

# Nutritional rickets: deficiency of vitamin D, calcium, or both?<sup>1-4</sup>

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## ABSTRACT

Nutritional rickets remains a public health problem in many countries, despite dramatic declines in the prevalence of the condition in many developed countries since the discoveries of vitamin D and the role of ultraviolet light in prevention. The disease continues to be problematic among infants in many communities, especially among infants who are exclusively breast-fed, infants and children of dark-skinned immigrants living in temperate climates, infants and their mothers in the Middle East, and infants and children in many developing countries in the tropics and subtropics, such as Nigeria, Ethiopia, Yemen, and Bangladesh. Vitamin D deficiency remains the major cause of rickets among young infants in most countries, because breast milk is low in vitamin D and its metabolites and social and religious customs and/or climatic conditions often prevent adequate ultraviolet light exposure. In sunny countries such as Nigeria, South Africa, and Bangladesh, such factors do not apply. Studies indicated that the disease occurs among older toddlers and children and probably is attributable to low dietary calcium intakes, which are characteristic of cereal-based diets with limited variety and little access to dairy products. In such situations, calcium supplements alone result in healing of the bone disease. Studies among Asian children and African American toddlers suggested that low dietary calcium intakes result in increased catabolism of vitamin D and the development of vitamin D deficiency and rickets. Dietary calcium deficiency and vitamin D deficiency represent 2 ends of the spectrum for the pathogenesis of nutritional rickets, with a combination of the 2 in the middle. *Am J Clin Nutr* 2004;80(suppl):1725S-9S.

**KEY WORDS** Nutritional rickets, vitamin D deficiency, dietary calcium deficiency, infants, children, pathogenesis

## INTRODUCTION

At the turn of the 20th century, nutritional rickets was epidemic among infants and young children in many areas of Asia, North America, and northern Europe. With the discovery of the role of ultraviolet light (sunlight) in curing vitamin D<sub>3</sub> deficiency rickets and the isolation of vitamin D ~80 y ago (1), effective inexpensive methods of preventing and treating nutritional rickets became available. Despite these developments, rickets remains a major public health problem in many developing countries (2-6), and its prevalence is reported to be increasing in several developed countries (7-12).

Until recently, it was generally accepted that nutritional rickets is caused by vitamin D deficiency alone and that dietary calcium deficiency might exacerbate the disease in the presence of vitamin D deficiency but by itself is not responsible for nutritional rickets (13). In the past 25 y, consensus regarding the

pathogenesis of nutritional rickets has shifted as studies have suggested that, among older children in developing countries in particular, dietary calcium deficiency plays a pivotal role. In this article, I review the evidence that nutritional rickets is caused by both vitamin D deficiency and dietary calcium deficiency and that the 2 combine to exacerbate the development of the disease among children.

## VITAMIN D DEFICIENCY

The peak age at which rickets is most prevalent is 3-18 mo (14, 15). Factors that have been shown to be important in the pathogenesis of rickets at this age include exclusive breast-feeding, maternal vitamin D deficiency, living in temperate climates, lack of sunlight exposure, and darkly pigmented skin. In the Middle East and other more-tropical climates, social and religious customs that prevent sunlight exposure appear to be important (15-17).

It is well recognized that breast milk normally contains insufficient concentrations of vitamin D or its metabolites (estimated as 20-60 IU/L) (18, 19) to ensure the normal vitamin D status of the nursing infant. Relatively high-dose maternal vitamin D supplements (2000 IU/d) are needed to increase maternal breast milk concentrations to levels that maintain the vitamin D status of the breast-fed infant (20). Specker et al (21) elegantly demonstrated that the vitamin D status of breast-fed infants is correlated with sunlight exposure rather than the vitamin D content of maternal breast milk.

Breast-fed infants are generally protected from vitamin D deficiency rickets during the first few months of life, because vitamin D metabolites, especially 25-hydroxyvitamin D [25(OH)D], do cross the placenta, such that neonatal 25(OH)D concentrations are approximately two-thirds of maternal values (22). It is estimated that the half-life of serum 25(OH)D is ~3 wk; therefore, even if neonates do not receive an exogenous supply of vitamin D during the first weeks of life, 25(OH)D concentrations should decrease to values associated with vitamin D deficiency

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only toward the end of the second month, provided that the maternal vitamin D status is adequate during pregnancy.

