

## Review Article

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# Nutritional bone disease in Indian population

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Syndromes of bone disease and deformities consequent to disorders of nutrition, bone and mineral metabolism constitute a serious national health problem. The studies on this subject are scanty. Data on nutritional bone disease are described and discussed. We had surveyed 337.68 million population residing in 0.39 million villages in 22 States of India during the period 1963 to 2005. Of the 4,11,744 patients identified with the disorders of bone and mineral metabolism, 2,13,760 (52%) had nutritional bone disease, 1,77,200 (43%) had endemic skeletal fluorosis and 20,784 (5%) had metabolic bone disease and in 41 patients (0.19%) the bone disease was rare, mixed or unidentified. Vitamin D deficiency osteomalacia and rickets caused by inadequate exposure to sunlight (290-315 nm), dietary calcium deficiency (<300 mg/day) and fluoride interaction syndromes, calcium deficiency induced osteoporosis and calcium and vitamin D deficiency induced osteoporosis in the elderly, were the commonest disorders responsible for bone disease and deformities, besides caused by endemic skeletal fluorosis as a single entity in endemic fluorosis villages. Calcium deficiency *per se* does not cause rickets, as revealed in our long-term follow up study on 47,500 calcium deficient children. Only mothers with severely depleted bone mineral and vitamin D stores gave birth to their babies with congenital rickets. Vitamin D deficiency rickets in children and osteomalacia in the mothers are the commonest disorders prevalent in the rural population of India. These disorders and the syndromes of calcium deficiency and fluoride interactions are largely responsible for the morbidity and mortality in the young and promising individuals, with economic consequences.

**Key words** Animal protein - calcium deficiency - fluoride interactions - osteomalacia - osteoporosis - rickets - tertiary hyperparathyroidism - vitamin D deficiency

Bone is a homeostatic and metabolically active organ and receives about 10 per cent of the cardiac output. The structural integrity and health of the adult skeleton is maintained by bone remodelling, the process whereby bone that has undergone fatigue damage from repetitive cyclical loading is replaced by new bone. The damaged or effete bone resorbed by osteoclasts is replaced at the same location by osteoblasts. It is the remodelling of the bone whether it occurs in the growing

or non growing skeleton, which decides the fate of the human skeleton and determines its health and disease throughout the life.

Good nutrition is as important for bone health as it is for general health. Although the adequate nutrient intakes of calcium, vitamin D, and protein are of critical importance for bone health, phosphorus and certain trace minerals (magnesium, manganese, copper, and

zinc) and vitamin C and K are also involved in bone health<sup>1</sup>.

Nutritional bone disease is defined as a syndrome of bone disease and deformities in which the bone is affected as a tissue, primarily as a consequence to deficiencies of vitamin D and calcium; or imbalances of the nutrients which are critically important for the growth and development of the bone; its mineralization and maintenance of calcium homeostasis and the structural integrity and health of the skeleton.

### Epidemiology of nutritional bone disease

With our projects aimed at applied research on disorders of bone and mineral metabolism in the rural population, we have personally surveyed 337.68 million population residing in 0.39 million villages located in 22 States of India, during the period 1963-2005<sup>2,3</sup>.

The total number of patients identified with the disorders of bone and mineral metabolism were 4,11,744. Among the surveyed population, 2,13,760 (52%) had nutritional bone disease; 20,784 (5%) had metabolic bone disease; and 1,77,200 (43%) had endemic skeletal fluorosis; and in 41 patients (0.19%), the bone disease was rare, mixed, or unidentified<sup>3-5</sup>. The epidemiological spectrum of nutritional bone disease is summarized in Table I.

**Table I.** Nutritional bone diseases<sup>3-5,7</sup>

Total patients with nutritional bone disease	2,13,760 (52)
Vitamin D deficiency osteomalacia	75,600 (35.3)
Vitamin D deficiency rickets	16,300 (7.6)
Congenital vitamin D deficiency rickets (newborns of osteomalacia mothers)	3 (0.1)
Vitamin D deficiency rickets in breast fed infants (newborns of osteomalacia mothers)	972 (0.45)
Dietary calcium deficiency (critical years of growth)	86,800 (40.6)
Dietary calcium deficiency (adults, premenopausal)	18,580 (8)
Calcium and vitamin D deficiency (elderly people)	14,205 (6.6)
Protein energy malnutrition (kwashiorkor, marasmus)	1,300 (0.6)
Dietary calcium deficiency rickets	None
Dietary phosphate deficiency rickets	None

Figures in parantheses are percentage value<sup>5</sup>. Dietary calcium deficiency indicates mean calcium intake <300 mg/day<sup>2,5</sup>.

