Dietary Calcium Deficiency

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There has been until recently a general consensus among experts in the field of metabolic bone disease, that a dietary lack of calcium produces few pathological consequences in man. Several workers have made statements such as "a low calcium intake per se does not cause rickets" (1) and there is a "wide range of intakes with which people in various parts of the world maintain themselves without apparent signs of either calcium deficiency or excess" (2).

Over the last two decades, however, concern has been expressed that the presently recommended dietary allowances for calcium may be insufficient to prevent a negative calcium balance in perimenopausal woman (3), and that preterm infants, especially very-low-birthweight infants (<1500 g), fed breast milk or standard infant formula are unable to maintain the expected intra-uterine calcium accretion rates (4). Furthermore, over the past 15 years several reports have appeared of presumed dietary calcium deficiency leading to rickets in infants fed feeds with low calcium content (5–7), and we have described rickets, osteomalacia, and bone deformities in children from rural areas of South Africa due to chronically low dietary calcium intake (8–12). Questions are also being asked as to whether increasing calcium intake during adolescence might influence the peak bone mass achieved in adulthood with a resultant decrease in the prevalence of, or rate of progression of post-menopausal and involutional osteoporosis.

This chapter reviews the recommended dietary allowances for calcium in infants and children, discusses the clinical and biochemical features of dietary calcium deficiency, and briefly describes some animal studies which support the contention that low dietary calcium intake may lead to clinical and biochemical abnormalities.

RECOMMENDED DIETARY ALLOWANCES FOR CALCIUM

Recommended dietary allowances (RDA) for calcium for infants and children have been drawn up by several bodies including the National Academy of Sciences (13) and the WHO/FAO (14). Table 1 lists the National Academy of Sciences' recommendations.
TABLE 1. Recommended dietary allowances for calcium (13)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Infants 0–0.5</th>
<th>Children 0.5–1.0</th>
<th>Adolescents 1–10</th>
<th>Adolescents 11–18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended dietary allowance (mg/day)</td>
<td>360</td>
<td>540</td>
<td>800</td>
<td>1200</td>
</tr>
</tbody>
</table>

It has been argued that the RDA for calcium set by the National Academy of Sciences is too high. One of the most cogent arguments is that the mean dietary calcium intake of children, particularly in many developing countries is well below the RDA (20–21), with values being generally between 200 and 400 mg/day. Despite intakes of approximately half the RDA, very few, if any, side effects have been ascribed to the dietary lack of calcium. This form of argument should be viewed with caution, as growth rates of children in many developing countries are lower than those of American children, and dietary factors such as protein intake may influence calcium absorption and retention (22). Furthermore the RDA is not the requirement of an individual, but rather the level considered to be adequate to meet the known nutritional needs of practically all healthy people (13). There is thus a safety margin built into the RDA.

Although the RDA for preterm infants has not been drawn up, their mineral requirements have received much attention recently (15–17). It has been assumed that breast milk provides adequate nutrition for the growing infant during the first three months of life, however the preterm infant, especially when weighing less than 1200 g at birth, is a special problem. In the last trimester of pregnancy, fetal calcium accretion rises rapidly from just over 100 mg/day at 28 weeks to approximately 350 mg/day at 35 weeks (18). Breast milk, with a calcium content of 300 mg/l, is unable to meet these demands if post-natal accretion rates, once the preterm infant has been delivered, are similar to intra-uterine rates. Ziegler et al. (19) have calculated the oral calcium requirement of a preterm infant (weighing between 800 and 1200 g) to be 188 mg/kg/day.

Several authors (18,23) have attempted to calculate the daily calcium accretion rates during growth from total body calcium data at various ages. Although there are some differences between the values obtained by the various groups, the patterns are very similar and the magnitude of the values provides a perspective. Calcium accretion rates drop rapidly in the first three years after birth to reach a nadir of between 70–100 mg/day. Values then rise to peak during the adolescent growth spurt with estimates ranging between 200 and 400 mg/day depending on the sex of the adolescent (Table 2). Boys peak later than girls and have higher peak values. The average daily accumulation of calcium between the ages of 10 and 20 years is 180 to 210 mg in boys and 90 to 110 mg in girls (18). Thus allowing for incomplete calcium absorption, endogenous fecal loss of calcium, and urinary and dermal losses, it is apparent that children in developing countries with intakes of between 200 and 400 mg/day are either only just in appropriate calcium balance or are not absorbing
DIETARY CALCIUM DEFICIENCY

TABLE 2. Estimated calcium accretion rates (mg/day) for boys and girls (23)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>89</td>
<td>70</td>
<td>70</td>
<td>105</td>
<td>125</td>
<td>173</td>
<td>269</td>
<td>394</td>
<td>166</td>
<td>60</td>
</tr>
<tr>
<td>Girls</td>
<td>93</td>
<td>71</td>
<td>83</td>
<td>105</td>
<td>147</td>
<td>217</td>
<td>330</td>
<td>240</td>
<td>101</td>
<td>40</td>
</tr>
</tbody>
</table>

enough calcium to meet the optimal requirements during growth. Is there any evidence that these children suffer from clinical, histological, or biochemical evidence of long-standing calcium deprivation?

