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Vitamin D and calcium nutrition in children in developing countries

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The past few decades have seen renewed interest in calcium and vitamin D nutrition, particularly concerning their roles in the prevention of osteoporosis and fractures in the elderly and in preventing rickets in children. Further, more recently, attention has also been focused on the role of vitamin D in reducing the long-term risks of contracting a number of chronic diseases, such as asthma, diabetes, and hypertension, schizophrenia, infectious diseases such as tuberculosis, and cancers of the prostate, breast and colon [1].

The classic physiological role of vitamin D is its central action in controlling intestinal calcium absorption and to a lesser extent bone resorption through its active metabolite, 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D). Thus, vitamin D together with parathyroid hormone plays a critical role in maintaining normal calcium homeostasis. Vitamin D exists in two forms, vitamin D_3 (cholecalciferol), which is formed through the action of ultraviolet (UV) irradiation (sunlight) on 7-dehydrocholesterol present in the dermis, and vitamin D_2 (ergocalciferol) which is formed in plants from the UV irradiation of ergosterol. Although, there is some controversy surrounding the equivalence of their activity, it is generally accepted that the two forms of vitamin D have similar actions and are equally effective in treating deficiencies of vitamin D.

In general, most populations are dependent on the dermal synthesis of vitamin D through the action of sunlight to ensure a supply of vitamin D that is adequate to maintain vitamin D sufficiency. Although, a number of foods in developed countries are fortified with vitamin D, naturally occurring foods are generally poor sources of vitamin D with the exception of oily fish. Thus, adults and children living in developing countries are largely dependent on sunlight exposure to ensure vitamin D sufficiency. Factors influencing the amount of vitamin D formed in the skin include: the latitude of the country (almost no UV light reaches the earth during the winter months at latitudes above 37°N or S), the degree of atmospheric pollution, cloud cover, the extent of the skin covered by clothing, the degree of melanin pigmentation in the skin, and the duration of exposure to UV irradiation. A number of these factors play important roles in the pathogenesis of vitamin D deficiency, which is present in the populations of developing countries despite the fact that many of these countries lie within the tropics and subtropics and have abundant sunshine [2].

Although, there is relatively little population data on the prevalence of nutritional rickets or vitamin D deficiency in developing countries, studies do suggest that vitamin D deficiency is common in countries and regions such as the Middle East, North India, China, Ethiopia, Yemen and Turkey [3]. In children in developing countries, vitamin D deficiency appears to have a bimodal distribution during infancy and adolescence, the latter being particularly applicable to females. Studies from a number of countries have also highlighted the high prevalence of vitamin D deficiency among pregnant women, with figures varying from 25% in the United Arab Emirates, to 80% in Iran, and 42% in north India [4].

Vitamin D deficiency during pregnancy plays an important role in exacerbating the prevalence and severity of rickets in the offspring during infancy. The foetus obtains its vitamin D through the placental transfer of 25-hydroxyvitamin D (25-OHD) from the mother; thus the vitamin D status of the mother has a direct influence on the vitamin D status of the foetus and neonate, with neonatal levels of 25-OHD being approximately two-thirds those of the mother. 25-hydroxyvitamin D has a half-life of approximately 3 weeks; thus low concentrations at birth as a result of maternal deficiency will rapidly lead to vitamin D deficiency in the neonate or young infant unless the newborn is provided with another source of vitamin D. In a study conducted during winter in South Africa, the 25-OHD concentrations of breastfed infants dropped from a mean of 8.9 ng/ml at birth to 1.1 ng/ml at 6 weeks of age, thereby emphasising the importance of the need

CONTENTS

for early vitamin D supplementation in infants who are born to vitamin D-deficient mothers [5]. Vitamin D deficiency in the mother is also associated with an increased prevalence of neonatal hypocalcaemia and, as a rare occurrence, with congenital rickets. There is also suggestive evidence that intrauterine vitamin D deficiency results in poorer intrauterine growth and possibly poorer bone mass in later childhood.

Factors that might be responsible for high prevalence of vitamin D deficiency during pregnancy in many developing countries include the degree of skin pigmentation, extensive skin coverage by clothing, and social beliefs and customs that result in pregnant women not spending time out of doors. In communities in which vitamin D deficiency during pregnancy is common, it would be prudent to consider the routine supplementation of all pregnant women with vitamin D (400-800 IU/d).

