

Review Article

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Vitamin D & bone mineral density of healthy school children in northern India

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Studies on bone mineral health in children have been primarily based on clinical, biochemical and radiological evidence. Measurement of vitamin D levels and bone mass by non invasive imaging techniques like dual energy X-ray absorptiometry (DEXA), have led to a plethora of data regarding various factors responsible for bone mineral health from various countries including India. We reviewed the currently available evidence on status of calcium-vitamin D-parathormone (PTH) relationship and bone mineral density (BMD) in apparently healthy children. High prevalence of clinical and biochemical hypovitaminosis D exists in apparently healthy school children from north India. Also, children from upper socio-economic strata (USES) from Delhi had significantly higher mean BMD values at distal forearm (BMDdf) and calcaneum (BMDca) than those from lower socio-economic strata (LSES). Age, nutrition, height and weight were seen to be significantly associated with BMD at peripheral sites.

Key words Bone mineral density - bone mineral health - hypovitaminosis D - 25(OH) D - parathormone (iPTH) - rickets - vitamin D

Optimal bone mineral health during childhood and adolescence leads to adequate peak bone mass which acts as a safeguard against osteoporosis and susceptibility to fractures in adulthood and old age. About 40-50 per cent of total skeletal mass is accumulated during childhood and adolescence. Studies show that 60-80 per cent variability in bone mass is due to genetic factors, with nutrition, lifestyle, physical activity and hormonal factors causing the rest¹⁻³. It is precisely during this period that any nutritional or non pharmacologic strategies are likely to have the greatest impact on peak bone mass.

Calcium and vitamin D nutrition appear to have greatest effect on bone mass, not only during period

of growth, but also during adulthood and old age. Considering this fact, industrialized countries in the West have made fortification of milk and other food products with vitamin D a routine practice. In contrast, food fortification with vitamin D was never considered in tropical countries like India due to the widely held notion that adequate sunshine is available. But the findings from hospital-based studies show evidence to the contrary, that vitamin D deficiency is present in a significant proportion of general population in India⁴⁻⁶. It has also been noted that osteoporotic fractures occur 10-20 yr earlier in Indian men and women, compared to Caucasians in the West⁷.

Clinical examination to detect overt cases of vitamin D deficiency would represent only the 'tip of an iceberg' of vitamin D insufficiency⁸. While severe vitamin D deficiency, usually associated with 25(OH) D levels <5.0 ng/ml, results in rickets and osteomalacia, even less severe deficiency has been associated with a number of negative skeletal consequences including secondary hyperparathyroidism, increased bone turnover, enhanced bone loss and fracture risk^{9,10}.

Bone mass is the most important determinant of bone strength. Bone mass measurements are useful in the early detection of bone loss, monitoring of therapeutic responses and prediction of fracture risk in osteoporosis. Prospective studies have noted an increased risk of fractures with decreasing bone density, and a 2-3 fold increase of fracture risk for every reduction in the standard deviation of bone mass at the spine and hips¹¹. Significant reduction in fracture risk has been shown in elderly women by (10-20%) after supplementation with calcium and vitamin D¹².

In developing countries like India, data on clinical and sub clinical vitamin D deficiency status are scarce. While there have been scattered epidemiological studies, few have provided detailed clinical and biochemical information on the prevalence of hypovitaminosis D in the population. Also, data are lacking on bone mineral density (BMD) measurements in India.

Vitamin D status in children

Clinical evidence: Metabolic bone disorders secondary to vitamin D deficiency continue to be prevalent in Indian subcontinent as reported by hospital-based studies. The earliest description of adolescent rickets in India dated back to 1925¹³. In a recent study, the prevalence of clinical evidence of vitamin D deficiency in 5-15 yr old children has been shown to be 0.19 per cent though objective diagnostic criteria were not mentioned¹⁴. In children of Indian origin residing in South Africa, the prevalence of knock knees and bow legs with gaps of 2.5 cm or more was 6.1-19.4 per cent¹⁵. In Asian migrants in the United Kingdom, the prevalence of clinical vitamin D deficiency in children and adolescents was shown to be 5 to 30 per cent¹⁶⁻¹⁹, while in studies using biochemical and radiological variables, prevalence was 12.5 to 66 per cent^{8,20,21}.

Adolescent period is prone to vitamin D deficiency state due to increased mineral demands of the growing skeleton^{22,23}. Our study demonstrated clinical evidence of vitamin D deficiency in 10.8 per cent of apparently

healthy adolescents in Delhi with no significant difference between the two socio-economic groups²⁴. In a similar age group, symptomatic rickets was observed in 68 per 100,000 years in Saudi Arabia²⁵ and 9.4 per cent in China²⁶.

