Nutritional rickets: deficiency of vitamin D, calcium, or both? 1–4

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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, 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 deficiency rickets and the isolation of vitamin D [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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concentrations increase only when 25(OH)D concentrations are insufficient is valid. Among young infants, it appears that PTH and children to determine whether the concept of vitamin D

departments. Although their calcium intakes (200 mg/d) were similar to those of subjects in South Africa, they were not different from those of age-matched control subjects living in the same environment. In South Africa, the Nigerians tended to be younger, with a mean age of presentation of 4–6 y, and to live in urban environments. Although their calcium intakes (200 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 ng/mL to 21 ng/mL; in the vitamin D-treated group, which responded less well, concentrations increased from 14 ng/mL to 35 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
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) that the elevation of 1,25(OH)2D concentrations through feeding of the rats with low-calcium or high-phytate diets resulted in increased catabolism of 25(OH)D to inactive metabolites and increased excretion of these products in the stool, with resultant reduction of 25(OH)D concentrations (75). Similarly, infusion of 1,25(OH)D led to a reduction in the serum 25(OH)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(OH)D was reduced by nearly 40% among patients with partial gastrectomies, secondary hyperparathyroidism, and elevated 1,25(OH)2D 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(OH)D to normal subjects was shown to reduce the circulating 25(OH)D half-life and to induce vitamin D deficiency among those with relatively low 25(OH)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(OH)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(OH)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(OH)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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REFERENCES


