronic diseases like cardiovascular disease, diabetes, and certain cancers. Given that young individuals are the primary workforce, raising awareness through educational programs and implementing targeted interventions can help maintain optimal bone health. Health professionals can use prevalence data to identify high-risk populations for screening and take targeted actions to improve public health outcomes and patient care.

Limitations and future aspects

Only 30 participants with vitamin D deficiency underwent bone mineral density assessments via DEXA scan. This limitation arose as participants were unwilling to come to the institute for the scans. To gain a more comprehensive understanding, it is recommended that similar studies be extended to other districts of Meghalaya and to assess the overall prevalence of vitamin D deficiency in the state.

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Conflicts of interest

There is no conflicts of interest.

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