Laboratory evidence: A comparison of our data on serum vitamin D with other studies may not be entirely appropriate given the fact that different studies have been conducted in different seasons and using different assays. Nonetheless, using the Lips classification¹⁰, severe hypovitaminosis D (<5 ng/ml) was seen in 8.6 per cent of our study population²⁴, while it was seen in 23.5 per cent of Finnish adolescents²² and 45.2 per cent of Chinese adolescents in winter²⁶. In the latter study, severe hypovitaminosis D was present in only 6.7 per cent when the cohort was evaluated in summer. In other studies from Finland, using cut-offs of 8-10 ng/ml, the prevalence of hypovitaminosis D was approximately 13.5 per cent^{22,26}, which compares with 37 per cent of children in this study having serum 25(OH)D <9 ng/ml (lower limit of manufacturer's normal range).

The mean serum concentration of 25(OH) D in the study on children from northern India was 11.8 ± 7.2 ng/ml²⁴. Other studies have also noted low serum 25(OH) D concentrations among adults of Indian origin both in India and in the United Kingdom^{4,5,27}. The mean 25(OH)D concentration in adolescents, in the above study²⁴, was lower than that reported in Western studies^{2,28,29} and in Brazil³⁰ and marginally higher than that in China²⁶.

Our study shows that adolescents from low socio-economic strata (LSES) had significantly lower mean 25(OH) D concentration compared to those from the upper socio-economic strata (USES)²⁴. The only other study, which has compared low and high socio-economic groups, has not revealed any difference in mean vitamin D concentration between the two groups³⁰. This difference is further supported by the observation that lower socio-economic group children also had higher intact parathyroid hormone (iPTH), higher alkaline phosphatase, and lower serum phosphorus concentrations. Since serum calcium concentration and sunlight exposure are comparable in the two groups, and dietary calcium intake is significantly lower in LSES, it suggests that nutrition plays an important role in causing these differences, as has been reported earlier^{31,32}. In addition, the lower serum phosphorus could also be correlated with the higher levels of iPTH in this group.

There was a negative correlation between 25 (OH) D and iPTH which is in agreement with the findings of other studies ($r = -0.202$, $P < 0.001$)^{2,33}. Surprisingly, only 10.3 per cent of subjects with vitamin D levels below 9 ng/dl had iPTH concentrations above normal. In another study, the serum iPTH was elevated in 37.5 per cent adolescent girls with low vitamin D concentrations²⁸. This could possibly be due to: (i) sufficient 25 (OH) D is being converted to 1, 25 (OH)₂D for maintenance of calcium homeostasis; and (ii) prolonged exposure to low vitamin D status and poor nutritional status in these children may have lowered the threshold for iPTH release.

Bone mineral density in children

There are various non-invasive techniques available to determine bone mass such as radiography, single and double X-ray absorptiometry (SXA, DXA), quantitative computed tomography (QCT) and quantitative ultrasound (QUS). Peripheral dual energy X-ray absorptiometry (pDXA) is used to measure bone mass in the radius (non-weightbearing) and calcaneum (trabecular site) with low precision errors, low radiation dose and short data acquisition time. Since measurement by pDXA at forearm and calcaneum has been shown to have good correlation with control DXA (cDXA) measurements, pDXA is now used to predict fracture risk in children and adults³⁴⁻³⁶.

However, role of pDXA in clinical practice in children is not clear because of lack of reference data and clearly set predictors of BMD at these sites. While studies looking into predictors of BMD have mainly focused on lifestyle and anthropometry, role of biochemical parameters and correlation with BMD has not been clearly defined.

In one study on BMD in 555 children (225 boys, 330 girls) from north India, those from LSES had significantly ($P < 0.01$) lower BMD values at the forearm than those from USES²⁴. Subsequent BMD studies carried out in 664 girls (369 LSES, 295 USES) showed significantly higher overall mean distal forearm BMD (BMDdf) (LSES 0.337 ± 0.070 , USES 0.366 ± 0.075 g/cm²) and calcaneal BMD (BMDca) (LSES 0.407 ± 0.073 , USES 0.464 ± 0.093 g/cm²) values in USES subjects than in LSES subjects ($P < 0.001$)³⁷. This could be due to poor overall nutrition as evidenced by low BMI, low dietary calcium intake³⁸, low serum 25(OH) D concentration and secondary hyperparathyroidism³⁹. No statistically significant correlation was seen between the BMD and 25(OH) D concentration and serum calcium levels in

our study, which is in agreement with other studies^{26,40,41}. However, some studies in different age groups did show a significant correlation^{6,42}. Another study carried out recently provides information on BMD in peripheral sites (distal forearm and calcaneum) in healthy Indian girls and its relationship with age, anthropometry and biochemical variables³⁷. It was found that the mean BMDdf values in LSES subjects were 0.358 ± 0.066 g/cm² while those in the USES subjects were 0.389 ± 0.067 g/cm², whereas the mean values of BMDdf in 12-16 yr old girls from China was 0.34 ± 0.05 g/cm²⁴³. In comparison, the only other study using peripheral densitometry was reported from Japan using a different densitometer and may not be appropriate for comparison^{44,45}.