### Vitamin D deficiency and osteomalacia

Vitamin D deficiency can conveniently be classified<sup>6</sup> as extrinsic, due to a combination of reduced endogenous skin synthesis and reduced dietary intake (negligible factor), and intrinsic, due to some combination of impaired intestinal absorption and increased catabolism, frequently initiated by malabsorption of calcium.

Nutritional (privational) vitamin D-deficiency osteomalacia is the commonest nutritional bone disease prevalent in Indian mothers and is characterized by a failure to mineralize the newly formed organic matrix (osteoid) of bone in a normal manner. It occurs due to inadequate exposure to sunlight (UVB 290-315nm) in the mothers who had depleted their bone, minerals and vitamin D stores during repeated pregnancies and prolonged lactations.

### Aetiopathogenesis

The most important misconception about vitamin D-deficiency osteomalacia especially in Asians living in UK is that it results due to their skin pigmentation, vegetarian diets, and consumption of unleavened *chapatis* made out of high extraction wheat flour rich in fibre and phytate contents<sup>7</sup>.

In our studies<sup>2,8,9</sup> we have performed separate measurements of serum 25(OH)D<sub>3</sub> (skin synthesized vitamin D<sub>3</sub>) and 25(OH)D<sub>2</sub> (dietary vitamin D<sub>2</sub>) and demonstrated that the contribution of 25(OH)D<sub>2</sub> to total circulating 25(OH)D in normal women of child bearing age was negligible, less than 8 per cent and over 92 per cent of serum 25(OH)D was endogenously synthesized, following exposure to sunlight (UVB 290-315nm)<sup>4,10</sup>, and confirmed the marginal or the negligible role of dietary vitamin D.

All women, house bound, living in crowded localities and dark alleys, with covered-up style of clothing and *purdah* and thus, deprived, of sun exposure, are at the highest risk of developing vitamin D-deficiency osteomalacia. Thus, the inadequate vitamin D synthesis in the skin due to lack of exposure to sunlight (UVR) is the fundamental abnormality which plays the pivotal role in the aetiopathogenesis of vitamin D-deficiency osteomalacia. This emerging fact has been strongly supported by the cure of vitamin D-deficiency osteomalacia, only by ultraviolet radiation from mercury vapor quartz lamp and the exposure to sunlight in several studies<sup>11-13</sup>.

### Geographic prevalence

Vitamin D-deficiency osteomalacia as defined and occurred in our patients has shown selective geographic distribution. The geographic prevalence of osteomalacia<sup>2</sup> showed that the women residing in the northern parts of India were heavily affected then those living south to Mumbai and Kolkata in the south to western and eastern States of India. This difference in the incidence of osteomalacia is due to North-South gradient of the solar ultraviolet radiations (UVR-B 219-315 nm) which are essential for the endogenous cutaneous synthesis of vitamin D<sub>3</sub>. Synthesis of vitamin D<sub>3</sub> in the skin is reduced by residence at northern latitudes distant from the equator and atmospheric pollution<sup>14,15</sup>.

### Biochemical and endocrine evolution of untreated osteomalacia

We had recognized six transitional metabolic states of secondary hyperparathyroidism 2<sup>o</sup>HPT during three major stages of evolution of untreated osteomalacia in 7,700 patients (1) hypocalcaemic, (2) normocalcaemic, (3) normocalcaemic with abnormalities intensified, (4) severe hypocalcaemic, (5) very severe hypocalcaemic, and (6) evolution of 2<sup>o</sup>HPT to the state of autonomous parathyroid adenoma (autonomous production of PTH) described as tertiary hyperparathyroidism<sup>16</sup>.

As a group, patients with osteomalacia have hypocalcaemia, hypophosphataemia, low serum 25(OH)D and secondary hyperparathyroidism with an unequivocally raised serum parathyroid hormone (PTH) concentration, increased urinary cyclic AMP excretion, increased tubular calcium reabsorption and decreased tubular phosphate reabsorption. Serum 25(OH)D is usually low (<3 ng/ml) or unmeasurable, 1,25(OH)<sub>2</sub>D levels are usually reduced or undetectable and 24 h urinary calcium excretion is low. The most diagnostic biochemical feature of osteomalacia is a low or undetectable serum 25(OH)D in the presence of secondary hyperparathyroidism with unequivocally raised serum parathyroid levels (Table II).

