

Review Article

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Vitamin D &/or calcium deficiency rickets in infants & children: a global perspective

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It was only in the early part of the 20th century with the discovery of vitamin D and of the role that ultraviolet light irradiation plays in vitamin D formation that rational and appropriate therapy became available and rickets was all but eradicated in a number of developed countries. Since then, there has been a resurgence of the disease in many countries such as in Europe and the USA probably due to an increase in the prevalence of breast feeding, the immigration of dark skinned families to countries of high latitude, and the avoidance of direct sunlight because of the risk of the development of skin cancers. The disease is also widely recognised in many developing countries, including some situated in subtropical regions. Studies have led to the realization that nutritional rickets may be caused by either vitamin D or calcium deficiency, but in the majority of situations variable combinations of both probably play a role. Although low dietary calcium intakes appear to be central to the pathogenesis of rickets in Nigeria, genetic and/or other environmental factors are likely to contribute. But to date no single factor has been isolated as contributing significantly. The results of a recently conducted study suggest that in situation of low dietary calcium intakes vitamin D requirements may be higher than normal, possibly predisposing those children with vitamin D levels in the low normal range to rickets. If this is so, it would indicate that the currently accepted normal range for vitamin D sufficiency would need to be adjusted depending on dietary calcium intakes. Yet we are still unclear as to the factors which predispose some children to the disease.

Key words Children - low calcium intake - nutritional rickets - vitamin D deficiency

Introduction

Nutritional rickets is gaining the attention of public health professionals and individual clinicians worldwide as the disease remains an endemic problem in many developing countries and has re-emerged in a number of developed countries, where it was thought that the disease had been almost eradicated¹. Interest has been heightened by the considerable discussion currently taking place about what should be the ideal or appropriate circulating levels of 25-hydroxyvitamin D

[25(OH)D] to reflect vitamin D sufficiency², as besides the classical effects of vitamin D on calcium and bone metabolism, attention is being paid to its possible roles in the prevention of certain cancers, neurological disorders, tuberculosis, insulin resistance and hypertension³.

Over the past decade, dietary calcium requirements have also come under the spotlight with North America increasing the recommended levels especially for adolescents and adult women⁴, yet many populations

in the developing world have habitual calcium intakes of 25-33 per cent of these recommended intakes. Thus, the question that needs to be asked is how relevant are these recommendations for populations in other parts of the world who are likely to have different lifestyles and genetic make-up.

This paper provides a global perspective of the prevalence of nutritional rickets and will discuss the pathogenesis of the disease as it relates to our increasing understanding of calcium and vitamin D homeostasis.

The prevalence of nutritional rickets

In North America and many countries in Northern Europe, nutritional rickets was almost eradicated in the 20th century following the discovery of vitamin D and the role that sunlight and dietary supplementation or food fortification with vitamin D play in its prevention. Since the 1960s reports of rickets from a number of countries in Europe and regions in North America have focused attention on ethnic groups and communities at risk from vitamin D deficiency. In the USA, nutritional rickets is almost exclusively confined to breastfed African American infants⁵, while in Europe it has been reported extensively in the children of recent immigrants from India, Pakistan and Bangladesh⁶, north Africa⁷ and the Middle East. A similar pattern is reported from Australia⁸. The common features in most of these situations are increased skin pigmentation and limited sun exposure due to clothing coverage in the mother, and prolonged breast feeding of the affected infant. A number of recent studies have highlighted that vitamin D deficiency is common during pregnancy in these at-risk groups, increasing the risk for and severity of vitamin D deficiency in their offspring^{9,10}, which is further aggravated by the breast-milk in such circumstances being almost devoid of vitamin D. Extensive studies in the United Kingdom amongst immigrants from the Indian subcontinent have also documented an increased risk of rickets among their older children and adolescents¹¹. Although vitamin D deficiency is probably the final common path in the development of the disease in this group, there is evidence that low dietary calcium and high phytate intakes might play a major role in the pathogenesis. This aspect will be discussed later in the paper.

In the Middle East, vitamin D deficiency and rickets continues to be a public health problem despite abundant all year sunshine in many of the regions. Infants, adolescent females and pregnant women are particularly at risk^{12,13}. Social and religious customs which prevent

adequate sunlight exposure of pregnant women and their adolescent daughters are major factors in predisposing the children and young infants to vitamin D deficiency and rickets¹⁴. Low dietary calcium intakes in a smaller percentage of children are also reported to play a role.