Comparison of BMD at calcaneum in Indian children³⁷ with data from healthy Caucasian children in the United Kingdom acquired with the same model of densitometer³⁴ showed that LSES subjects had lower values and USES subjects had higher values. In the study conducted in China⁴³, the mean BMDca values in 12-16 yr old girls were 0.47 ± 0.06 g/cm²; values which were higher than those of LSES subjects (0.429 ± 0.064 g/cm²) and lower than USES subjects (0.488 ± 0.083 g/cm²) from our study³⁷. Earlier studies assessing the increase in BMD through age have used single photon absorptiometry (SPA) and DXA. Our study showed that BMDdf had a progressive increase with age till the age of 16 yr with a tendency to plateau thereafter, especially in the LSES group³⁷. Other studies using pDXA⁴⁴, DXA^{46,47} and SPA^{48,49} have also recorded similar findings. However, some studies using SPA have shown an increase in BMD beyond the age of 16 yr^{50,51}. We cannot make an exact comparison because the methodology and region of interest of measurements could be different in these studies.

Unlike BMDdf, BMDca shows an increase till the age of 12 yr with a tendency to plateau thereafter³⁷. The only other study which provides age-wise values of BMDca by pDXA estimated calcaneal BMD by pDXA shows an increase in BMD through all the ages³⁴. Two studies using ultrasound bone densitometry at the calcaneum, variably show plateauing at the ages of 12 and 16 yr^{45,52}.

Our data show a significant association of body weight and age with BMDdf and the model incorporating age, height and weight explains approximately 50 per cent of the variance at this site³⁷. Several studies have shown association of age, height

and weight with BMDdf. Pettifor & Moodley⁵³ have shown that the combined effect of age, height and weight was 57 per cent. Other studies using multiple regression analysis have noted that models incorporating age, height, weight and sexual maturation explained about 46-79 per cent of the variability in BMDdf^{48,49,54-57}. The relative individual contribution of each of these variables is not entirely derived because of interdependence of each of these factors.

Similarly, approximately 50 per cent of the variability in BMD at calcaneum is explained by age, height and weight³⁷. Ultrasound measurements have noted a significant association of weight and pubertal status with BMDca^{58,59} and multiple regression models incorporating age, height, weight and sexual maturation explained about 40 per cent of the variability in BMDca⁵⁹. No study using pDXA has provided a multiple regression analysis of age, height and weight to explain the variability in BMDca.

On multiple regression analysis, after adjusting for the association of other factors we did not find any significant association of either 25 (OH)D or PTH on either site³⁷. Also, other studies available on adolescent subjects did not find any association of BMDdf with either 25-OHD^{24,28,60} or PTH^{24,28}. No study using DXA has found a direct positive association of 25 (OH)D with BMD at peripheral sites in growing children, although one group noted that subjects with 25 (OH)D concentration of <40 nmol/l had low BMD values at BMDdf compared to those with values >40 nmol/l²⁸. It is clear that the relationship between 25 (OH)D and BMD is complex and is often influenced by other factors. To the best of our knowledge, no study has specifically looked into the relationship of PTH and 25 (OH)D with BMDca.

Among the common bone mineral parameters, we found that only serum alkaline phosphatase (ALP) had a significant negative association with BMDdf³⁷. One study has shown that serum ALP has a negative correlation with BMDdf and subjects with ALP >300 IU had lower BMD than those with normal levels⁵³. Another study conducted in adolescent girls had documented that serum osteocalcin was negatively correlated with BMD at ultra distal and proximal radius of the forearm⁶¹. However, most studies in children looking into the effect of bone formation markers on BMD have mainly focused on total body, lumbar spine and femoral neck with variable association⁶²⁻⁶⁵.

There was no association between serum ALP and BMDca in this study³⁷, which could be due to the differential effect of PTH on cortical and cancellous bone.

Conclusion & Recommendations

There is a high prevalence of clinical and biochemical hypovitaminosis D in apparently healthy school children in India. The significant difference in BMD between the two socio-economic groups from the same ethnic origin, suggests that nutrition plays a significant role in attaining optimal bone density. Age, height and weight remain the best predictors of BMD at the distal forearm and calcaneum. The only bone mineral parameter which had a significant influence on BMDdf was alkaline phosphatase.

In view of high prevalence of hypovitaminosis D in apparently healthy children because of lifestyle changes and cultural practices, awareness needs to be generated about benefits accrued by direct sunlight exposure. Future prospective studies measuring BMD in children should take into account pubertal status to validate the observations of present cross-sectional studies. Significantly low BMD in LSES children when compared to those from USES, suggests the need for interventional studies to evaluate the role of nutrition in improving BMD and peak bone mass. Appropriate BMD norms for Indian children should be generated from children of upper socio-economic strata in view of significantly low BMD in children from poor background.

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