Several studies from the Middle East, North America, and northern Europe have highlighted the prevalence of low circulating concentrations of 25(OH)D during pregnancy (23–27). Factors found to be important include increased skin pigmentation, immigration from non-European countries to countries of high latitude, limited skin exposure as a result of religious and social customs, and vegetarian diets. Congenital rickets has been observed in such situations, although its occurrence is rare (28–30), and neonatal hypocalcemia is more frequent among neonates born to mothers with low 25(OH)D concentrations than among those born to mothers with normal vitamin D status (31).

The development of clinical vitamin D deficiency rickets is dependent not only on the severity of the vitamin D deficiency [circulating concentrations of 25(OH)D] but also on the duration of the deficiency, on the rate of the child's growth (which influences calcium demands), and on the dietary calcium content. Studies from northern Europe and North and South America have highlighted the marked seasonal fluctuations in serum 25(OH)D concentrations, with values being lowest in late winter and highest in late summer or early autumn (32–35). Several studies have documented spontaneous healing of radiologically evident rickets during the summer months (36) and seasonal fluctuations in serum parathyroid hormone (PTH) (37) and 1,25-dihydroxyvitamin D [ $1,25(\text{OH})_2\text{D}$ ] (38) concentrations in association with changes in serum 25(OH)D concentrations. Clinical vitamin D deficiency rickets also is well recognized to have seasonal fluctuations in prevalence, with the highest prevalence being in spring and early summer (14).

The seasonal changes in 25(OH)D concentrations, the lag period between the decrease in 25(OH)D concentrations and the development of biochemical, radiologic, or clinical rickets, and the influence of diet on the development of rickets have made it difficult to define a clear division between vitamin D deficiency and sufficiency on the basis of serum 25(OH)D concentrations. Nevertheless, there is widespread agreement in the pediatric literature that vitamin D deficiency should be defined as 25(OH)D concentrations of  $< 10\text{--}12\text{ ng/mL}$  (39, 40). The value varies, however, depending on the assay method used to determine 25(OH)D concentrations (41). In the past decade, considerable discussion has taken place regarding the definition of vitamin D sufficiency and what should be considered the normal range for serum 25(OH)D concentrations (42, 43). In population studies, the term vitamin D insufficiency has been used to indicate serum 25(OH)D concentrations between those associated with vitamin D deficiency and those considered to be optimal. Vitamin D insufficiency is associated with mildly elevated PTH concentrations, although values remain within the normal reference range (44). Few studies have been conducted among infants and children to determine whether the concept of vitamin D insufficiency is valid. Among young infants, it appears that PTH concentrations increase only when 25(OH)D concentrations are in the vitamin D<sub>3</sub>-deficient range (31). Studies with adolescents found that PTH concentrations increased when 25(OH)D concentrations decreased below  $12\text{--}16\text{ ng/mL}$  (45, 46), whereas Docio et al (47) suggested that perturbations in calcium homeostasis occur among prepubertal children when 25(OH)D concentrations are between 12 and 20 ng/mL. Therefore, it appears that, if the concept of vitamin D insufficiency is valid for children, values are very close to the upper limit of what is

defined as vitamin D deficiency, a pattern that is very different from that reported for adults (48).