THE CLINICAL PICTURE OF DIETARY CALCIUM DEFICIENCY

From a pathophysiological point of view, the clinical picture of dietary calcium deficiency could have several presentations. Figure 1 outlines the possible pathogenesis of the biochemical and histological disturbances that might occur in prolonged dietary calcium deprivation.

![FIG. 1. The possible pathogenesis of the biochemical and clinical abnormalities associated with dietary calcium deficiency.](image-url)
In childhood, there are three situations in which clinical disease due to dietary calcium deprivation has been reported:

The Very-low-birthweight Infant

The problem of osteopenia and rickets in the very-low-birthweight infant (especially in those less than 1200 g at birth) has been extensively reviewed (16,24,25; see chapter by J. Senterre). Osteopenia, generally diagnosed radiographically, and biochemical evidence of altered mineral homeostasis (hypophosphatemia and elevated serum alkaline phosphatase values) are frequent findings during the first six to twelve weeks of life in the very small premature infant. Radiological rickets is much less frequently diagnosed. Several factors appear to predispose the preterm neonate to the development of metabolic bone disease; these are: (a) severe prematurity; (b) breast milk or soy-based formula feeds, (c) prolonged respiratory distress often associated with the use of furosemide and, (d) prolonged parenteral nutrition. There is general consensus that the major pathogenetic mechanism is an inadequate supply of phosphate either by the enteral or parenteral route to meet the requirements in the rapidly growing neonate. Biochemical features compatible with this mechanism include hypophosphatemia, marked renal conservation of phosphorus with its almost absent excretion in urine, normal parathyroid hormone concentrations, elevated 1,25-dihydroxyvitamin D (1,25(OH)\(_2\)D) levels and hypercalciuria.

Phosphate supplementation of the feed leads to increased serum phosphorus levels, increased renal phosphate excretion, decreased renal calcium excretion, and an improvement in calcium retention (26).

Vitamin D deficiency or an abnormality in vitamin D metabolism has also been suggested as a pathogenetic mechanism. In countries where vitamin D deficiency is common or where the maternal vitamin D status is inadequate, vitamin D deficiency may aggravate the already compromised mineral status of the preterm infant. Hillman and co-workers (27) have shown that infants supplemented daily with 400 IU of vitamin D have a higher prevalence of features suggestive of altered mineral homeostasis and osteopenia than those supplemented with 800 IU. Their data also suggests that there may be an impairment in the hepatic hydroxylation of vitamin D. Despite mild fat malabsorption and impaired vitamin D absorption and a possible defect in 25-hydroxylation, premature infants are able to increase circulating 1,25(OH)\(_2\)D concentrations in response to appropriate stimuli, provided adequate substrate is present (28). It thus appears that provided adequate vitamin D supplements are given (800 IU/day), abnormalities of vitamin D metabolism and/or vitamin D deficiency play minor roles in the etiology of metabolic bone disease in preterm infants.

Of more relevance to the present discussion, is the role that an inadequate calcium intake plays in the pathogenesis of the bone disease. As discussed earlier, dietary phosphate deficiency appears to be the major etiological factor, however dietary calcium deficiency may play a secondary role which becomes more apparent once
an adequate phosphate intake is assured. Human milk provides approximately 60 mg calcium/kg/24 h to a premature infant, whose calcium accretion rate in utero is double that. It has been suggested that the low calcium intake prevents the development of hypercalcemia, which is so characteristic of the phosphorus-deficiency syndrome seen in older phosphorus-deficient animals and humans (24). Further dietary calcium lack probably predisposes the preterm infant to hypocalcemia and secondary hyperparathyroidism if phosphorus supplementation alone is attempted (29). Our own studies on the use of a breast milk fortifier in the feeding of very-low-birthweight infants indicate that despite both calcium and phosphorus supplementation, the dietary calcium intake might still have been a limiting factor as serum calcium values correlated inversely with alkaline phosphatase concentrations at the end of the trial when the infants weighed 1800 g (30). These findings are supported by Hillman et al. (31), who have demonstrated that those infants who had the lowest calcium intake were also the ones likely to have radiological evidence of osteopenia.

In conclusion, it appears that the metabolic bone disease of very-low-birthweight infants is primarily related to phosphorus deficiency, however both an inadequate vitamin D intake and dietary calcium lack may aggravate the situation. Recommendations have been made that for very-low-birthweight infants both the calcium and phosphorus content of milk feeds should be increased above that of breast milk and standard infant formulas. The most suitable levels of calcium and phosphorus in milk formulas for premature infants probably still need to be determined, as do the calcium to phosphorus ratio and the most appropriate form in which calcium and phosphorus should be added to the formula to prevent precipitation (see chapter by J. Senterre).

