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Nutritional rickets around the world: causes and future directions

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Abstract

Introduction: Nutritional rickets has been described from at least 59 countries in the last 20 years. Its spectrum of causes differs in different regions of the world.

Methods: We conducted a systematic review of articles on nutritional rickets from various geographical regions published in the last 20 years. We extracted information about the prevalence and causes of rickets.

Results: Calcium deficiency is the major cause of rickets in Africa and some parts of tropical Asia, but is being recognised increasingly in other parts of the world. A resurgence of vitamin D deficiency has been observed in North America and Europe. Vitamin D-deficiency rickets usually presents in the 1st 18 months of life, whereas calcium deficiency typically presents after weaning and often after the 2nd year. Few studies of rickets in developing countries report values of 25(OH)D to permit distinguishing vitamin D from calcium deficiency.

Conclusions: Rickets exists along a spectrum ranging from isolated vitamin D deficiency to isolated calcium deficiency. Along the spectrum, it is likely that relative deficiencies of calcium and vitamin D interact with genetic and/or environmental factors to stimulate the development of rickets. Vitamin D supplementation alone might not prevent or treat rickets in populations with limited calcium intake.

Introduction

Nutritional rickets results from impaired bone mineralisation in children, primarily owing to inadequate calcium or phosphorus at the growth plate. Available calcium for mineralisation may be limited either by inadequate dietary intake or inadequate absorption, while phosphorus deficiency occurs generally through increased renal losses secondary to hyperparathyroidism.

Classically, nutritional rickets has been attributed primarily to vitamin D deficiency, resulting in impaired calcium absorption and secondary phosphorus depletion. Vitamin D is metabolised to 25-hydroxyvitamin D (25(OH)D), then to 1,25-dihydroxyvitamin D, which acts primarily on vitamin D receptors in the gut to increase calcium absorption. The serum concentration of the intermediate metabolite, 25(OH)D, is the best indicator of vitamin D status. Measurement of 25(OH)D has been possible over the last 30 years, but reliable measurement requires radio-immunoassay.¹ Vitamin D-deficiency rickets is generally associated with 25(OH)D concentrations below 5 ng/ml (12.5 nmol/L). Although

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vitamin D fortification of foods, especially infant formulae, provides a dietary source of vitamin D in many high-income countries, most infants and children in developing countries depend on sunlight exposure to ensure adequate vitamin D status.

Recently, it has been reported that inadequate calcium intake causes nutritional rickets, despite adequate vitamin D status. Currently, the burden of nutritional rickets is greatest in developing countries where it is often underreported or ignored. Several authors have described a resurgence of nutritional rickets in high-income countries where rickets was once considered to be eradicated. Although reviews of rickets have recently been published,²⁻⁴ none has provided a comprehensive global assessment of the disease. Geographic variations in the aetiology and epidemiology of nutritional rickets can result from differences in ultraviolet light exposure, skin pigmentation, diet and religious or custom-based habits.⁵ We conducted a systematic review of the characteristics of nutritional rickets from around the world.

Methods

We searched PubMed and Google for studies published within the last 20 years on nutritional rickets. We used the search terms 'rickets' or 'vitamin D' and individual country names. Additional articles were obtained from the authors' collections. Information extracted from each article included the prevalence and presumed causes of rickets, the methods of confirming the diagnosis, whether 25(OH)D concentrations were reported, and the response to treatment or preventive interventions.

Results

Rickets in Europe

Vitamin D deficiency rickets has been a major cause of morbidity and mortality in

Northern Europe and the United Kingdom for at least the last 400 years, and was so common in England that it was termed 'the English disease'. With the discovery of vitamin D and an understanding of the importance of sunlight for the prevention and treatment of rickets in the early 1900s,⁶ the prevalence of the disease fell as interventions such as vitamin D supplementation and food fortification were introduced. Nevertheless, vitamin D deficiency and rickets remain a clinical problem in certain communities and in families with unusual dietary patterns.⁷