Being breastfed (as opposed to formula-fed) is also a major risk factor for the development of vitamin D deficiency and rickets during infancy. Breast milk normally contains only small amounts of vitamin D and its metabolites, estimated to be equivalent to between 25 and 70 IU vitamin D per litre of breast-milk. It is thus apparent that breast milk alone is insufficient to maintain a normal vitamin D status in the infant, and the breastfed infant requires an additional source of vitamin D, such as sun exposure or vitamin D supplements. In a study looking at risk factors for the development of rickets in infants in the United Arab Emirates, the following were found to be significant: being breastfed, not receiving vitamin D supplements, and the lack of sunshine exposure[6]. The simplest and most cost-effective way to ensure that infants maintain an adequate vitamin D status would be to encourage limited amounts of sunshine exposure daily. However, there are concerns about the association between sunshine exposure and skin malignancies in Caucasian populations. It is of interest that in China and in other countries in Asia, it was customary to oil the skin of the infant and to massage the baby in the sun for a while. However, if sunshine exposure is not possible, then vitamin D supplementation of the breastfed infant (200-400 IU/d) until the infant is walking is recommended. A few studies have investigated the effect of maternal supplementation on the vitamin D content of breast milk, and have shown that maternal supplementation at a dose of 6400 IU/d results in a dramatic increase (approximately 10-fold) in the anti-rachitic activity of breast milk. Furthermore, at this dose of supplementation to the mothers, the breastfed infants maintained and improved their vitamin D status over 6 months[7]. However, it should be noted that doses this high are still experimental and closely monitored, and should not be considered appropriate or recommended at this stage.

One cannot discuss vitamin D requirements in children without discussing those for dietary calcium. In developed countries the recommended calcium intakes for pubertal children range from 800-1300 mg/d [8]; yet the FAO has estimated the per capita calcium intake in developing countries to average 344 mg/d, a long way below the level suggested to be required for normal bone growth and development in developed countries. Despite this obvious discrepancy between the ideal suggested intake and that which is being consumed in developing countries, is there any evidence that children in developing countries are being disadvantaged by not meeting the recommended requirements?

Some thirty years ago, we were the first group of investigators to suggest that low dietary calcium intakes might be responsible for the development of rickets in otherwise healthy children outside the infant age range[9]. We investigated a series of rural children in South Africa, who presented with lower limb deformities and biochemical, radiological and histological evidence of rickets. Dietary calcium intakes were estimated to be approximately 200 mg/d, due largely to a lack of consumption of dairy products. Unlike children with vitamin D deficiency rickets, these children had normal 25-OHD and consistently elevated 1,25-$(OH)_2$D concentrations. Furthermore the bone disease healed biochemically and radiographically on calcium supplements alone. Since then studies in Bangladesh[10] and Nigeria[11] have confirmed the importance of low dietary calcium intakes in the pathogenesis of rickets in children who characteristically are older than those who are typically at risk of vitamin D deficiency. Several studies in India have also emphasised the role of dietary calcium intakes in children who develop rickets[12].

In both Nigeria and Bangladesh, the calcium intakes of affected children have been estimated to be very similar (≈200 mg/d) to those recorded in rachitic children in South Africa. Unlike the South African study, however, where the affected children had significantly lower calcium intakes than control children living in the same community, no difference in calcium intakes was found between the affected and control children in Nigeria. As a consequence of the latter finding, we have proposed that, although low dietary calcium intakes are central to the pathogenesis of rickets in these children, other factors might contribute to or exacerbate the onset and severity of the disease. Several factors have been considered, including dietary constituents such as phytates or oxalates that could impair calcium absorption, and an inability of affected children to adapt appropriately to stress of the low dietary calcium intakes possibly because of an inability to increase intestinal calcium absorption. We have been unable to document any differences in the oxalate or phytate contents of the diets of affected and control children, but the phytate content is high, given the high content of cereal staples in the diet. We have investigated further the possibility of an impaired response to low dietary calcium intakes, which could result from an inability to optimise 1,25-$(OH)_2$D concentrations or from the intestinal mucosa being less responsive to the circulating levels of the active metabolite of vitamin D.