Infants and Toddlers

As far as the author is aware, five infants have been reported to have developed radiological rickets due to presumed dietary calcium deficiency (5–7). In two of the infants (5,6) prolonged diarrhea had resulted in the patients being placed on a meat-based diet with no added calcium supplements over a period of approximately nine months in both cases. In the other three infants, the reasons for them being placed on a low calcium containing soya drink is not given but they had been on the feed for at least six months at the time of presentation.

Table 3 lists the age of presentation and the biochemical features in the five infants. The biochemical abnormalities are similar to those found in privational vitamin D deficiency, except that in four of the cases, serum 25-hydroxyvitamin D (25(OH)D) were within the normal range and in the remaining infant, vitamin D supplementation (400 IU/day) had been provided throughout the period of low calcium intake. In the three infants in whom 1,25(OH)_2D concentrations were measured, the values were found to be elevated. The serum vitamin D metabolite profiles militate against the diagnosis of vitamin D deficiency rickets, as serum 25(OH)D values are usually less than 4 ng/ml in those patients with radiological rickets. Serum 1,25(OH)_2D is gen-
**TABLE 3. The biochemical features of calcium deficiency rickets in infants**

<table>
<thead>
<tr>
<th>Age at presentation (months)</th>
<th>Serum calcium (mg/dl)</th>
<th>Inorganic phosphate (mg/dl)</th>
<th>Alkaline phosphatase (x normal)</th>
<th>25(OH)D (ng/ml)</th>
<th>1,25(OH)2D (pg/ml)</th>
<th>PTH (x normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref. 5 13</td>
<td>9.1 (2.27)</td>
<td>2.0 (0.6)</td>
<td>10 x</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ref. 6 12</td>
<td>7.6-8.4 (1.9-2.1)</td>
<td>2.5-3.2 (0.81-1.03)</td>
<td>6 x</td>
<td>36</td>
<td>172</td>
<td>4 x</td>
</tr>
<tr>
<td>Ref. 7 15-18</td>
<td>7.8 (1.95)</td>
<td>4.4 (1.42)</td>
<td>6.4 x</td>
<td>13.6</td>
<td>118</td>
<td>4 x</td>
</tr>
<tr>
<td></td>
<td>9.2 (2.3)</td>
<td>3.1 (1.00)</td>
<td>3.7 x</td>
<td>9.2</td>
<td>118</td>
<td>4 x</td>
</tr>
<tr>
<td></td>
<td>7.8 (1.95)</td>
<td>3.5 (1.13)</td>
<td>1.5 x</td>
<td>9.9</td>
<td>123</td>
<td>3 x</td>
</tr>
</tbody>
</table>

Serum calcium and inorganic phosphate values in mmol/l are given in parentheses.

Dietary calcium deficiency is generally not considered to be a useful indicator of vitamin D deficiency as normal or even elevated values have been reported (32).

The calcium content of the diets provided to the five infants was extremely low. The soya drink provided 17 mg/dl, while the meat-based formulas provided 1 mg/dl and between 7 and 12 mg/100 g. Total daily calcium intakes were calculated at 180 mg and 21-36 mg in two of the infants (5,6). Phosphorus intake was considered to be adequate in all the infants although the total phosphorus and the phytate phosphorus content of the soya drink is not stated. In none of the patients was a therapeutic trial of calcium supplementation of the diet alone tried, however it is reported that in two of the infants a change to a calcium-rich diet (vitamin-D-free skimmed milk or cow’s milk and vitamin D) resulted in correction of the biochemical and radiological abnormalities.

**Children and Adolescents**

It could be considered that the patients discussed in the previous two sections represent those in very abnormal circumstances or situations, and that dietary calcium deficiency is not a problem in free-living communities. We believe that we have evidence to suggest that the latter statement is not true, and that dietary calcium deficiency may be an unrecognized problem in communities, where calcium intake is habitually low.

Over the past 12 years, our unit has investigated 34 children, who presented with biochemical and radiological features of rickets and osteomalacia and whom we considered to suffer from dietary calcium deficiency.

The clinical presentation of the first nine children studied was reported in 1978 (8), and is representative of the presentation of the larger group of children described here. The children (14 boys and 20 girls) were aged between 4 and 15 years at the time of admission to hospital for progressive deformities of the legs. All the children had lived most of their lives in the rural areas of South Africa, and spent a considerable amount of time each day outside their homes in the open. Half the children presented with knock-knees, while the remainder presented with bow-legs or wind-swept deformities (a combination of valgus and varus deformities) (Fig. 2). Muscle
weakness and bone pain were not features of the presentation, and most of the children were able to walk long distances to school or to fetch water without obvious impairment. Although growth retardation was a feature, evidence of protein-energy malnutrition was not found.