In the United Kingdom, low concentrations of serum 25(OH)D are common during the winter months in all ethnic groups.^{8,9} However, rickets was particularly prevalent in the 1960s among recent immigrants from India, Pakistan and Bangladesh.¹⁰ Although vitamin D deficiency was the common final pathway in the pathogenesis of the disease, it has been proposed that the low calcium and high phytate contents of the typical Asian diet¹¹ combine to exacerbate the problem by increasing the catabolism of relatively low stores of vitamin D from limited sun exposure, resulting in vitamin D deficiency and rickets.¹² Numerous studies have highlighted the problem, resulting in public health measures to promote awareness of the condition among affected communities (e.g. 'the Stop Rickets campaign') and preventive strategies through vitamin D supplementation of at-risk children. The national Department of Health recommends vitamin D supplements for all infants under 3 years of age and for all at-risk children until 5 years of age.¹³ Despite these measures, which resulted in a decline in the incidence of the disease, reports over the last 2 decades indicate that rickets has not been eradicated. Its incidence is once again on the increase, not only in infants and young children but also in adolescents in the same communities.¹⁴⁻¹⁶ Several factors are thought to play a role in the rising incidence, including increased prevalence of prolonged

breastfeeding,¹⁷ maternal vitamin D deficiency,¹⁸ limited sunlight exposure¹⁹ and poor utilisation of vitamin D supplements.^{20–22} Particular attention is now being paid to the importance of maternal vitamin D deficiency in predisposing to earlier and more severe vitamin D deficiency in infants, resulting in recommendations for vitamin D supplementation of at-risk women during pregnancy.^{15–18} Although most attention has been given to the problem in Asian communities, reports suggest that African and African-Caribbean immigrant families are not immune.²³

The English scientific literature contains less information on the prevalence of rickets in the remainder of Europe over the last 20 years. However, several reports have highlighted the marked seasonal variation of serum 25(OH)D levels in children in various countries, with concentrations frequently falling into the vitamin D-deficient range (<25 nmol/L) during winter and early spring.^{24–28} Over 40% of young adults in Western and Central Europe were vitamin D-deficient during the winter months.²⁹ The apparent anomaly of a higher prevalence of vitamin D insufficiency in the elderly in Southern Europe (Greece, Italy and Spain) than in northern Europe and Scandinavia during winter is probably owing to greater use of vitamin D supplements and dietary fortification in northern European countries.³⁰

As in the United Kingdom, low vitamin D status and rickets are more prevalent in immigrant children than in indigenous populations in the Netherlands, Denmark, Norway and Spain.^{31–34} Although vitamin D supplements are recommended for all young children in France, there is no such recommendation for older children and adolescents, and frank rickets has been reported in this age group.³⁵ In Greece, rickets was not uncommon in infants some 40 years ago. However, little has been reported since then, although a case of congenital rickets was recently described in a young infant born to a Caucasian mother living on a Greek island.³⁷ We found no recent information on the

prevalence of rickets in Russia or Eastern European countries.

The role played by macrobiotic and low calcium diets in the causation of rickets in young children has been noted in Ireland,⁷ the Netherlands³⁸ and Belgium.³⁹

Rickets in the Middle East

As the world is increasingly interconnected, some awareness of rickets in the Middle East comes from reports of immigrants. A Russian child developed rickets while on a restricted diet and then emigrated to Israel; calcium deficiency was identified to be the cause of the rickets.⁴⁰ Conversely, in a study of 126 patients with rickets and/or vitamin D deficiency in Australia, 11% had origins in the Middle East.⁴¹ These immigrant patients showed inconsistent relationships between PTH and 25(OH)D values, raising the question of whether or not calcium deficiency might have been an important aetiological factor in some patients.⁴¹

Rickets has been well described in Saudi Arabia. Despite abundant sunshine, cultural habits limit sun exposure in pregnant women and young children.⁴² Among women delivering in an urban Saudi hospital, 59% of them and 70% of newborns had vitamin D deficiency (<25 nmol/L).⁴³ Hospital studies show that up to 1% of children have rickets, but community-based prevalence figures of rickets or vitamin D deficiency in young children have not been determined.⁴² A study of 21 adolescents (20 girls) with symptomatic rickets in a discrete population suggested a prevalence of approximately 68/100,000.⁴⁴ Both radiological and biochemical evaluations were helpful in diagnosing and determining the severity of rickets in Saudi children.⁴⁵ During a 7-year period, 42 older children and adolescents were found to have rickets, and poor calcium intake and limited sun exposure were both identified as important aetiological factors.⁴⁶ In another adolescent study, rickets was linked to vitamin D deficiency in 59% of patients and to low

calcium intake in 12% (with other cases related to genetic conditions).⁴⁷ Because cultural constraints limit increasing adolescent girls' exposure to the sun, it has been suggested that vitamin D supplementation is indicated.⁴⁸