Despite a large part of Africa lying within the tropics and subtropics, vitamin D deficiency rickets due to restricted sunlight exposure is still seen in infants and young children in many African countries, such as Ethiopia, Egypt, Sudan, Algeria and Libya¹. Social and religious customs which prevent adequate sunlight exposure probably play a major role, but rickets has also been associated with severe undernutrition and poverty¹⁵ and is 13-fold more common in children with severe pneumonia than controls¹⁶. Rickets has also been described in older toddlers and children, in whom a lack of sunlight exposure appeared to be an unlikely factor. Originally described in children between the ages of 4-16 yr in South Africa¹⁷, extensive investigations have been conducted more recently on similar but younger children in Nigeria¹⁸. In both of these groups, habitually low dietary calcium intakes have been proposed as being the primary cause of the disease, as in the majority of children 25(OH)D concentrations were above 25 nmol/l, which is considered by many researchers in the field to be the upper limit of vitamin D deficiency associated with classical vitamin D deficiency rickets. Furthermore, dietary calcium supplementation leads to a speedy and complete correction of the biochemical and radiological abnormalities^{19,20}, and in one randomized controlled study was more effective than vitamin D in curing the disease¹⁹.

In the Indian subcontinent, rickets in infants, older children and adolescents has been described from India, Bangladesh and Pakistan. A number of factors have been indicated as being responsible for a high prevalence of vitamin D deficiency and rickets, including religious customs²¹, atmospheric pollution²², increased skin pigmentation, vegetarian diets²³, and maternal vitamin D deficiency²⁴. Further, low dietary calcium and high phytate diets are also considered to play a major role in some communities. In one study it was suggested that low dietary calcium intakes were important as a factor in young children while in adolescent children vitamin D deficiency was mainly responsible²⁵. Endemic fluorosis in children may also manifest with severe rachitic-like bone deformities and radiographic features of rickets at the growth plates²⁶. Some 18 of the 33 States in India have problems with excessive fluoride concentration in ground water²⁶. It

is suggested that in the face of low dietary intakes, the increased calcium requirements associated with the increased mineralization of fluorotic bone may induce reduce 25(OH)D concentrations which together with the low calcium intakes induce rickets²⁷.

Recently attention has been focused on the apparently high prevalence of rickets in children living in the south-eastern coastal region of Bangladesh. Reports suggest that the disease has only been prevalent in the last two decades. Studies provide evidence that the pathogenesis is related to dietary calcium deficiency^{28,29}, possibly due to the introduction of irrigation which has been associated with an increase in the size of the annual rice harvest and a reduction in dietary variation.

In other parts of Asia, such as the northern parts of China (including Tibet), Mongolia and Afghanistan rickets appears to be mainly due to vitamin D deficiency associated with the high latitude, cold winters and limited skin exposure¹.

A unifying concept of the pathogenesis of rickets

Vitamin D deficiency is clearly the major cause of nutritional rickets in countries lying at high latitudes

both north and south of the equator. It has been shown convincingly that vitamin D production in the skin is negligible at latitudes greater than 35° during November through March in the northern hemisphere³⁰. Similar findings have been reported from Cape Town, South Africa (32°S) from May through August³¹. The increased risk of vitamin D deficiency in darker skinned individuals such as African American and South Asian people living in these countries is due in the main part to decreased dermal synthesis of vitamin D as a result of the absorption of UV radiation by the increased melanin pigmentation³². However of interest is one study, which was conducted in the north-eastern part of the USA. In that study, low dietary calcium intakes in mainly African American infants who developed rickets post weaning, were considered to play a major role as 25(OH)D concentrations were above generally accepted levels of vitamin D deficiency in many of them³³ and one child had responded to increased calcium intake alone. A similar mechanism has been proposed in Indian and Pakistani children living in the UK³⁴, whose diets are typically low in calcium and high in phytate. In the majority of these south Asian children with rickets, 25(OH)D concentrations are also in the vitamin D deficient range. Studies in rats and humans