On admission to hospital, the biochemical abnormalities were in keeping with the
TABLE 4. The biochemical values (Mean ± SD) of children and adolescents with dietary calcium deficiency

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1 ± 3.6 years</td>
<td></td>
</tr>
<tr>
<td>Serum calcium</td>
<td>2.06 ± 0.23 mmol/l</td>
</tr>
<tr>
<td>(8.24 ± 0.92 mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>1.47 ± 0.35 mmol/l</td>
</tr>
<tr>
<td>(4.55 ± 1.06 mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>972 ± 496 IU/l</td>
</tr>
<tr>
<td>25(OH)D</td>
<td>16.4 ± 6.7 ng/ml</td>
</tr>
<tr>
<td></td>
<td>2.25–2.75</td>
</tr>
<tr>
<td></td>
<td>1.3–1.8</td>
</tr>
<tr>
<td></td>
<td>&lt;350</td>
</tr>
<tr>
<td></td>
<td>10–50</td>
</tr>
</tbody>
</table>

diagnosis of calciopenic rickets (Table 4). The biochemical picture is characterized by hypocalcemia, elevated alkaline phosphatase values, and variable levels of serum phosphorus. Serum 25(OH)D levels were within the normal range, and in a small number of children in whom they were measured, serum 1,25(OH)₂D and parathyroid hormone concentrations were elevated (10). The urinary findings were in keeping with serum biochemical changes; urinary calcium excretion was low, the tubular reabsorption of phosphorus was variable with the majority of children having values within the normal range, urinary cyclic AMP excretion was elevated in those children in whom it was measured, and there was a generalized increase in amino acid excretion.

Radiologically, the features were also typical of those of calciopenic rickets (Fig. 3). Osteopenia was a frequent finding. The severity of the metaphyseal changes diagnostic of rickets was variable, with some of the children having evidence of only minor degrees of impaired endochondral calcification, while others had more florid changes typical of a more severe degree of mineralization failure. Features of hyperparathyroidism as evidenced by loss of the lamina dura around the teeth were detected in all the children, however subperiosteal erosions of the cortices of the phalanges were only rarely visible.

Bone histomorphometry has been obtained on iliac crest biopsies from 11 children. The histology revealed features typical of osteomalacia and secondary hyperparathyroidism (12) (Fig. 4).

Treatment of all the children consisted of a normal ward diet containing approximately 1000 mg calcium/day and 800 mg phosphorus/day. No vitamin D supplements were provided. The vitamin D content of the diet was minimal as milk and milk products are not routinely vitamin D fortified. The diets of a few of the children were supplemented with extra calcium. On this therapy serum calcium values rose and alkaline phosphatase levels fell. 25(OH)D concentrations remained relatively constant, while parathyroid hormone and 1,25(OH)₂D concentrations decreased to normal values over a period of several months (10). Figure 5 depicts the typical changes in serum and urinary variables in response to therapy over a period of six months. Radiological changes improved in parallel with the improvement in the bio-
FIG. 3. Typical radiographic abnormalities in children with dietary calcium deficiency.
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FIG. 4. Dietary calcium deficiency: the histomorphometric bone abnormalities on admission to hospital, and after 3 to 6 months therapy in those children who had repeat biopsies. The shaded areas are the normal ranges for children.

chemical abnormalities, and in those children on whom repeat bone biopsies were performed at the time of orthopedic correction of their leg deformities, the bone histology showed a marked decrease in the features of osteomalacia although the variables had not returned to normal (Fig. 4).

Although the pathogenesis of rickets and osteomalacia could not be definitively determined from the study of the children admitted to hospital, the pattern on the biochemical abnormalities were indicative of calciopenic rickets. Further, the finding of normal 25(OH)D and elevated 1,25(OH)2D concentrations indicated that neither vitamin D deficiency nor a defect in vitamin D metabolism were possible pathogenic mechanisms. The most likely explanation therefore was that of a dietary deficiency of calcium, although the possibility of some dietary factor inhibiting calcium absorption could not be excluded.

In order to investigate these latter two possibilities further, several studies were conducted in a rural community from which a number of children with rickets and osteomalacia had been seen (9,11,33). School-going children between the ages of 7 and 12 years in the community had a significantly higher prevalence of biochemical abnormalities (hypocalcemia (13.2%), elevated alkaline phosphatase concentrations (41.5%), and low urinary calcium excretion (76.2%)) than children of similar ages in two urban communities (9). Furthermore within the rural community, those children with hypocalcemia and elevated alkaline phosphatase levels had significantly lower
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FIG. 5. The response to dietary therapy in a typical child admitted with rickets due to dietary calcium deficiency. From Pettifor JM, et al. (8).

calcium intakes than those with normal biochemistry (Table 5) (33). Protein and phosphorus intakes were similar in the study and control groups. Data from the same study revealed that radial bone mineral densities were also lower in those children with biochemical abnormalities than in their normal peers.