### DIETARY CALCIUM DEFICIENCY

Among adult subjects, low dietary calcium intakes are thought to produce osteoporosis, rather than osteomalacia, through secondary hyperparathyroidism and increased bone turnover. A similar view was held to be true for children until the 1970s, when several case reports of rickets among infants attributable to extremely low dietary calcium intakes in the presence of adequate vitamin D intakes were published (49–51). In the same decade, we in South Africa suggested that rickets among rural children was attributable to low dietary calcium intakes and not vitamin D<sub>3</sub> deficiency. These children presented with active rickets at ages of 4–16 y (52). Their diets were characteristically devoid of dairy products and high in phytate. Their calcium intakes were estimated to be  $\sim 200\text{ mg/d}$  and were significantly lower than those of age-matched control subjects living in the same community (53). Vitamin D deficiency was considered an unlikely cause, because the children spent a considerable part of the day playing outside in the sunshine; this was confirmed by normal serum 25(OH)D concentrations and elevated  $1,25(\text{OH})_2\text{D}$  concentrations. Furthermore, the radiologic, histologic, and biochemical features of rickets improved with calcium supplements alone (54, 55).

Since then, several reports from Nigeria highlighted the role of low dietary calcium intakes in the pathogenesis of rickets among children in that region (5, 56–58), although vitamin D deficiency was also proposed (59, 60). A recent study from Bangladesh suggested that rickets among children outside the infant age range in the Cox's Bazaar District might be related to low dietary calcium intakes (61). In India, a study of the response of children with rickets to either calcium or calcium and vitamin D suggested that low dietary calcium intakes are responsible for rickets among younger children, whereas vitamin D deficiency is mainly responsible among adolescents (62). Unlike the children in South Africa, the Nigerian children tended to be younger, with a mean age of presentation of  $\sim 4\text{ y}$ , and to live in urban environments. Although their calcium intakes ( $200\text{ mg/d}$ ) were similar to those of subjects in South Africa, they were not different from those of age-matched control subjects (63).

In a randomized controlled trial of 123 children with active rickets, Thacher et al (64) showed that calcium supplements alone or in combination with vitamin D were equally effective in treating the disease and were more effective than vitamin D alone. Not only were 25(OH)D concentrations normal for most children at presentation but also, among those treated with calcium alone, the concentrations increased little during the 6 mo of treatment, from a mean of  $16\text{ ng/mL}$  to  $21\text{ ng/mL}$ ; in the vitamin D-treated group, which responded less well, concentrations increased from  $14\text{ ng/mL}$  to  $35\text{ ng/mL}$  during the same period. The findings highlight the importance of low dietary calcium intakes in the pathogenesis of the disease, but the inability to show differences in calcium intakes between patients and control subjects raises the possibility that the pathogenesis may be more complex than simple dietary calcium deficiency.

A major characteristic of the diets in both South Africa and Nigeria is the high content of unrefined cereal, which raises the possibility of dietary constituents such as phytates impairing calcium absorption. In the Nigerian studies, it was not possible to

quantify the phytate contents of the diets; therefore, it is not known whether there were differences between subject and control diets in this respect. Studies are currently underway to assess intestinal calcium absorption among children with and without rickets and to determine the effects of phytate on absorption.

Another intriguing finding in both the South African and Nigerian studies is the higher prevalence of a history of bone deformities and clinical rickets among family members and first-degree relatives of children with active rickets (63). Although it is possible that similar environmental and socioeconomic factors among family members might be responsible for the disease, this finding does raise the possibility that genetic factors might also play a role. An attractive hypothesis is that children who develop rickets are less able to adapt to low-calcium diets than are children who do not develop the disease. To date, no evidence has been found; serum  $1,25(\text{OH})_2\text{D}$  concentrations among untreated patients were higher than those among age-matched control subjects (63), and intestinal calcium absorption was similarly elevated in the 2 groups. In a study of vitamin  $\text{D}_3$  receptor polymorphisms, children with rickets exhibited a higher frequency of the *F* allele than did nonrachitic subjects in the community, although the significance of this finding is unclear (65).

Therefore, in developing countries where calcium intakes are characteristically low and the population relies heavily on cereal-based staples, with few or no dairy products, dietary calcium deficiency appears to be the major cause of rickets among children outside the infant age group. An intriguing study by DeLucia et al (12) suggested that low dietary calcium intakes might also be responsible for rickets among mainly African American toddlers in the New Haven, Connecticut, area of the United States. Three-quarters of the children had  $25(\text{OH})\text{D}$  concentrations well within the normal range, and most had been breast-fed for prolonged periods and then weaned onto a diet low in dairy products. The authors concluded that nutritional calcium deficiency might be a feature not only in developing countries but also in North America.