In Kuwait, rachitic rosary was found in 75 newborns, most of whom were vitamin D-deficient. Only a minority had increased alkaline phosphatase levels and abnormal radiographs, but all had hypophosphataemia.⁴⁹ Compared with controls, 103 infants with more typical rickets had lower 25(OH)D levels, older age at weaning to semi-solid foods, and lower quality weaning foods.⁵⁰ Children whose rickets was related to limited sun exposure responded better to parenteral than to oral vitamin D treatment, presumably owing to poor compliance with the prescribed oral treatment.⁵¹

In Yemen, rickets was identified clinically in 27% of young children in immunisation clinics but seemed to resolve spontaneously by the age of 5 years.⁵² In children hospitalised with pneumonia, rickets was identified in 50% and was a strong risk factor for a fatal outcome.⁵³ In Jordan, 11% of hospitalised children had rickets, and 85% of those had been admitted for respiratory infection.⁵⁴ Similarly in Iran, rickets was associated with respiratory infection.⁵⁵ In the United Arab Emirates, rickets in children was directly linked to maternal vitamin D deficiency⁵⁶ and routine vitamin D supplementation of breastfeeding infants and mothers has been suggested.⁵⁷

In Turkey, rickets was identified in 42 infants under 3 months of age and was linked to limited sun exposure and low maternal and infantile levels of vitamin D.⁵⁸ Interestingly, however, in an area of Turkey where 23% of children were identified as having rickets, the strontium level in the soil was linked statistically to local variations in the prevalence of rickets, suggesting that ingested strontium might interfere with calcium metabolism and increase the risk of rickets.⁵⁹ In 42 Turkish children

with rickets, treatment with calcium improved alkaline phosphatase values and radiographic findings over 1 month, but less so than vitamin D.⁶⁰

Thus, in the Middle East, rickets is common in at least some areas and is linked largely to vitamin D deficiency related to maternal and infantile protection from the sun. Nonetheless, dietary factors limiting calcium intake and/or absorption are also important in some children. For cultural reasons, exposure to the sun is not always readily acceptable and vitamin D supplementation has been suggested for women and infants.

Rickets in Asia

In India, the use of purdah (covering) among Muslims results in rickets rates 3–4 times higher than among Hindus.⁶¹ Overclothing, sunless city dwellings, air pollution and pigmented skin compromise vitamin D status. Calcium intake is low at all ages.⁶² A diet low in calcium, high in oxalates (green, leafy vegetables) and high in phytate (unleavened bread) also contributes to development of rickets. The odds ratio for developing rickets with a daily calcium intake below 300 mg was 4.8. Daily calcium intake was significantly lower in young children with rickets (285 mg) than in controls (404 mg). Both groups had similar sun exposure but children with rickets had non-significantly lower 25(OH)D levels [mean (SD) 49 (38) *vs* 61 (36) nmol/L].⁶³ Children with rickets healed completely in 3 months on calcium alone or with vitamin D.

Adolescents with rickets in India had lower calcium intakes than controls [mean (SD) 305 (196) *vs* 762 (183) mg] and less sun exposure [mean (SD) 16 (15) *vs* 27 (17) min/m²/day].⁶³ Serum 25(OH)D concentrations were significantly lower than controls [mean (SD) 12.6 (7.1) *vs* 46 (45) nmol/L]. Adolescents showed no response to calcium alone but had complete healing with calcium and vitamin D in 3–9 months, suggesting that vitamin D deficiency was the

primary cause. Despite 30 minutes of sun exposure daily, Indian school children had a mean (SD) 25(OH)D level of only 29.5 (18.0) nmol/L, putting half at risk of vitamin D deficiency.⁶⁴

A study of 400,000 children in rural India reported that 45% of the drinking water sources had a high fluoride content (1.5–25 ppm).⁶⁵ Excess fluoride exacerbates calcium deficiency, leading to skeletal fluorosis with symptoms similar to rickets.⁶⁶ This disorder was more prevalent among children with low calcium intakes, but serum calcium and 25(OH)D values were normal.