The diet of the rural black child is quite simple and relatively monotonous; it consists of a staple, maize meal, cooked to a porridge of varying consistency depending on whether it is eaten in the morning or evening. Traditionally there are only two meals a day, the morning meal consisting of the maize meal porridge, bread and tea (usually black), and the evening meal consisting of maize meal porridge (thicker than in the morning) and a stew of vegetables in season and of meat when it is available. The only discernible difference in the diet between those children with biochemical abnormalities and those without, was in the amount of milk con-
TABLE 5. Calcium intakes (mean ± SD) of children with biochemical abnormalities suggestive of rickets and those of their age-matched control*

<table>
<thead>
<tr>
<th>Calcium intake</th>
<th>3–5 year old</th>
<th>8–10 year old</th>
<th>13–16 year old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>study</td>
<td>control</td>
<td>study</td>
</tr>
<tr>
<td>mg/24 h</td>
<td>249±182</td>
<td>282±144</td>
<td>199*±127</td>
</tr>
<tr>
<td>mg/kg/24 h</td>
<td>16.4*±11.0</td>
<td>19.9±9.9</td>
<td>7.1**±3.2</td>
</tr>
</tbody>
</table>

* From Eyberg CJ (33).
Values significantly different from controls: * p < 0.05; ** p < 0.005.

Assumed. Milk consumption is generally low in rural children, but in those with biochemical abnormalities it was virtually absent. Calcium intake is habitually low in those communities eating maize as a staple, unless dairy products are incorporated into the diet, as maize is particularly low in calcium (13 mg/100 g). The dietary calcium intake in those children with biochemical evidence of rickets varied from approximately 90 to 300 mg/day, while in the control children the intake varied between approximately 200 and 500 mg/day.

In order to assess the effect of dietary calcium supplementation on children in the community, a randomly selected group were supplemented with 500 mg calcium/day for a period of three months. This resulted in a significant rise in serum calcium values from 2.38 ± 0.12 mmol/l (9.52 ± 0.48 mg/dl) to 2.51 ± 0.10 mmol/l (10.04 ± 0.40 mg/dl), while alkaline phosphatase values fell significantly but less dramatically from a mean value of 265 IU/l to 247 IU/l over the same period (11).

From the results of the above mentioned studies, we believe that chronically low dietary calcium intake is responsible for (i) the biochemical abnormalities (hypocalcemia, elevated alkaline phosphatase levels, and hypocalcuiuria) found in a number of rural school children; and (ii) the radiological and histological rickets and osteomalacia in the children admitted to hospital. We, however, are still uncertain as to whether dietary constituents, such as a high oxalate intake associated with some of the green leafy vegetables used in the stews, or the high phytate content of the maize, might further compromise an already unacceptably low dietary calcium intake.

Support for the hypothesis that low dietary calcium intake per se is responsible for the biochemical and radiological abnormalities is provided by the finding of significant correlations between the calcium intake (mg/kg/24 h) of children aged between 8 and 16 years and serum calcium (r = 0.408, p < 0.01), serum alkaline phosphatase (r = −0.329, p < 0.05), and urinary calcium excretion (r = 0.344, p < 0.05) (33).

The long-term sequelae of chronically low dietary calcium intake in children are unclear. Walker (1,20,34) argues very convincingly that there is little evidence from developing countries, including South Africa, to suggest that low dietary calcium
intake predisposes to long-term demineralization of the skeleton and osteoporosis in adults. We have no data to refute this point of view. Whether low dietary calcium intake hastens the onset of clinical osteoporosis in post-menopausal women in more developed countries is an area of current controversy (35), as several factors such as race, physical activity, and protein intake might adversely affect an individual’s adaption to a low dietary calcium intake.

It is our contention that within a community where calcium intake is marginal, it is those children on the lowest intake for the longest periods who will manifest with bone deformities and rickets. The majority of the other children will be asymptomatic, and manifest only biochemical changes (progressing from hypocalciuria and elevated alkaline phosphatase values to hypocalcemia). Decreased bone mineral density and osteopenia might be a feature of decreased calcium intake in childhood, but once growth has stopped, the calcium intake is probably large enough to maintain the adult in calcium balance and to correct any biochemical abnormalities and mineralization defect.

From a public health point of view, until evidence of long term sequelae from low dietary calcium intake are documented, the argument for a general recommendation to calcium supplement the diet of rural communities is tenuous. Considerably more research needs to be conducted to confirm the findings discussed above and to document the long term effects of dietary calcium deprivation in children and in adults, especially during pregnancy and lactation. With the development of the newer non-invasive techniques, such as dual energy x-ray densitometry, for the measurement of total body calcium and vertebral bone mineral content, more accurate assessments of the influence of dietary calcium intake on bone homeostasis should be forthcoming.