### Manifestations

The classic symptoms<sup>16-18</sup> of osteomalacia are low back pain, bone pains and tenderness, muscle weakness (proximal limb girdle), inability to rise without support, difficulty in walking or climbing stairs, classic duck-like waddling gait and tetany. Because osteoid tissue is pliable, it is unable to resist weight bearing or mechanical loads, the generalized softening of the bones so caused leads to crippling deformities in patients with severe osteomalacia.

Radiological changes in bone result from impaired mineralization and increased PTH secretion. The best known radiographic feature of osteomalacia is the Looser's zone, a lucent band perpendicular to the periosteum. Looser's zones occur most commonly in the ribs, pubic rami and outer border of the scapulae, femoral neck and less commonly in the metacarpals and shafts of the long bones. They are usually associated with local tenderness and pain on activity. The triradiate pelvis with multiple, symmetrical Looser's zones in the ischio-pubic rami without the callus in the absence of treatment, is diagnostic of osteomalacia.

Looser's zones show up on bone scans as localized regions of increased uptake and are often the sites of local tenderness and pain on activity. Other features include symmetrical vertebral biconcavity and findings of high bone turnover as intracortical porosity, cortical striations in the metacarpals and phalanges. Reduction in bone density is the non specific observation. Vertebral compression fractures, femoral and true fractures do not occur in osteomalacia unless complicated by tertiary hyperparathyroidism with osteitis fibrosa<sup>2</sup>.

### Histomorphometric analysis of bone

In mild osteomalacia mineralization is delayed in onset and proceeds more slowly, and in severe osteomalacia mineralization fails to occur at all (Table III)<sup>19</sup>. In the early stages of the disease the characteristic features of osteomalacia may not occur and the ultimate diagnosis in such cases is only possible on histomorphometric measurements of bone, which allow direct observation of the state of mineralization and dynamics of bone turnover<sup>19,20</sup>.

### Tertiary hyperparathyroidism (3<sup>o</sup>HPT) in vitamin D deficiency osteomalacia

We have used the term tertiary hyperparathyroidism to describe the state in which the active parathyroid cell mass evolves into an adenoma (autonomous production of PTH) in one gland on the background of longstanding secondary hyperparathyroidism in mothers with vitamin D deficiency osteomalacia and the remaining parathyroid glands remain hyperplastic, with hypercalcaemia and osteitis fibrosa as the major hallmarks of the disease. In all the 32 patients with 3<sup>o</sup>HPT, we found inverse relationship between serum 25(OH)D the best indicator of vitamin D nutrition and the adenoma weight, the index of increased parathyroid cell number and proliferation<sup>21</sup>. The adenoma weight

**Table II.** Different stages (I-III) of evolution of untreated vitamin D deficiency osteomalacia<sup>16</sup>  
(N = 7700)

Parameters	◀ HVD	I	II		III		
			A	B	A	B	C
Calcium	N	↓	N	N	↓↓	↓↓↓	↑↑↑
Phosphate	N	N	↓	↓↓	↓↓	↓↓	↓↓↓
Alk. Ptase.	N	↑	↑↑	↑↑↑	↑↑↑	↑↑↑↑	↑↑↑↑
Ca xP	N	LN	↓	↓↓	↓↓↓	↓↓↓	↓↓↓
25-OHD	LN	↓	↓↓	↓↓↓	↓↓↓	Undetectable	↓↓↓
1,25-OHD	N	N	↓ N ↑	↓↓	↓↓↓	Undetectable	↓↓↓
NcAMP	N	↑	↑↑	↑↑	↑↑↑	↑↑↑	↑↑↑↑
IPTH	N	↑	↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑↑
<i>Urine:</i>							
Calcium	N	LN	↓	↓↓	↓↓↓	↓↓↓	↓↓↓
Phosphate	N	N	↑	↑↑	↑↑	↑↑↑	↑↑↑
Aminoaciduria	N	O+	++	+++	++++	++++	++++
Clinical 2 <sup>o</sup> HPT (%)	Risk factor	Hypocalcaemic • 15%	Normocalcaemic 25%	Normocalcaemic Severe 75%	Hypocalcaemic Severe 80%	Hypocalcaemic ■ Very severe 20%	Tertiary Hyperparathyroidism 0.8%

