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Pediatric vitamin D and calcium nutrition in developing countries

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Abstract Over one billion humans have insufficient circulating levels of vitamin D, and dietary insufficiency of calcium is common in developing countries. Worldwide, nutritional rickets is considered to be the most common non-communicable disease of children. Rickets can be due either to primary deficiencies of vitamin D or calcium or to combined deficiencies of both elements. Vitamin D deficiency is also increasingly linked to non-skeletal complications. Even without laboratory and radiologic resources, the diagnosis of rickets is considered clinically when a child presents with limb deformities and has beaded ribs and widened wrists and ankles. Prevention is possible through increased sun exposure and dietary enhancement. Treatment of nutritional rickets involves provision of adequate vitamin D and calcium. Further research is needed to elucidate the precise epidemiology of vitamin D and calcium deficiencies in developing countries, to determine the roles of additional pathologic factors contributing to the development and morbidity of rickets, to improve affordable and feasible means of diagnosing rickets in resource-limited areas, to better target at-risk populations for preventive interventions, to identify accurate dosing and delivery of therapeutic interventions, and to evaluate the long-term consequences of vitamin D and calcium deficiencies in childhood.

Keywords Calcium · Vitamin D · Rickets · Nutrition

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1 Introduction

In resource-limited areas of the world, significant proportions of the population are living with suboptimal intakes of calcium and poor vitamin D status [1–3]. At the same time that vitamin D and calcium deficiencies are increasingly recognized to cause rickets in many children in developing countries [2], additional diseases are being linked to vitamin D deficiency [4, 5]. This paper reviews the epidemiology, pathophysiology, diagnosis, and treatment of vitamin D and calcium insufficiencies in developing countries with an emphasis on childhood rickets but with concurrent mention of adult and non-skeletal implications of these pediatric nutritional problems.

2 Epidemiology

2.1 Definitions—sufficiency and requirements

While it is clear that many children throughout the world do not receive adequate amounts of vitamin D [6] and calcium [7], it is less clear just how adequacy of either vitamin D [8, 9] or calcium [10] should be defined. In addition, there is evidence that insufficiency of either one of these nutrients increases the requirement for the other [11].

25-Hydroxyvitamin D is the metabolite measured in serum to determine the adequacy of vitamin D status. While reference ranges of 25-hydroxyvitamin D are determined by statistical analysis of findings in populations (with lower limits of "normal" being identified along a range from 20–38 nmol/L [6]), vitamin D sufficiency has been defined variably as the level necessary to avoid rickets (12–20 nmol/L) or as the minimum level at which there are no compensatory elevations of 1,25-dihydroxyvitamin D and/or parathyroid hormone (75–100 nmol/L in adults). Using fracture risk in adults as an indicator, researchers have suggested that "optimal" bone health is dependent on levels of at least 50 to 80 nmol/L [6, 12]. With recognition that vitamin D sufficiency is necessary not only for the skeleton, however, it has been suggested that similar levels are also needed for non-skeletal benefits of vitamin D. Sun exposures and dietary intakes necessary to achieve these levels have also been debated. Solar ultraviolet B radiation, with a wavelength of 290–315 nm, penetrates skin to convert 7-dehydrocholesterol to previtamin D3 which rapidly isomerizes to vitamin D3 [4]. Acknowledging individual differences in skin pigmentation and variations in sunlight exposure at various latitudes, twice weekly exposure of arms and legs to 5–30 minutes of mid-day sunlight often stimulates adequate vitamin D3 production in older children while twice weekly head and shoulders exposure is often adequate in infants. Vitamin D3 is then stored in body fat and can be released during winter months when there is less natural sun-induced vitamin D3 production [4]. Little or no dermal vitamin D synthesis occurs during the winter months at latitudes greater than 37° N or S, due to the lack of UV radiation reaching the earth's surface. Realizing that sun exposure is not always adequate, especially in areas far from the equator or as a result of the use of sunscreen to prevent skin damage and skin cancer, 200 IU of daily oral vitamin D ingestion (in fortified drinks or via supplementation) is said to provide adequate vitamin D to maintain sufficient circulating 25-hydroxyvitamin D levels to prevent vitamin D-deficiency rickets in children in North America [8]. However, vitamin D intakes up to 2000 IU daily are considered safe in children and may provide optimal serum concentrations, although no long term population studies have confirmed this yet. It is not known whether supplemental vitamin D is actually needed in tropical and sub-tropical areas; similarly, one could dispute the priority and feasibility of trying to implement such un-targeted supplementation in resource-limited areas of the world.