#### RELATIONSHIP BETWEEN VITAMIN D AND DIETARY CALCIUM INTAKES

The role of low dietary calcium intakes in exacerbating the development of vitamin D deficiency rickets has been known for many years. More than 80 years ago, Mellanby (66) showed the deleterious effects of low dietary calcium intakes on the development of rickets among vitamin D-deficient animals. More recently, we demonstrated a similar effect with the addition of unrefined maize to a vitamin D-deficient diet for baboons (67). However, the mechanisms were not known.


Among humans, one of the most well-studied communities with a high prevalence of rickets has been the Asian community in the United Kingdom. Since the early 1960s, numerous studies have highlighted the predisposition of this community to rickets and osteomalacia (68–73). Several pathogenetic mechanisms have been proposed, including lack of sunlight exposure, increased skin pigmentation, lack of dietary vitamin D intake, genetic predisposition, low-calcium diets, and high phytate contents in the diet. It was not until the seminal work of Clements (74), however, that a plausible synthesis of the various factors could be developed. In a rat model, it was possible to demonstrate that elevation of  $1,25(\text{OH})_2\text{D}$  concentrations through feeding of

the rats with low-calcium or high-phytate diets resulted in increased catabolism of  $25(\text{OH})\text{D}$  to inactive metabolites and increased excretion of these products in the stool, with resultant reduction of  $25(\text{OH})\text{D}$  concentrations (75). Similarly, infusion of  $1,25(\text{OH})_2\text{D}$  led to a reduction in the serum  $25(\text{OH})\text{D}$  half-life and a 7-fold increase in  $24,25$ -dihydroxyvitamin D production by the kidney (76). In human studies, the half-life of  $25(\text{OH})\text{D}$  was reduced by nearly 40% among patients with partial gastrectomies, secondary hyperparathyroidism, and elevated  $1,25(\text{OH})_2\text{D}$  concentrations (77), and similar findings were noted among patients with intestinal malabsorption (78) and subjects consuming high-fiber diets (79). The administration of  $1,25(\text{OH})_2\text{D}$  to normal subjects was shown to reduce the circulating  $25(\text{OH})\text{D}$  half-life and to induce vitamin D deficiency among those with relatively low  $25(\text{OH})\text{D}$  concentrations (80).

Therefore, it was proposed by Clements (74) that the pathogenesis of rickets in the Asian community in the United Kingdom is attributable to the high-cereal, low-calcium diet, which induces mild hyperparathyroidism and elevation of  $1,25(\text{OH})_2\text{D}$  concentrations, with a resultant reduction in vitamin D status. In situations in which the vitamin D status is marginal, because of reduced sun exposure, increased skin pigmentation, and/or limited dietary vitamin D intake, the reduction in  $25(\text{OH})\text{D}$  half-life is sufficient to produce vitamin D deficiency and rickets. It follows that rickets in the Asian community can be treated either by increasing the vitamin D intake or by reducing the phytate content of the diet. Both of these treatments have been found to be effective (69, 81).

The role of low dietary calcium intakes in the pathogenesis of vitamin D deficiency is probably greater than originally recognized. This has been proposed as a mechanism for rickets among young children in India (62) and among toddlers in the United States (12) and probably accounts for the lower  $25(\text{OH})\text{D}$  concentrations among rachitic subjects, compared with control subjects, in Nigeria (64).

#### CONCLUSIONS

From this discussion, it is clear that the pathogenesis of nutritional rickets, a disease once thought to be attributable solely to vitamin D deficiency, should be viewed as having a spectrum of mechanisms, with classic vitamin D deficiency, as observed among breast-fed infants, at one end and dietary calcium deficiency, as typified by the children studied in Nigeria and South Africa, at the other. Between these 2 extremes, it is likely that vitamin D insufficiency and low dietary calcium or high phytate intakes combine to induce vitamin D deficiency and rickets, which may be the most frequent cause of rickets globally. 

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