N=Normal, LN=Low normal, • IPTH-Immunoreactive PTH, Uncompensatory HPT – increased osteoid surface but only slight increase in the width of osteoid seams. ■ Extreme hypocalcemic vitamin D deficiency syndrome Transition change (A,B,C) : ↓↑ Mild ↓↓ ↑↑ Moderate ↓↓↓ ↑↑↑ Severe ↓↓↓↓ ↑↑↑↑ Very severe ◀HVD = Hypovitaminosis D (Preosteomalacia), may occur in women with mean para of >2.6, and may be detected by estimation of serum 25OHD in lactational phase of second pregnancy. Aminoaciduria. 0 = none, + = increase in glycine only, ++ = increase in glycine, serine, alanine and glutamine, +++ = generalized, ++++ generalized severe. Minimal urine pH after ammonium chloride 0.1g per kg body weight ranged from 4.8 – 5.2. No pregnancy – No osteomalacia

**Table III.** Histomorphometric evolution of untreated vitamin D deficiency osteomalacia<sup>19</sup>

Variables	Stage I (N=96)	Stage II (N=105)	Stage III (N=105)
Osteoid surface (OS/BS) %	↑	↑↑	↑↑↑
Osteoid seam thickness (μm)	N	↑	↑↑
Osteoid volume (OV/BV) %	↑	↑↑	↑↑↑
Mineral apposition rate (MAR) μm/day	↓	↓↓	↓↓↓
Mineralization lag time (Mlt), days	↑	↑↑	↑↑↑
Labeled surface (MS/OS) %	↓	↓↓	↓↓↓ or zero

is an important determinant of severity of 3<sup>0</sup>HPT and osteitis fibrosa cystica. Phenotypic nodular histologic pattern of chief cell transformation (nodular hyperplasia and adenoma) has been the characteristic feature in all our patients with 3<sup>0</sup>HPT<sup>22-24</sup>.

### Primary hyperparathyroidism with vitamin D deficiency

Based on our experience it is suggested that all the patients of primary hypercalcaemic adenomatous hyperparathyroidism with severe vitamin D deficiency, osteitis fibrosa and larger parathyroid adenoma<sup>22-24</sup> should be investigated for tertiary hyperparathyroidism, evolving on the background of prolonged secondary hyperparathyroidism in mothers with vitamin D deficiency osteomalacia<sup>25-28</sup> to avoid erroneously high estimation of primary hyperparathyroidism in Indian perspective. If you see primary hyperparathyroidism in mothers with vitamin D deficiency osteomalacia, think of tertiary<sup>24</sup>.

### Vitamin D deficiency: secondary hyperparathyroidism and osteoporosis

As originally described by Albright<sup>29</sup>, "osteoporosis" referred to the occurrence of apparently spontaneous symptomatic vertebral fractures in postmenopausal women, but the term is now applied more generally to increased fracture risk associated with low bone mass at any site, the upper femur being the most important. Low bone mass reflects some combination of too little accumulation during growth and too much loss after skeletal maturity; age related bone loss is a universal feature of human biology that results from incomplete replacement of resorbed bone during the process of remodelling. The remodelling imbalance is mainly due to increased depth of resorption when bone loss is rapid and mainly due to decreased formation thickness when bone loss is slow.

Vitamin D deficiency increases fracture risk because secondary hyperparathyroidism<sup>30</sup> increases bone turnover and accelerates the age related loss of cortical bone in the peripheral skeleton. Vitamin D deficiency also causes muscle weakness and increased propensity to fall and so is a risk factor for hip fracture for several reasons. These populations include the elderly, the institutionalized, housebound, and those who are critically ill, and diseases causing diminished ambulation. Such patients frequently have circulating levels of 25(OH)D in the borderline range (10 to 20 ng/ml). The reduced intestinal calcium absorption seen in osteoporosis is related to a reduced 1,25(OH)<sub>2</sub>D receptor density and also the reduced supply of the active metabolite 1,25(OH)<sub>2</sub>D, related to age, dependent decline in renal function<sup>26</sup>.