Calcium homeostasis is tightly controlled by interactions between vitamin D metabolites and parathyroid activity. While serum calcium levels decrease with advanced rickets, serum calcium concentrations are not a reliable indicator of total body calcium sufficiency. Adequate calcium intakes have been proposed by consensus, but there is not full agreement as to how much calcium is actually required for optimal health. Factors that may be important in evaluating the optimal calcium intake include calcium retention and accretion of bone mass. Increased protein and sodium intake promotes urinary calcium excretion. In general, calcium needs increase as children grow – for Caucasian children on normal western diets and lifestyles the figures range from about 300 mg per day during the early months of life to 1,400 mg per day during adolescence [13].

2.2 Limited intake and rickets

Whatever the exact need and normal ranges are for vitamin D and calcium, there is ample evidence that insufficiency is widespread. It is estimated that over one billion humans have insufficient levels of vitamin D [4]. Nearly half of North American children are vitamin D insufficient, and European children seem similarly at risk in spite of widespread supplementation efforts [4]. Women and children with more darkly pigmented skin are at greatest risk, and neonatal hypovitaminosis D is commonly seen [14]. Breast milk generally has a low vitamin D content and less calcium than cow's milk, and prolonged breast feeding has been associated with rickets in infants in western countries [15, 16]. High dose vitamin D supplementation during lactation may increase the vitamin D concentration in breast milk to levels sufficient to maintain vitamin D adequacy and prevent rickets in the suckling infant [17]. In tropical areas with more sunlight exposure, vitamin D levels are less often low despite diets containing minimal amounts of vitamin D. Nonetheless, hypovitaminosis D is not infrequently seen in women and children who, for cultural reasons, are shielded from sunshine. In Saudi Arabia, for instance, 59% of women delivering in an urban hospital were vitamin D deficient, as were 70% of their newborns [18]. There are not many population-based surveys of 25-hydroxyvitamin D levels in children in developing tropical countries, but control subjects in rickets studies in these areas have generally normal 25-hydroxyvitamin D levels [19, 20]. On the Indian subcontinent, more and more studies are highlighting the high prevalence of vitamin D deficiency in certain groups, especially pregnant and lactating women and adolescent girls [3].

The majority of children in North America, despite increases over recent decades, have inadequate calcium intakes [21]. In several North American studies, approximately three-fourths of girls and nearly two-thirds of boys aged 6 to 11 years have inadequate calcium intakes, and the proportion of 12 to 19 year olds with inadequate intakes was even higher [21]. Calcium insufficiency has been postulated as a cause of approximately half the cases of rickets in North America [22]. In developing countries of

Asia, Africa, and Latin America, the calcium content of complementary foods provided to children during the first year of life is well less than 50% of what is suggested [7]. In India, daily calcium intakes of children vary from 314 mg (low socio-economic groups) to 713 mg (high socio-economic groups) [23]. Similarly low calcium intakes have been reported from Kenya (314 mg/day) [24], South Africa (463 mg/day girls, 528 mg/day boys) [25], Ghana [26], Nigeria (214 mg/day) [19], Malaysia [27], and China (374 mg/day urban, 324 mg/day rural) [28].

Nutritional rickets has re-emerged in many northern countries and is still commonly seen in many tropical areas (Fig. 1) [2]. The prevalence of rickets is relatively high in Africa, East Asia, and South Asia [2]. In fact, rickets is now said to be the most common non-communicable childhood disease in the world [29].

Rickets is seen in children with normal vitamin D levels and with calcium intakes of 20–25% the recommended quantity in South Africa, Nigeria, and Bangladesh [2]. The prevalence of calcium insufficiency rickets in young children in some parts of Nigeria is approximately 9% [20].

2.3 Future epidemiologic research

It is clear that dietary insufficiencies of vitamin D and calcium are common around the world. Further research is needed, however, to better identify populations at highest risk of insufficiency and to determine what modifiable factors are present in those populations. It is not clear that merely altering dairy intake will affect total calcium intake [21] or future bone health [10], and careful epidemiologic studies linking various dietary factors with outcomes would be helpful. Intakes of substances that bind dietary calcium and prevent its absorption, such as phytates and oxalates that are prominent in grains and green leaves commonly consumed in developing countries, could aggravate a restricted calcium intake. In areas where calcium insufficiency rickets is common, there are not major identifiable dietary factors differentiating rachitic from non-rachitic children [19]. Variations in breastmilk calcium content appear to be associated with rickets [30], but it would be helpful to further delineate epidemiologic factors that might determine why just some of the calcium-deprived children to develop rickets.