In Bangladesh, a large study reported a 1.2% prevalence of lower limb deformities consistent with rickets in children 1–4 years of age.⁶⁷ In a study of 30 villages, 8.7% of children aged 1–15 years had clinical features of rickets but only 0.9% had radiographic evidence of active rickets and elevated alkaline phosphatase.⁶⁸ Insufficient calcium intake seems to be the primary cause of rickets in Bangladesh. Among children with active rickets based on clinical signs, radiography and serum alkaline phosphatase, 70% had normal 25(OH)D levels.⁶⁹

Rickets in Pakistan has a reported prevalence of <2%.^{70,71} Community surveys have identified rickets in Afghanistan but no prevalence figures are available.^{72,73}

A survey of children aged 0–2 years in rural north-east China found a prevalence of clinical rickets of 49.3%, the highest prevalence being in children aged 7–12 months.⁷⁴ The most conservative prevalence rate of clinical rickets reported among children under the age of 5 years in China is 15.9%, with rates among infants of 26.7%.^{75,76}

Based on the combination of clinical signs, radiographs and elevated alkaline phosphatase, the prevalence of rickets in early spring in Chinese children aged 12–24 months was 3.7%.⁷⁷ Relying on clinical and ALP results alone resulted in a rate of rickets of 5.9%.

Wrist radiography in 1248 girls aged 12–14 years in Beijing revealed no active rickets. However, the following signs of previous rickets were observed: bow-legs 19.4%, rachitic rosary 3%, pectus carinatum 2.5%, knock-knees 0.3% and wide wrists 0.2%.⁷⁸

Among rural children aged 12–24 months, 65.3% had 25(OH)D levels below 12 ng/ml (30 nmol/L) in early spring.⁷⁷ In rural and urban areas of Beijing, 12–14-year-old girls had mean 25(OH)D values of 5.1 ng/ml (12.8 nmol/L) in winter and 9.5 ng/ml (23.8 nmol/L) in summer. Their mean (SD) daily dietary calcium intake was only 356 (97) mg.⁷⁹ In general, Chinese children have low calcium intakes [mean (SD) 244 (26) mg/day].⁸⁰ Lack of vitamin D fortification of foods also puts large numbers of people at risk of vitamin D deficiency.⁸¹

Mongolia's northern location puts people at risk of vitamin D deficiency during the winter. A survey of 977 randomly sampled households described a prevalence of clinical rickets of 69.8% in 441 children aged 0–60 months.⁸² The diagnosis was based on at least one of three clinical signs: rachitic rosary, Harrison's groove or delayed closure of the fontanelle. As in China, such high rates are based on clinical signs only and do not reflect the true rate of active rickets. Among 40 Mongolian children with signs of rickets, the mean (SD) plasma 25(OH)D concentration was 7.1 (0.8) nmol/L compared with 41.3 (3.3) nmol/L in 22 apparently healthy children.⁸³ The average dietary calcium intake in children under 5 years of age was very low (265 mg/day). Vitamin D deficiency coupled with low calcium intake results in rickets in Mongolia.

There are unofficial reports of rickets among children in North Korea,⁸⁴ but no prevalence rates have been reported. Cases of rickets in recent years have been reported in Japan. Children with rickets tend to have dietary restrictions resulting in low 25(OH)D values and hypocalcaemia.^{85,86} However, vitamin D deficiency is expected

to increase in Japan because the sale of vitamin D syrup and multivitamin granules including vitamin D was stopped.