### Vitamin D deficiency rickets

Vitamin D deficiency or privational deficiency of calciferol is still numerically the most common cause of rickets in India. Rickets is a disease of children in which growing skeleton is involved; defective mineralization of cartilage takes place in the epiphyseal cartilage growth plate so that disorganization of cellular development ensues, which leads to widening of the ends of lone bones and, possibly, retardation of growth and skeletal deformities. Infact vitamin D deficiency rickets results only due to the lack of exposure to sunlight (UVB 290-315 nm)<sup>4,31,32</sup>. As previously mentioned, vitamin D deficiency stimulates both hormone secretion and cell proliferation in the parathyroid gland, both directly as the result of reduction in plasma calcitriol levels and indirectly via hypocalcaemia. These effects will be intensified if calcium intake is also very low.

### Geographic prevalence

Children residing in the northern parts of India are heavily affected than those living south to Mumbai and Kolkota in the southern States of India. Synthesis of vitamin D<sub>3</sub> in the skin is reduced by residence at latitudes distant from the equator and atmospheric pollution. In northern parts of India the striking angle of UVR on the skin is narrow and of shorter duration, while in southern States the striking angle is broad and of longer duration. In children who remain housebound, institutionalized or living in orphanage homes or dark and crowded localities with no penetration of sunlight are at the highest risk of developing rickets<sup>3</sup>. It is inevitable that the children who do not maintain their vitamin D production by adequate (minimum 30 min

to 1 h/day) exposure to sunlight of their unprotected skin are at risk of developing rickets. The hallmark of vitamin D deficiency rickets is a low (<10 ng/ml) or undetectable serum levels of 25(OH)D<sup>31</sup>. The secondary hyperparathyroidism and low (Ca)X(PO<sub>4</sub>) ion product is responsible for the increase in unmineralized osteoid or cartilaginous matrix, which is the hallmark of rickets<sup>32</sup>.

### Biochemical and endocrine evolution of rickets<sup>32</sup>

Vitamin D deficiency rickets is characterized by low serum concentrations of 25(OH)D, 1,25(OH)<sub>2</sub>D<sub>3</sub>, phosphate and elevated serum levels of alkaline phosphatase and parathyroid hormone. Its characteristic evolution occurs in three stages as given below:

*Stage 1:* In this stage impaired intestinal calcium absorption and calcium resorption from bone lead to hypocalcaemia with secondary hyperparathyroidism. Serum 25(OH)D is low and serum phosphate is normal.

*Stage 2:* The secondary hyperparathyroidism (2<sup>o</sup>HPT) and associated increase in serum 1,25(OH)<sub>2</sub>D normalize calcium concentration by mobilizing it from bone and increased intestinal absorption of calcium. Hyperaminoaciduria and hyperphosphaturia occur as a result of 2<sup>o</sup>HPT. Serum 25(OH)D level further decreases, with the rise in serum alkaline phosphatase concentration.

*Stage 3:* It encompasses symptomatic rickets. In this stage hypocalcaemia develops again, mainly because of the absolute or relative deficiency of 1,25(OH)<sub>2</sub>D caused by further depletion of its substrate, 25(OH)D. The combination of hypocalcaemia and the worsening hypophosphataemia causes a marked reduction of the product (Ca)X(PO<sub>4</sub>) with severe clinical, radiological, biochemical, and histological rickets. Severe hyperaminoaciduria and hyperphosphaturia occur in this stage as a result of severe 2<sup>o</sup>HPT. In very severe cases with rickets, serum levels of 25(OH)D and 1,25(OH)<sub>2</sub>D may be very low or even undetectable, the state we prefer to label as an "extreme vitamin D deficiency syndrome". In 13 per cent of the children with vitamin D deficiency rickets, authors had noted decreased ability of the kidneys to make an acid urine<sup>32</sup>.

### Manifestation

The features specific for rickets include widened and thickened ends of long bones, muscular hypotonia and bony leg deformities (bowlegs, genu valgum, genu

varum, rotational), waddling gait, rachitic rosary, pigeon breast, Harrison's grooves, frontal bossing, tetany and rachitic dwarfism. Adolescents are at risk for vitamin D deficiency rickets if they have reduced exposure to sunlight because of institutionalization, clothing that covers the body and living in homes in northern climates. These patients usually present with genu valgum deformity. Vitamin D-deficient tetany may exist in either a latent or a clinically manifest stage<sup>31,32</sup>.

Radiological features with specificity include widened and irregular epiphyseal line, metaphyseal splaying widening and cupping, pseudofractures, Harris lines of arrested growth and findings of secondary hyperparathyroidism. Sub-metaphyseal band of osteoporosis is the finding specific for pubertal and adolescent rickets<sup>27</sup>.