**FLUOROSIS AND DIETARY CALCIUM DEFICIENCY**

Endemic fluorosis and bone abnormalities have been described from several areas of the world, in particular from India (36). Teotia and co-workers have extensively investigated the problem and have described severe bone deformities, including rickets, in children living in areas with water fluoride concentrations between 24–26 ppm (37). The biochemical abnormalities reported in these children include elevated alkaline phosphatase values, low urinary calcium excretion, and decreased tubular reabsorption of phosphate (37). Serum calcium levels are typically normal. These researchers suggest that there is a correlation between the degree of severity of the metabolic bone disease and deformities caused by exposure to fluoride and the severity of the dietary calcium deprivation (36), and that the safe limit of fluoride in drinking water is less than 0.5 ppm.

Fluorosis as a possible cause of the rickets and biochemical abnormalities described in the previous section has been excluded as the fluoride content of the drinking water in the community in which many of the studies were conducted ranged
between 0.05 and 0.11 ppm. Nevertheless, bone deformities due to endemic fluorosis have been described in children in South Africa (38), and we have recently studied nine such children between the ages of 9 and 18 years, who presented with leg deformities and came from areas where the water fluoride content varied from 8 to 13 ppm. The biochemical presentation was very similar to that described in the children presenting with dietary calcium deficiency (Table 6). However the ages of the children with fluorosis tended to be older than those with dietary calcium deficiency, and radiographically the skeleton showed evidence of axial sclerosis and more severe features of hyperparathyroidism (coarse trabeculation of the long bones and subperiosteal erosions of the phalanges), while the features of rickets were less prominent. Histomorphometry of the iliac crest bone biopsies revealed severe osteomalacia and secondary hyperparathyroidism.

It is postulated, in agreement with Teotia et al. (36), that the onset of fluoride bone disease in these children was hastened by habitually low dietary calcium intake. Although the cellular actions of fluoride on bone are poorly understood, fluoride excess stimulates osteoid formation and impairs mineral resorption. The increased osteoid formation probably increases calcium demands of the body, which the low dietary intake cannot meet. The consequent fall in serum calcium leads to secondary hyperparathyroidism and elevated 1,25(OH)_{2}D concentrations, with the resultant histological features of secondary hyperparathyroidism and osteomalacia.

### ANIMAL STUDIES

Osteoporosis and nutritional secondary hyperparathyroidism due to calcium deprivation, are well-known syndromes to the veterinarian. The conditions have been described in rats (39), cats (40), dogs (41), and horses (42) and are ascribed to unfavorable dietary calcium to phosphorus ratios with resultant secondary hyperparathyroidism. The osseous histological lesions seen are generally in keeping with the diagnosis of secondary hyperparathyroidism although osteomalacia and rickets have been described in both animals (43) and birds (44).

Anderson and co-workers (45) caution that findings in non-primate animals might
not be relevant to man. In a study conducted over a period of up to 88 months, they were unable to show significant differences in the bone radiographs or histology between groups of young monkeys fed diets varying in calcium to phosphorus ratios. However, this study was aimed at assessing the effect of varying calcium to phosphorus ratios rather than the effect of a low calcium diet per se, as the lowest dietary calcium content was 0.3% (450 mg/day).

Our own studies (46) conducted in young baboons, demonstrated that diets low in calcium (0.04%), or calcium (0.04%) and phosphorus (0.04%) led to the development of radiological rickets and histological features of osteomalacia over a period of 16 months. Those baboons fed the diet low in calcium only tended to have lower serum calcium and higher phosphorus values than the control group, while alkaline phosphatase levels rose significantly above those of the control group in the latter half of the study. The discrepancy in results between our study and those of Anderson et al. (45) might be explained on the degree of dietary calcium deprivation provided by the diets. The calcium content of the low calcium diet was nine times lower in our study than that in the study of Anderson and co-workers (45).

Studies by Baylink and his group (47) have highlighted the cellular effects of calcium deprivation in vitamin D replete rats. Dietary calcium deficiency produces a marked increase in serum parathyroid hormone and 1,25(OH)2D concentrations in association with a fall in serum calcium values. At the bone cell level, both the number and activity of osteoclasts are increased; osteoblast number increases in parallel with the increase in osteoclast number, however unlike the change in activity of osteoclasts, osteoblastic activity is decreased in calcium deprivation. At the bone surface, calcium deficiency results in a mineralization defect with a delay in osteoid maturation and an increase in osteoid seam width; both of which are features of osteomalacia.