Using stable isotopes of calcium, the intestinal calcium absorption levels of untreated children with active rickets were compared with those of age-matched controls. In both groups, the fractional calcium absorption was good (>60%) and was unrelated to 25-OHD concentrations[13]. Of interest was the finding of differences in vitamin D metabolite concentrations between affected and control children. 25-hydroxyvitamin D concentrations (13 vs 21 ng/ml) were lower and 1,25-$(OH)_2$D concentrations (134 vs 115 pg/ml) higher in the affected children than in the controls. We have ascribed the lower 25-OHD concentrations in affected children to increased catabolism of vitamin D/25-OHD through the stimulation of 24-hydroxylase by the elevated 1,25-$(OH)_2$D concentrations[14]. Support for this

hypothesis is provided by the finding of a progressive increase in 25-OHD concentrations over a 6-month period in those affected children who were treated with dietary calcium supplements alone. During this period 1,25-$(OH)_2$D concentrations fell, as would be expected.

We have also investigated the response in untreated children to a single oral bolus of vitamin D_2 (50,000 IU)[15]. As expected, serum concentrations of 25-OHD rose to peak at day 3 and then fell slowly over the next 10 days to approach initial values. What surprised us, however, was the change in 1,25-$(OH)_2$D concentrations associated with the change in 25-OHD values. The pattern of change in 1,25-$(OH)_2$D concentrations was similar to that seen with 25-OHD values rising to peak at day 3 and then falling to initial values at day 14. At days 0, 3 and 7 there were significant associations between 25-OHD and 1,25-$(OH)_2$D concentrations. Even though 1,25-$(OH)_2$D concentrations were elevated at time 0, they nearly doubled from a mean of 184 pg/ml to 349 pg/ml on day 3, suggesting that, in the face of low dietary calcium intakes, 25-OHD values were not adequate to optimize serum levels of the active metabolite of vitamin D, 1,25-$(OH)_2$D. In other words, the children presenting with active dietary calcium deficiency rickets had relative vitamin D insufficiency. This probably explains why we found that children who were treated on vitamin D alone for dietary calcium deficiency rickets, did partially respond to the therapy, but not as well as children treated on calcium supplements alone[11].

These studies have allowed us to conclude that nutritional rickets does not have a single aetiology. Both vitamin D deficiency and dietary calcium deficiency alone can result in rickets but it is likely that the majority of patients with nutritional rickets have varying degrees of combined vitamin D insufficiency/deficiency and low dietary calcium intakes. Furthermore, our results suggest that the calcium content of the diet influences vitamin D requirements, with low intakes being associated with an increased catabolism of 25-OHD and thus, an increased requirement for vitamin D to maintain an acceptable vitamin D status. It is also likely that 25-OHD concentrations need to be higher to increase 1,25-$(OH)_2$D concentrations sufficiently to maximize intestinal calcium absorption in the face of low dietary calcium contents.

Thus, in conclusion, very low dietary calcium intakes do have deleterious effects on bone homeostasis, but it appears that the vast majority of children living in developing countries show no ill effects from dietary calcium intakes substantially below those recommended in some developed countries. It is apparent that considerably more research needs to be done to assess the requirements of both vitamin D and calcium in children in developing countries, but practitioners should be cautious about accepting recommendations developed in industrialised nations for children who have very different dietary patterns and lifestyles.

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FOUNDATION NEWS

At the request of Health Mission and Deptt of Social Welfare of NCT Delhi , Nutrition Foundation of India has undertaken a two day skill development training programme in February and March 2009. About 250 CDPOs, ICDS supervisors and ANMS are being trained under this programme with the objective of improving their skills

- in weighing and detection of undernutrition using the WHO 2006 growth standards .
- in providing appropriate nutrition education to pregnant women and mothers of preschool children for prevention and management of undernutrition

NUTRITION NEWS

The 41st Annual Conference of the Nutrition Society of India will be held in November 2009 at National Institute of Nutrition, Hyderabad. The details of the conference can be downloaded from the website http://www.nutritionsocietyindia.org.