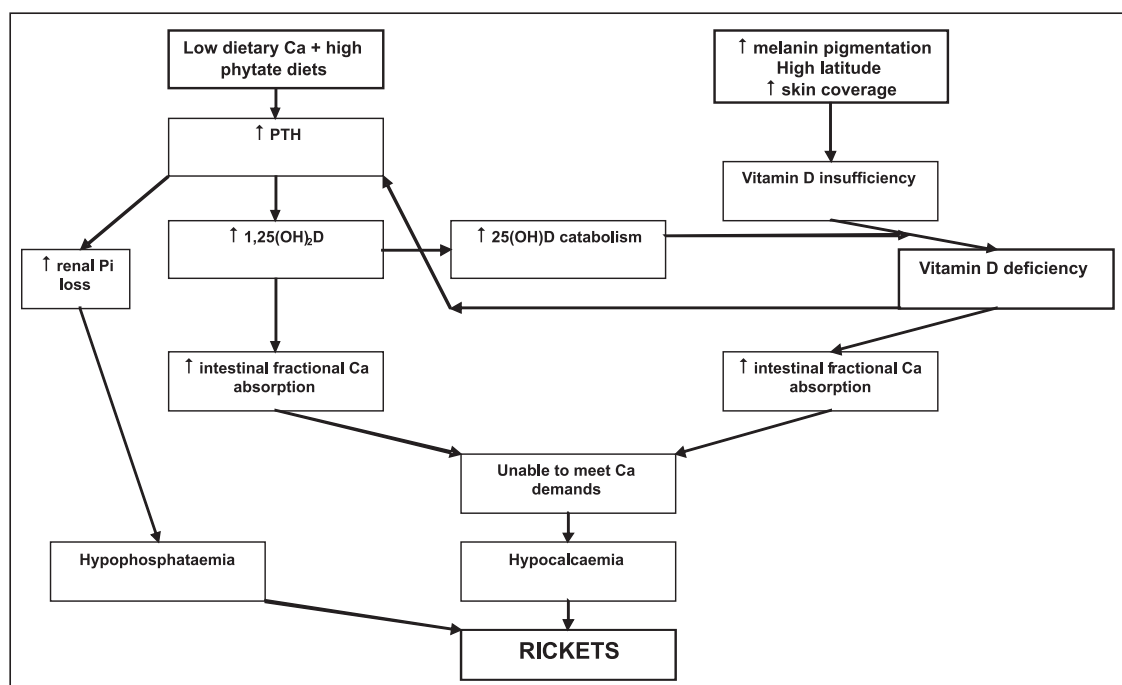


Fig. The pathogenesis of nutritional rickets. The final common path is an inability to meet the calcium needs of the growing skeleton resulting in hypocalcaemia and elevated parathyroid hormone (PTH) concentrations which in children with low dietary calcium intakes but vitamin D sufficiency increase 1,25(OH)₂D concentrations and vitamin D catabolism. If vitamin D status is poor, this may result in vitamin D deficiency compounding the effects of low dietary calcium intakes.

have shown that low dietary calcium intakes increase serum $1,25(\text{OH})_2\text{D}$ concentrations which in turn decrease the half life of $25(\text{OH})\text{D}$ probably through increasing the catabolism of $25(\text{OH})\text{D}$ ³⁵. The net effect is an increase in vitamin D requirements which, if not met, results in a reduction of $25(\text{OH})\text{D}$ concentrations into the vitamin D deficiency range⁶. Thus in these children in the UK rickets is induced by the combined effect of low dietary calcium intakes and vitamin D deficiency. Studies in this group indicate that the disease is effectively cured by increasing the vitamin D status of affected children, although the removal of the high phytate content of the diet has also been shown to be beneficial with vitamin D supplementation⁶.

In most parts of Africa the traditional diet is low in calcium and high in phytate, as is the case in many developing countries, where cereal staples are the major constituent of the diet and dairy products are expensive or unobtainable. In South Africa children and adolescents with rickets were found to have calcium intakes of between 150-250 mg/d, which were significantly lower than those of age-matched controls living in the same community³⁶. In these children calcium supplements were shown to heal the disease without altering serum $25(\text{OH})\text{D}$ concentrations. Unlike the South African situation, most studies in Nigeria have been unable to show a difference in calcium intakes between rachitic subjects and controls, however both groups had low mean intakes of approximately 200 mg/d³⁷. Despite this, the pathogenesis of the bone disease is linked to low dietary calcium intakes as it responds rapidly to calcium supplements, which are more effective than vitamin D supplementation¹⁹. Support for the role of calcium deprivation being important in the aetiology comes from the finding of higher concentrations of $1,25(\text{OH})_2\text{D}$ in affected than control children³⁷ and fractional intestinal absorption of calcium being similar to that of controls at about 60 per cent³⁸. Other possibly related factors in affected children include the finding of a higher frequency of a vitamin D receptor gene polymorphism allele (FF) in affected children³⁹ and lower breast-milk calcium concentrations in mothers of children with rickets than in mothers with unaffected children⁴⁰. Studies that are currently ongoing suggest that vitamin D requirements may be influenced by dietary calcium intakes (Thacher TD unpublished results). This concept is not surprising as low calcium intakes increase vitamin D catabolism thus increasing requirements to maintain a normal circulating concentration of $25(\text{OH})\text{D}$.

The Figure depicts a unifying concept for the pathogenesis of nutritional rickets. The final common pathway in the pathogenesis is an inability to meet the calcium needs of the growing skeleton, whether from vitamin D deficiency in the face of a good calcium intake at one of the spectrum, or from dietary calcium lack in the face of vitamin D sufficiency at the other. It is likely that a combination of vitamin D insufficiency and low dietary calcium intakes play a synergistic role in most children who develop rickets.

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