CONCLUSIONS

Over the past 20 years, data has been accumulating to suggest that low dietary calcium intake in infants and children is not as innocuous as has been thought in the past. Evidence suggests that calcium deprivation might aggravate the metabolic bone disease of breast-milk fed very-low-birthweight infants. Furthermore a non-calcium supplemented milk-free diet during infancy has been incriminated in causing rickets, despite adequate vitamin D intake. Finally, in rural communities in South Africa, calcium deprivation appears to be responsible for rickets and osteomalacia in a small number of children and adolescents. The majority of children in these communities are asymptomatic, and only manifest biochemical evidence of inadequate calcium intakes, as judged by hypocalcemia, elevated alkaline phosphatase values, and low urinary calcium excretion. The long term sequelae in these asymptomatic children is unknown, and further research is required to establish the need for calcium supplementation in these communities.
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REFERENCES


DISCUSSION

Dr. Marx: Since calcium accretion has a nonlinear relation to age, with a striking peak during the adolescent growth spurt, would it be possible for you to express biochemical indices as a function of anticipated body needs. For example, have you examined the relation to bone age or Tanner development stage?

Dr. Pettifor: We haven't in fact done that but it is one of the reasons why we took three different age groups to look at calcium intake. The 3–5-year-old age group has probably the lowest level of calcium accretion rate in childhood. The 13–15-year-old group probably reflects the period of the pubertal growth spurt. It was assumed that if calcium deficiency was to manifest in the children, it would most probably be during this latter period.

Dr. Guesry: When we speak of calcium deficiency it is very important not to speak only of calcium intake but of calcium bioavailability. As you know, calcium bioavailability is increased by some carbohydrates like lactose, and decreased by phosphate, fibers. Even soya protein itself seems to play a negative role in calcium absorption, as well as saturated fat. All together this could reduce calcium absorption by a large proportion making this factor as important as calcium intake.

Dr. Pettifor: I accept your comments. However if a child is already on an intake of less than that which appears to meet accretion requirements, the child has a problem. Even if one gets 100% absorption you are not going to meet the natural needs for growth. The rural diet is mainly corn-based, and has several factors which might impair calcium absorption: a high phosphorus, and phytate and oxalate content. These constituents further compound the deficit.

Dr. Glorieux: You are dealing with a large pediatric population with very low calcium intake. Only some of these children develop rickets, while the majority of them seem to adapt to the situation. Do you have an explanation for this?

Dr. Pettifor: I think the children with rickets are the tip of the iceberg. Those that manifest with bone deformities are in fact a very small percentage of the children in the rural communities. They tend to be the poorest and have the lowest calcium intake. The other children may have reasonable quantities of milk with tea or coffee. I really don't know what are the other factors involved or whether there are other factors, such as intestinal absorption ability. Certainly we do see a number of members in the same family manifesting with the same problem, but we haven't been able to say whether this is because of a genetic link or because of the socioeconomic background and diets which are very similar in that particular family.

Dr. Glorieux: In discussing the pathophysiology of the bone disease, you indicated that the mineralization defect was caused by calcium deficiency, and also phosphate deficiency secondary to hyperparathyroidism. You also suggested that high 1,25(OH)_{2}D levels were directly involved in the mineralization defect. We heard yesterday that 1,25(OH)_{2}D was probably not necessary for normal bone formation, now you imply that it aggravates the picture. Is it correct?
Dr. Pettifor: Yes, that is what I meant. The studies of Puzas et al. (1), looking at rats that were vitamin D replete but calcium deficient, indicate that elevated 1,25(OH)\(_2\)D levels may well play a role in impairing mineralization.

Dr. Glorieux: Dr. Fraser said yesterday that rat and man may behave differently.

Dr. Arnaud: The radiological and biochemical characteristics of your patients are close to those of the vitamin D-deficient subjects described by Dr. David, even down to normal levels of 25(OH)D and increased concentrations of 1,25(OH)\(_2\)D. How do you know that these children were not vitamin D deficient, but received some form of vitamin D supply in the course of getting to you? I wonder whether we may be more like rats than we think we are in the sense that rats even vitamin D deficient do not get rickets or osteomalacia, unless their calcium phosphate ratios are altered considerably. It is conceivable that, in humans, you must also alter that ratio in order to see florid disease. Then, calcium deficiency may in fact be required to induce rickets or osteomalacia.

Dr. Pettifor: I believe that vitamin D deficiency is not a factor because these rural children spend 6-7 hours a day out of doors. They present much later than those with the vitamin D deficiency whom we usually see under the age of 18 months, before they are able to walk and get out into the sunshine. Further, all 25(OH)D levels measured in the rural community were normal. During calcium treatment, in our patients, there was usually no change in 25(OH)D levels despite a fall in 1,25(OH)\(_2\)D levels. We haven't looked at the effect of vitamin D supplementation in rural environments. Certainly by calcium supplementation alone, we were able to increase serum calcium levels and drop alkaline phosphate levels, suggesting that there was no evidence of major calcium malabsorption.

Dr. Arnaud: We have measured 25(OH)D levels in a large number of Minnesota farm children, and found them very low in the mid winter and well as into the spring. There was no evidence that these children had rickets, but their calcium intake was astronomical, in the form of non-vitamin D supplemented milk and this may have been sufficient to prevent rickets. Maybe, we are more like rats than we would like to think.