### Congenital vitamin D deficiency rickets

Congenital rickets due to maternal vitamin D deficiency is a well recognized entity<sup>33,34</sup>. We have studied three sets of mother-baby pairs, a rare situation where the mothers with severe vitamin D deficiency osteomalacia gave birth to newborns with congenital rickets. Extremely low serum 25(OH)D (undetectable to 2.5 ng/ml) suggested that the transplacental transport of 25(OH)D and calcium to the foetuses, became negligible, only when the maternal stores of vitamin D and calcium had been completely exhausted (intrauterine foetal priority). Each mother received 2 g of elemental calcium per day and two doses vitamin D<sub>3</sub> (7.5 mg) given intravenously. The mother-baby pairs were protected from direct sunlight. The first dose of vitamin D<sub>3</sub> healed the osteomalacia but did not appear to heal the rickets of their totally breast-fed infants. A second dose given at three months interval to the mothers, healed the rickets in their infants and biochemistry of the mother and the baby returned towards normal. Mothers, thus had priority for vitamin D and secreted it in the breast milk only after they had first replenished their own stores (extrauterine maternal priority for vitamin D). A unique situation has been described<sup>33</sup> where both the mothers and their newborns had osteomalacia and rickets respectively with secondary hyperparathyroidism and low serum 25(OH)D and calcium. Mothers alone being treated healed their osteomalacia as well as the rickets in their babies kept totally breast-fed. Healing of rickets on breast milk alone indicated secretion of vitamin D and its biologically active metabolites and calcium in the maternal breast milk.

### **Protein energy malnutrition: Rickets and osteoporosis**

Undernutrition in childhood leads to a skeletal deficit that cannot be repaired during adolescent life and presumably, therefore, may lead to an increase in the risk of osteoporotic fracture in later life. During growth, an adequate supply of calories, protein, mineral and vitamin D is a prerequisite for the attainment of peak bone mass.

We had studied 1300 children of protein energy malnutrition. None of the children showed any clinical, radiological or biochemical evidence of rickets. However, osteopaenia or osteoporosis were the uniform observation in their skeletal radiographs. The histology of undecalcified sections of iliac crest biopsies studied in 65 children did not reveal any evidence for mineralization defects<sup>35</sup>. However, following the correction of malnutrition, 13 per cent of the growing children developed clinical and radiological features of rickets at the growth plates, confirming our paradigm “No growth - No rickets”.

### **Calcium deficiency *per se* does not cause rickets: Scientific revelation**

In our extended epidemiological studies we covered cross-sectional population of 47,500 rural children with dietary intake of calcium <300 mg/day, 23,200 living in the villages endemic for fluorosis (mean water fluoride  $11.70 \pm 3.63$  ppm) and 24,300 in the villages non endemic for fluorosis (mean water fluoride  $0.55 \pm 0.07$  ppm). All the children had similar outdoor exposure to sunlight (mean  $6.5 \pm 2.2$  h/day) and comparable outdoor physical activity. All had identical dietary intakes of calcium, protein and calories. Clinical and radiological examination showed that 90.5 per cent of the children in endemic group had varying features of rickets, secondary hyperparathyroidism and bony leg deformity such as genu valgum, genu varum, bowing, rotational and wind-swept deformities. We had not observed any evidence for rickets or bony deformities in the non endemic group. Our observations<sup>36-38</sup> provided scientific proof of evidence that calcium deficiency alone does not produce rickets and inspired us to investigate the reports published on calcium deficiency rickets for possible interactions with fluoride.

The rural black children reported from South Africa<sup>39,40</sup> had been reported drinking water with fluoride ranging from 5.5 to 14.5 ppm, the children reported from Nigeria<sup>41-42</sup> had been using ground water