Rickets in Africa

Most of Africa lies within the sunny tropics. In the past, vitamin D deficiency from restricted sunlight exposure has been presumed to be the cause of rickets in African children. More recently, calcium deficiency has been described as a cause of rickets in South Africa⁸⁷ and Nigeria.^{88,89} A South African study demonstrated lower calcium intake in those with rickets than in control children (~200 mg *vs* 330–378 mg, respectively),⁹⁰ but this finding was not replicated in Nigerian children.⁹¹ However, one of the few randomised, controlled trials of treatment of rickets demonstrated that calcium with or without vitamin D was superior to vitamin D alone in healing rickets in Nigerian children.⁹² Vitamin D deficiency was distinctly uncommon in Nigerian children.⁹³ Fractional calcium absorption of over 60% and very high 1,25-hydroxyvitamin D concentrations in Nigerian children with rickets lend further support to the absence of vitamin D deficiency.⁹⁴

In Ethiopia, a 13-fold greater prevalence of rickets was found in children under the age of 5 years with pneumonia than in controls without pneumonia.⁹⁵ Values of 25(OH)D have not been reported in Ethiopian children, but rickets has been associated with reduced sunshine exposure.^{96–98} Investigators in Ethiopia reported no difference in daily calcium intake between children with rickets and controls (665 *vs* 646 mg, respectively).⁹⁸ The majority of Ethiopian children with rickets presented in the 1st year of life, which is consistent with vitamin D deficiency.

Rickets has been described in the north African countries of Egypt,^{99–101} Sudan,¹⁰² Algeria,¹⁰³ Libya^{32,104} and Tunisia.¹⁰⁵ Very low values of 25(OH)D were reported in children with rickets in Egypt,⁹⁹ whereas

only about half the children with rickets in Libya had low 25(OH)D values.¹⁰⁴

Nutritional rickets was reported in 40 older children [mean (SD) age 4.6 (3.7) years] in The Gambia,¹⁰⁶ all with normal values of 25(OH)D. Rickets has also been described in Ghana,¹⁰⁷ Tanzania^{108,109} and Kenya.¹¹⁰ However, 25(OH)D was not measured in any of these studies. Although not formally reported, rickets also occurs in the Central African Republic (M. Onimus, personal communication), Benin and Senegal (C. Thierry, personal communication).

Nutritional rickets in Africa occurs predominantly in settings of low dietary calcium intakes. Calcium intakes of 200–300 mg/day have been reported from Egypt, Kenya,¹¹¹ Nigeria,⁹¹ Gambia¹⁰⁶ and South Africa.⁹⁰ Dairy product intake is minimal and diets are rich in substances that reduce the bio-availability of calcium. Phytic acid in grains, oxalates in green leaves, tannic acid in tea and saturated fat in palm oil all inhibit absorption of ingested calcium and all are commonly consumed in Africa. Few studies of children with rickets in Africa report 25(OH)D values. Where they have been measured, normal values of 25(OH)D are found in the majority of children with rickets. However, rickets in children under 18 months of age, as found in north African countries, might result primarily from vitamin D deficiency. Rickets in children over 2 years of age, as found in Nigeria and South Africa, is more likely to result from insufficient dietary calcium.

Rickets in Australia and Oceania

In Australia and New Zealand, vitamin D deficiency rickets occurs in immigrant infants whose parents come from Mediterranean, African, Middle Eastern and southern Asian regions.^{41,112–114} Of 123 cases of rickets reported, 73% presented with 25(OH)D less than 20 nmol/L.⁴¹ Rickets might be expected among the extremely dark-skinned Aborigines, but it has not been reported.

Rickets in South America

South America extends in latitude from some 10° north of the equator to approximately 55° south, the latter being about the same latitude south as northern Canada and northern Europe are north of the equator. Thus, the majority of countries in South America should have adequate sunlight and UV exposure to maintain vitamin D status. This is borne out by the lack of reports of vitamin D deficiency from the majority of countries and confirmed by finding higher concentrations of 25(OH)D in children living in Brazil than in Europe¹¹⁵ and the lack of radiological rickets in a study of malnourished and well nourished children living in the same country.¹¹⁶

Argentina is the only country from which detailed studies of the prevalence of vitamin D deficiency rickets have been reported and an increase in prevalence is noted as one moves south.¹¹⁷ The increasing prevalence of rickets corresponds with the reduction in circulating 25(OH)D concentrations noted in children and the limited UV radiation during winter in the southernmost region of the country (Ushuaia).^{118,119} In this country, vitamin D supplementation is recommended during the winter months to prevent the high prevalence of vitamin D deficiency during that time.