Dr. Pettifor: I think we were seeing a continuum. If one is vitamin D deficient for a prolonged period of time, no matter what the calcium intake is, you end up with problems. If the vitamin D intake is marginal and the calcium intake is good, you probably cope much longer than if your calcium intake was low. If the vitamin D intake is adequate but the calcium intake low, no matter what you do, you are not going to absorb enough calcium to meet your requirements.

Dr. Holick: Coming back to the issue of elevated 1,25(OH)\(_2\)D levels and their inhibitory effect on bone mineralization, we need to put into perspective that the ultimate biologic function of vitamin D is not for bone mineralization, but to maintain adequate serum calcium levels, and normal neuromuscular and other body functions. It has been shown by Raisz et al. (2) that, in osteosarcoma cells, 1,25(OH)\(_2\)D inhibits collagen synthesis. So high circulating levels of 1,25(OH)\(_2\)D may maintain serum calcium levels despite inhibition of bone mineralization.

Dr. Marx: It is difficult to infer from an osteosarcoma cloned-cell model what might be regulating mineralization in vivo. Very high serum 1,25(OH)\(_2\)D is a universal occurrence during the healing phase after nutritional deficiency of vitamin D. Obviously the bones replenish themselves extremely well, perhaps even at the optimal rate, under these conditions.

Dr. Pettifor: Perhaps we are seeing the bone disease more rapidly in these individuals because they have increased bone turnover, associated with hyperparathyroidism. If we take hypoparathyroidism, for instance, where one has low 1,25(OH)\(_2\)D, low PTH values, and
hypocalcemia, it is very exceptional that one sees evidence of osteomalacia. Whether one manifests osteomalacia or not may well be related to the degree of bone turnover.

Dr. Marx: An important feature of hypoparathyroidism is hyperphosphatemia, which contrasts importantly with the hypophosphatemia that contributes to the impairment of bone mineralization in most rachitogenic states.

Dr. Pettifor: Phosphate levels in our patients tend to be normal, between 1.5 and 1.7 mmol/l. Interestingly PTH challenges did not elicit the normal phosphaturic response. There may have been down regulation of the renal PTH receptors.

Dr. Mautalen: Do the children you described with endemic fluorosis come from a different area?

Dr. Pettifor: Yes, they were from a specific area, unrelated to the children I presented previously. We were thus looking at two separate pictures. We checked fluoride consumption in these children whom we believed to have dietary calcium deficiency, and found fluoride levels in the water to be exceptionally low. I believe that we must separate out these two conditions.

Dr. Bonjour: Was phosphate intake normal with respect to age and body needs in your patients? And what about TmPi/GFR? Was there any evidence of phosphate depletion?

Dr. Pettifor: Maize (corn) is a high phosphate containing cereal, so average intake was approximately 900 mg of phosphate a day. As far as TmPi/GFR values, they correlated positively very well with serum phosphate levels.

Dr. Marx: There is uncertainty and controversy as to whether calcium intake during childhood or adolescence has a role in pathophysiology of the osteoporotic states that occur later on. Do you have any data relevant to this issue?

Dr. Pettifor: Not in those particular children, but if we look at the prevalence of osteoporosis in the black population in South Africa, it is an uncommon problem. The incidence may be rising slightly with urbanization, but certainly nowhere near the problem that it is in the Caucasian population. Obviously there are many factors that relate to the development of postmenopausal osteoporosis. I don't believe that dietary calcium intake is a major determinant in the development of postmenopausal osteoporosis in our black community. Exercise, genetic inheritance of bone mineral content, body mass, and similar factors are probably far more important than calcium intake in determining the peak bone mass.

Dr. Bonjour: With respect to the low prevalence of osteoporosis in the black community and the consequence of a low calcium supply, the source of proteins may be an important determinant. Experimentally, it has been shown that soy protein as compared to casein induced less age related bone loss (3). Thus, for the same intestinal absorption, the body retention of calcium could be more positive according to the prevailing type of alimentary protein.

Dr. Pettifor: I agree with you.

Dr. Delvin: Your patients have hypocalcemia with high 1,25(OH)_2D and iPTH levels. Besides this biochemical hyperparathyroidism do they have signs of functional hyperparathyroidism?

Dr. Pettifor: By histomorphometry, there is evidence of increased bone resorption. Radiologically, we do not see subperiosteal erosions on the phalanges, but there is loss of the lamina dura around the teeth. Because of the lack of a phosphaturic effect, following PTH infusion, there may well be down regulation of the renal PTH receptors. This defect corrects itself, once serum calcium values become normal and the bone disease has improved. It is very much like the pseudohypoparathyroidism that Stanbury described in longstanding vitamin D deficiency in Asian adolescents (4).
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