3 Pathophysiology

3.1 Physiology and pathophysiology of vitamin D metabolism

Ordinarily, sunlight containing ultraviolet B radiation with a wavelength of 290–315 nm penetrates the skin to cause the conversion of 7-dehydrocholesterol to previtamin D3 which is rapidly transformed to vitamin D3 (cholecalciferol) [4],

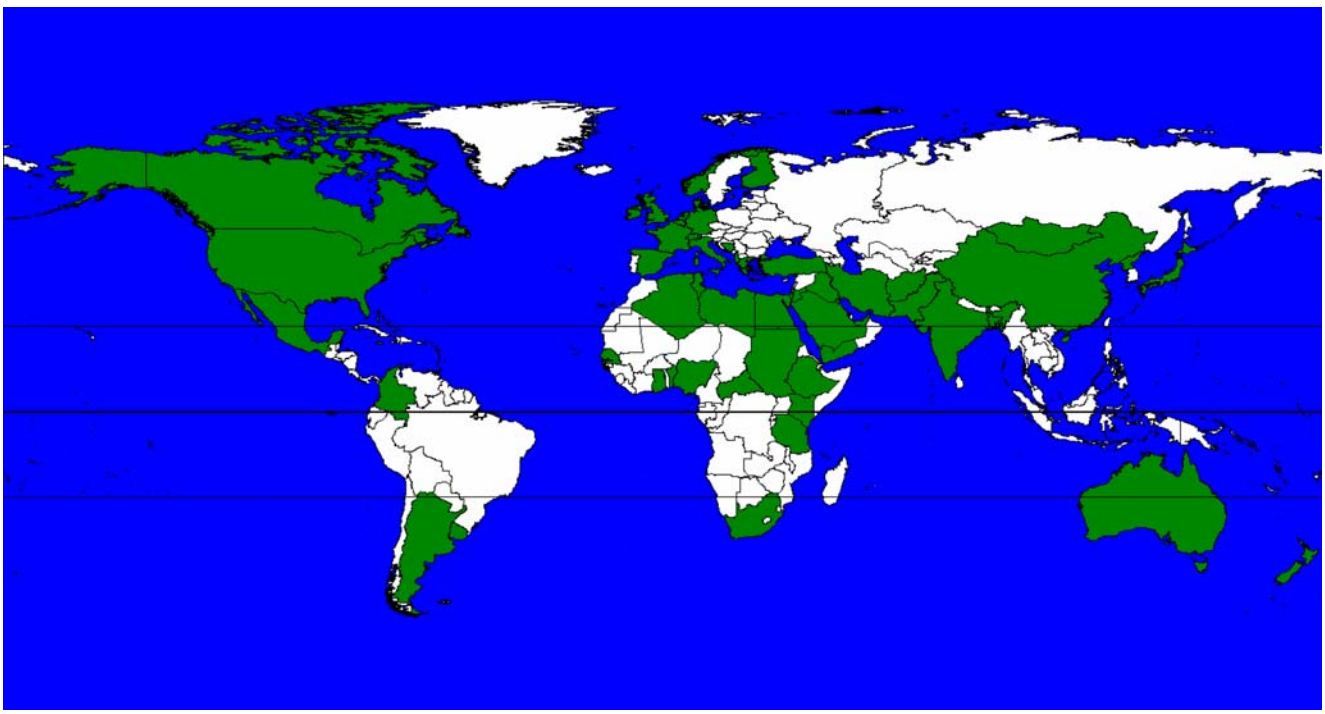

Fig. 1 Countries (*in green*) reporting nutritional rickets since 1985 *adapted from (Thacher et al. [2] Ann Trop Paediatr)

this process is attenuated by reduced exposure of the skin to sunlight (northern latitudes with decreased direct sun exposure, air pollution, confinement indoors, clothes covering all the skin, broad use of sunscreens, increased skin pigmentation) or in dermatologic conditions such as ichthyosis in which sun inadequately penetrates the epidermis [31]. Alternatively, vitamin D is absorbed from the intestine following oral ingestion of foods (especially fish or fish oils) containing vitamin D3 (cholecalciferol). In addition, food or vitamin preparations may be fortified with vitamin D2 (ergocalciferol, which is produced by the ultraviolet irradiation of ergosterol from yeast) or vitamin D3 (cholecalciferol, produced by the ultraviolet irradiation of 7-dehydrocholesterol from lanolin) [4]. Intestinal absorption of vitamin D is hindered by fat malabsorption states such as cystic fibrosis or hepatic disorders.

Whether or not vitamin D2 and D3 are pharmacologically equivalent is unclear. Older studies in adults have suggested that vitamin D2 is less effective than vitamin D3 and that higher doses of vitamin D2 than vitamin D3 are required either as supplements or as treatments to achieve similar results [32]. More recently, however, vitamin D3 and D2 have been shown to have similar effectiveness in an adult population [33]. Pending definitive studies in children, monitoring of clinical effect and biochemical change in children will help determine if interventions have been effective.