Rickets has also been reported in Uruguay¹²⁰ and Columbia.¹²¹ The biochemical features of rickets described in Columbia are very similar to calcium deficiency rickets as described in Africa, with normal values of 25(OH)D, elevated 1,25-hydroxyvitamin D concentrations and normal fractional absorption of calcium.¹²²

Rickets in North America

Rickets has been known and characterised for centuries, and it is expected that this condition was common in antiquity.¹²³ Nonetheless, a historical review of the indigenous Aztec people in the pre-Hispanic era found no evidence of rickets.¹²⁴

Over the course of the past century, the story of rickets in North America has been characterised as following epidemiological 'waves.'¹²⁵ During the first 'wave' leading into the early 20th century, nutritional rickets was widespread. Through fortification of dairy products with vitamin D, rickets became extremely rare in developed areas of North America.

From the 1960s through the 1980s, however, there were ongoing reports of nutritional rickets in at-risk groups. An aboriginal population in Manitoba, Canada did not routinely use vitamin D-fortified milk and rickets remained common.¹²⁶⁻¹²⁸

In the 1970s, rickets was seen repeatedly in urban Philadelphia and was associated with dark skin, religious customs (Muslims and Seventh Day Adventists with extensive clothing covering the body and with dairy-free, vegetarian diets) and vitamin D deficiency in both nursing mothers and case patients.¹²⁹ Other reports of rickets also identified restrictive diets as a cause.^{130,131} A child in Canada developed rickets while on a restricted diet, and calcium deficiency was demonstrated to be important in the pathogenesis.¹³² Children in a rural area of Jamaica were also found to have rickets, and both dietary factors and limited sun exposure were thought to be relevant.¹³³

Around the 1990s, nutritional rickets experienced a 'wave' of resurgence and was increasingly reported from around North America in breastfed, (almost universally) darkly pigmented babies who received no supplemental vitamin D. Eighteen such children were reported from Washington,¹³⁴ three in Michigan,¹³⁵ nine from New Jersey,¹³⁶ four in New York,¹³⁷ 19 mostly immigrant children without significant sun exposure in Toronto,¹³⁸ five in Alaska,¹³⁹ nine in Texas,¹⁴⁰ 30 in North Carolina,¹⁴¹ four in Arizona,¹⁴² five in Georgia,¹⁴³ 51 in Wisconsin, the 'dairy state',¹⁴⁴ and others elsewhere.¹⁴⁵ Almost without exception, the affected children were breastfed without receiving vitamin supplementation and were darkly