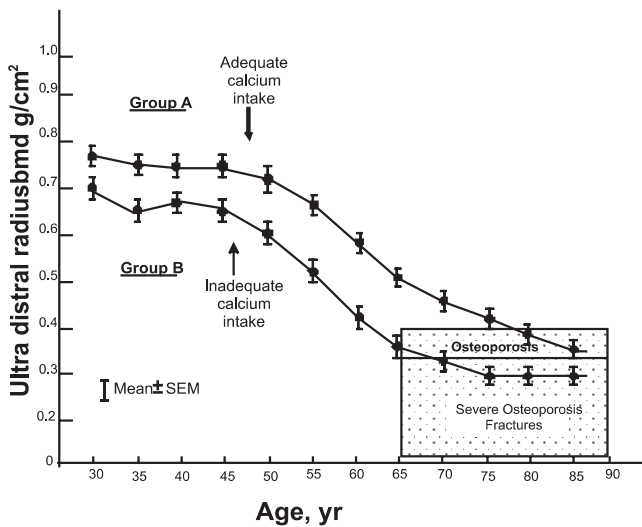
source containing 2.4 to 4.5 ppm, the children reported from south India<sup>43</sup> drinking water ranging from 1.4 to 4.5 ppm and children reported from Bangladesh<sup>44</sup> had been drinking water from the superficial open wells and the hand pumps with a fluoride content ranging from 2.9 to 5.6 ppm. We could not analyze the water consumed by the children reported from Lucknow<sup>45</sup>, north India, as no information was available about their residential locations. However, the villages practically in all the districts around Lucknow are endemic for fluorosis and the most affected are the districts of Raebareli and Unnao (water fluoride 1.8 to 25 ppm).

It was concluded that calcium deficiency *per se*<sup>46</sup> does not cause rickets and the children reported with calcium deficiency rickets are in fact the “syndromes of calcium deficiency and fluoride interactions”. This scientific revelation is bound to change medical practice for ever. It is suggested that each case of calcium deficiency presenting as rickets should be investigated for underexposure to sunlight (vitamin D deficiency) and overexposure to endemic fluoride (also fluoridated water) or some combinations<sup>36-38</sup>.

### **Calcium nutrition and female osteoporosis**

We had measured the bone mineral density (BMD g/cm<sup>2</sup>) at the site ultra distal radius in two groups of women (age 20-90 yr)<sup>42</sup>, Group A, who consumed the milk life-time and Group B, who consumed less or no milk, both groups had similar physical activity. In Group A median Ca intake was 800 mg per/day (520 - 980 mg) and in Group B median Ca intake was 480 mg/day (380 - 675 mg). In each age group BMD was measured in 78-92 females. The peak bone mass (PBM) and its subsequent maintenance in the later life was significantly greater in females of group A ( $P < 0.05$ ). The beneficial effects of Ca intake were evident, as the females with adequate intakes entered the osteoporosis and the fracture zones at about 10 yr later than those with inadequate intakes<sup>47</sup>.

Low calcium intakes early in life not only predispose to osteoporosis later in life, but make bones more fragile in childhood and adolescence as well. Similarly in early marriage even the genetic potential to achieve peak bone mass is lost. Calcium intakes are positively correlated with bone mass at all ages (Fig.1) but most especially at old age, when the requirement rises and the calcium intake tends to drop<sup>47</sup>. Calcium is required for the bone formation phase of bone remodelling. Calcium also affects bone mass through its effects on the remodelling rates. With ageing, there



**Fig. 1.** Bone mineral density (BMD)  $\text{g}/\text{cm}^2$  in females with life-time milk consumption (Group A-adequate calcium intake, Median 800 mg/day) as compared with females who consumed less or no milk (Group B-inadequate calcium intake, Median 480 mg/day). Females in group A entered the osteoporosis zone at the age 75 yr and fracture zone at 85 yr whereas in group B corresponding age were 65 and 70 yr<sup>47</sup>.

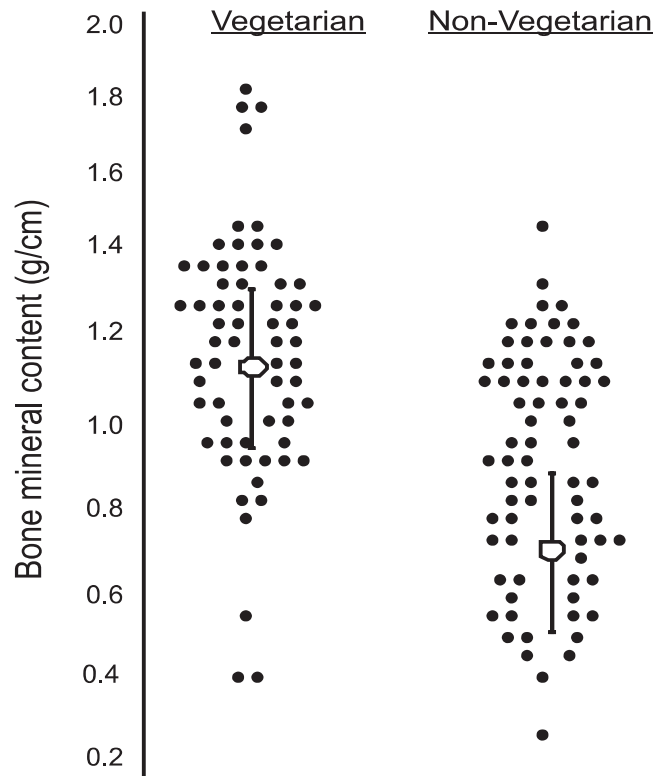
is a decline in calcium absorption efficiency in men and women. This is related to loss of intestinal vitamin D receptors or resistance of these receptors to the action of  $1,25(\text{OH})_2\text{D}$  and reduced renal production of  $1,25(\text{OH})_2\text{D}$ .