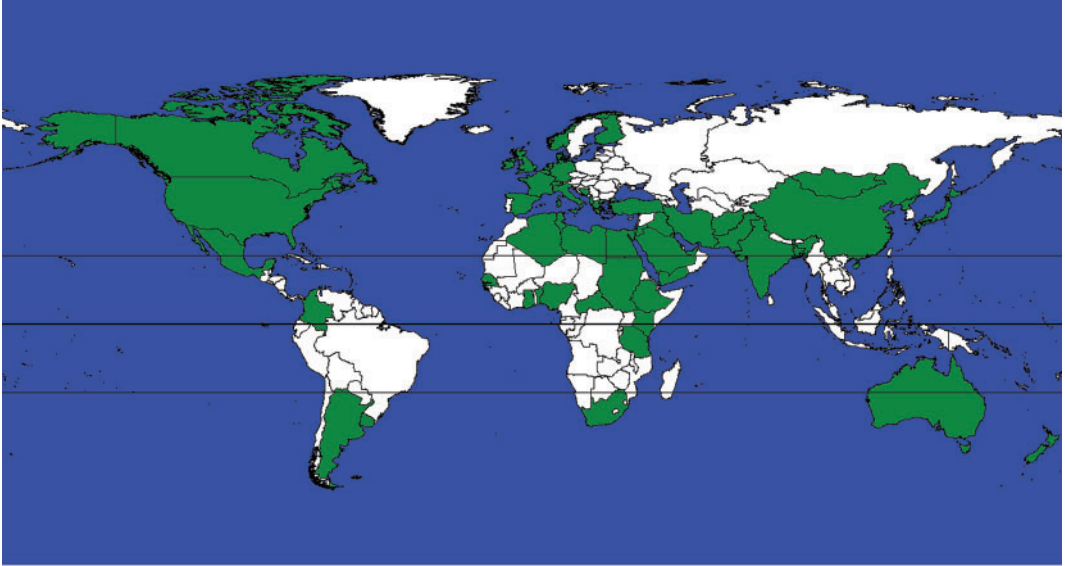


FIG. 1. Countries with reports of nutritional rickets since 1987 (horizontal lines represent the equator and the Tropics of Cancer and Capricorn).

pigmented (mostly black, some Hispanic, only rarely Caucasians); some were kept out of the sun for religious reasons, and a few had been weaned to restrictive diets.

Interestingly, the resurgence of rickets in North America in the 1990s co-occurred with skin cancer prevention campaigns that discouraged sun exposure.¹⁴⁶ It is also clear that vitamin D deficiency is common in infants in the far north (Alaska) and that this deficiency poses risks apart from the extreme cases of rickets.^{139,147} While some have argued that rickets is a climatic rather than a nutritional disease¹⁴⁸ and while sun exposure is still effective in preventing vitamin D deficiency,¹⁴⁹ the prevention and treatment of vitamin D deficiency and vitamin D deficiency rickets can be accomplished through food fortification and nutritional supplements. Indeed, the American Academy of Pediatrics responded to the wave of reports of rickets with new guidelines that suggested vitamin D supplementation for all breastfed newborns.¹⁵⁰ Others, however, have disputed the need for supplementation of all breastfed babies rather than solely of those in higher risk groups related to skin pigmentation.¹⁴⁵

An additional wave of understanding the epidemiology of rickets in North America is still breaking. Despite all the cases suggesting that rickets is simply caused by vitamin D deficiency, as classically reported through history, there is evidence that calcium deficiency is still critically important. Some of the North American patients with rickets have had unusual diets, and calcium deficiency has been implicated in some of them.^{132,151} Others, with rickets attributed to vitamin D deficiency, recovered on treatment regimens that concurrently included both vitamin D and calcium.^{136–138} Most of 43 rachitic children carefully evaluated in Connecticut fitted the pattern of being darkly pigmented and breastfed.¹⁵² However, some had received vitamin D supplementation before developing rickets, most did not have extremely low levels of vitamin D, and one recovered on calcium treatment without receiving vitamin D.¹⁵²

Thus, vitamin D-deficiency rickets has persisted in North America in individuals and groups where sun exposure and vitamin D supplementation are limited, and cases were increasingly identified in the 1990s among darker-skinned, breastfed babies.



FIG. 2. A: Nigerian child with nutritional rickets before treatment. B: 3 years after treatment with calcium.

Careful evaluation of cases, however, suggests that calcium deficiency might also contribute to rickets in North American toddlers who have been weaned.

Discussion

Nutritional rickets has been described from at least 59 countries in the last 20 years (Fig. 1). Increasingly over the past decade, it has become clear that the aetiology of nutritional rickets exists along a spectrum ranging from isolated vitamin D deficiency to isolated calcium deficiency.¹⁵³ Along the spectrum, it is likely that relative deficiencies of calcium and vitamin D interact with as

yet incompletely understood genetic and/or environmental factors to stimulate the development of rickets. It seems, too, that the requirement or optimal level of one factor, such as vitamin D, is altered by variations of the other factor, calcium.^{154,155}

Ideally, rickets would be prevented by ensuring that all children receive adequate amounts of both vitamin D and calcium. Some experts have suggested that all newborns be supplemented with daily vitamin D at doses between 200 and 400 IU while others suggest targeting at-risk infants.^{150,156} Even though in the United States the cause of rickets exists on a spectrum, calcium deficiency might play a significant role.¹⁵² Thus, ensuring adequate

calcium intake after the cessation of breast-feeding is important in preventing the disease. In some parts of the world and in certain communities, maternal vitamin D deficiency is frequent, aggravating and exacerbating the prevalence of rickets in the young infant. Thus attention to vitamin D intake/status during antenatal care is imperative if the problem of infant rickets is to be addressed.¹⁵⁷

There are few data on the prevalence of rickets even in countries where the disease is common. Many studies relied on a variety of clinical features to diagnose rickets. Children with clinical signs of rickets do not necessarily have radiographically active rickets. A validated prediction rule has been

developed for the clinical diagnosis of rickets in low-income settings.¹⁵⁸ However, when radiographic facilities are available, they should be used for accurate diagnosis of active rickets. Radiographic severity correlates well with alkaline phosphatase values.¹⁵⁹ Few studies reported measurement of 25(OH)D to permit distinguishing vitamin D deficiency from calcium deficiency, yet many investigators concluded that nutritional rickets in their populations was owing to vitamin D deficiency. Many of these populations also have calcium intakes below 300 mg/day, placing them at risk of calcium deficiency. Vitamin D-deficiency rickets usually presents in the 1st 18 months of life, whereas calcium deficiency typically

TABLE 1. *Children with nutritional rickets.*

Region	Rickets prevalence	Characteristics	Exceptions
Africa	High Primarily in children aged >18 m	Low calcium intake, dietary inhibitors of calcium absorption. Majority with normal serum 25(OH)D	Vitamin D deficiency in those with sun avoidance
East Asia	High Primarily in children age <2 y	Low sun exposure, prevalent vitamin D-deficiency, low calcium intake.	High fish consumption in Japan and vitamin D-fortified foods result in low rates of rickets
South Asia	High In infancy and in adolescence	Dark skin, clothes covering results in vitamin D-deficiency. Foods poorly fortified with vitamin D. Low calcium intake, dietary inhibitors of calcium absorption.	
Australia & Oceania	Low	Immigrant Asian populations. Adequate sun.	
Middle East	Moderate	Mostly linked to maternal and infant sun protection. Calcium insufficiency a factor for older children and adolescents.	
North America	Low	Mostly vitamin D deficiency in unsupplemented breastfed babies with darkly pigmented skin. Increasing evidence of associated calcium deficiency.	
Europe	High	Among Asian immigrant communities. Associated with low calcium intakes and vitamin D insufficiency.	
South America	Low	Uncommon in the indigenous populations. Latitude-dependent. Vitamin D deficiency common in southern Argentina.	

presents after weaning and often after the 2nd year of life. Development of a simple, affordable and accurate 25(OH)D assay would greatly advance our understanding of nutritional rickets in the developing world.

A variety of vitamin D preparations is available to treat children who are deficient. A single intramuscular injection (stoss therapy) of 300,000–600,000 units provides full treatment for 3–6 months.¹⁶⁰ Otherwise, oral vitamin D (~5000 IU/d) can be given therapeutically.

Where low calcium intakes are considered to be an aetiological factor, therapeutic calcium doses have been effective at 350¹⁶¹ to 1000 mg⁹² of elemental calcium per day. Treatment for 3–6 months is effective,^{92,161} but ongoing adequacy of calcium and vitamin D status must be ensured even after completing the therapeutic dose to avoid recurrent rickets.

Some centres advocate bracing curved extremities to limit the extent of the ultimate deformity. However, no data exist to indicate that bracing adds benefit to medical therapy. Even extreme deformities can self-correct with subsequent longitudinal growth following resolution of active rickets (Fig. 2), but orthopaedic intervention (osteotomy or epiphyseal stapling) can correct severe deformities with significant functional compromise after resolution of active bone disease.

Thus, nutritional rickets continues to be a problem in many countries around the planet. The aetiology hinges on interacting degrees of calcium deficiency and vitamin D deficiency coupled with as yet incompletely elucidated aggravating factors. Preventive and curative therapy is based on correcting identified deficiencies, and good recovery is possible. Where rickets is prevalent, it is reasonable to ensure that all children receive adequate amounts of calcium and adequate sun exposure.¹⁴⁹

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