### Osteoporosis: Bone mineral content in vegetarians vs non vegetarians

We measured the bone mineral content (BMC) ( $\text{g}/\text{cm}$ )<sup>47</sup> in two groups (65 women in each) of women (at age 60 yr), life-term vegetarians and life-term non vegetarians in order to assess the impact of the consumption of animal protein on BMC. The BMC was significantly greater ( $P < 0.001$ ) in vegetarians (BMC  $1.095 \pm 0.255 \text{ g}/\text{cm}$ ) than age matched non vegetarians (BMC  $0.734 \pm 0.203 \text{ g}/\text{cm}$ ). Downward displacement of values is seen in non-vegetarians in (Fig.2). Thus excessive dietary intakes of animal protein has been implicated in the pathogenesis of more severe osteoporosis in the non vegetarians. It is the effects of acid load of such diets<sup>47</sup>.

### Treatment of vitamin D deficiency rickets and osteomalacia

Objectives of treatment include (i) disappearance of clinical symptoms and signs, (ii) radiological and histological healing of ricketic bone disease that has



**Fig. 2.** Radial BMC values ( $\text{g}/\text{cm}$ ) is compared in the life-time vegetarian and non vegetarian females at age 60 yr. Note the downward displacement of the values in non vegetarian females indicating low BMC values. The mean BMC in the non vegetarian females was 40 per cent less than the age matched vegetarians. ( $P < 0.001$ ), BMC was significantly greater in vegetarians than in non-vegetarians.

developed as a consequence of the deficiency of  $25(\text{OH})\text{D}$ , (iii) normalization of biochemical abnormalities, and (iv) achievement of adequate vitamin D nutrition status and suppression of secondary hyperparathyroidism.

The therapeutic regime, which we have evaluated and found most effective, is the treatment with vitamin D and calcium combined and administered orally<sup>16,21,30-32</sup>. We prefer to start treatment with vitamin  $\text{D}_3$  (Cholecalciferol) as it is the first component missing in the synthetic pathways of vitamin D metabolites and provides the necessary substrate that submits to physiologic regulation of vitamin D metabolites production. Also vitamin D itself is the ideal form of treatment because of its long plasma half-life and low cost. Looser's zone is the first radiological finding and is the most rapid to heal (2-3 wk). Low serum calcium is the earliest abnormality to appear and to return to normal.

Normalization of serum 25(OH)D and calcium and increase in urinary calcium excretion with disappearance of aminoaciduria are the important biochemical indices of healing osteomalacia. Raised serum parathyroid hormone, alkaline phosphatase and histological evidence of osteomalacia are the early abnormalities and resolve slowly.

Hyperplastic parathyroid glands undergo very slow involution and may not involute completely in one's lifetime and remain a constant risk to evolve into an autonomous adenoma (3<sup>o</sup>HPT). Prevention of osteomalacia and rickets is only through ultraviolet (290 to 315nm) sunbath everyday for minimum 30 min of unprotected skin or 400 to 800IU of vitamin D<sub>3</sub> orally per day.

Despite having a large series of patients with nutritional bone disease, we are still missing the valuable knowledge to our experience with vitamin D intoxication.

Vitamin D deficiency rickets in children and osteomalacia in the mothers are the commonest disorders prevalent in the rural population of India. Low calcium intakes early in life not only predispose to osteoporosis later in life, but make bones more fragile in childhood and adolescence as well. These disorders and the syndromes of calcium deficiency and fluoride interactions are largely responsible for the morbidity and mortality in the young and promising individuals, with economic consequences.

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