Once produced or absorbed, both the vitamin D2 and vitamin D3 forms pass through the liver where they are hydroxylated at the 25 position to produce 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3. (These vitamin forms may be measured separately using mass spectroscopy, but most clinical laboratories measure the two together as "25-hydroxyvitamin D".) Subsequently in the kidneys, 25-hydroxyvitamin D is further hydroxylated at the 1 position to form 1,25-dihydroxyvitamin D, that is biologically active. Renal hydroxylation is stimulated by parathyroid hormone and by low circulating calcium and phosphorus levels, and renal hydroxylation is reduced in chronic renal disease. Fibroblast growth factor 23, elevated in patients with some tumors and hypophosphatemic forms of rickets, can also suppress 1-hydroxylation [34]. 1,25-Dihydroxyvitamin D binds to vitamin D receptors in the intestine to stimulate transcellular absorption of calcium and phosphorus [35]. In addition, there is separate paracellular calcium absorption which depends on the dietary calcium content but not on 1,25-dihydroxyvitamin D [35]. Inadequate calcium intake could cause insufficient intestinal calcium absorption through both the trans-cellular and the para-cellular routes to meet the needs of the body. Calcium absorption could also potentially be hindered by the presence of other competing divalent cations such as lead, by the presence in the intestine of dietary phytates, oxalates, and tannates which bind calcium and decrease its availability for absorption, or by malabsorptive states. The PTH–1,25-dihydroxyvitamin D axis regulates the absorption of intestinal calcium and the deposition and release of bone calcium. There are conflicting data about whether or not increasing dietary calcium intakes above habitual levels increases bone mineral accretion in such a way as to provide for long-term increases in bone mineral content, bone growth, and peak bone mass [36, 37]. Peak bone mass is related to subsequent risk of osteoporosis and fractures during adulthood and varies with gender and genetic factors as well as with the degree of pre-pubertal and adolescent weight-bearing exercise and, possibly, calcium intake [38]. Interventions targeting adolescents with poor bone health might help obviate subsequent adverse outcomes during later adult years [39].

3.2 Problems of calcium homeostasis

Calcium homeostasis during infancy is influenced by prenatal factors. As discussed earlier, many mothers in developed and developing countries are vitamin D deficient with the result that their infants are born with poor vitamin D status [14]. These children are then often exposed to their own independent risk factors (protection from sunlight, for instance) that increase their risk of becoming symptomatic from vitamin D deficiency. Not only is there some evidence that children born to vitamin D-insufficient mothers grow poorly but they may subsequently also have reduced bone mineral content at 9 years of age [40].

3.3 Pathophysiology of rickets

Rickets is a condition of bony deformity due to inadequate mineralization of growing bones. Rickets was carefully described in the 17th Century, and the link with vitamin D deficiency was characterized approximately 100 years ago. Vitamin D deficient infants, whether deficient due to maternal hypovitaminosis D or their own lack of sun exposure and dietary supplementation, increase parathyroid hormone levels in an effort to stimulate further 1-hydroxylation of the deficient vitamin D metabolite and maintain adequate circulating calcium levels. With ongoing compensatory hyperactivity of the parathyroid glands, parathyroid hormone stimulates bone resorption and the release of calcium from bone into the circulation. Similarly, inadequate intestinal calcium absorption stimulates a compensatory increase in 1-hydroxylation which also leads to release of calcium from bones through enhanced bone remodeling. In both situations (calcium or vitamin D deficiency), there is a failure of mineralization of the growth plates of long bones with the resultant development of the radiographic features of rickets [41].

Historically, nutritional rickets was thought to relate merely to vitamin D deficiency. With case reports of rickets

in prematurely born babies who were calcium deprived [42] and with case series of calcium insufficiency rickets in South Africa [43] and Nigeria [44], further investigation was undertaken into the possibility that calcium deficiency could serve as an independent cause of rickets. During the 1990s and subsequently, further evidence revealed that calcium insufficiency was indeed responsible for rickets in parts of Africa [45] and Asia [46], and there was evidence that calcium deficiency even accounted for some North American rickets previously presumed to be due to vitamin D deficiency [22].

Etiologically, it is now understood that nutritional rickets develops along a spectrum from vitamin D deficiency to calcium deficiency with affected children sometimes having mixed insufficiencies of each element [47]. Calcium-deprived children are more susceptible to even mild deficiencies of vitamin D, and calcium deprivation seems to increase a child's need for vitamin D [11].

What is not yet clear is why only some calcium-deprived children develop rickets within population groups where calcium-insufficient diets are common. Subtle differences in breast milk calcium content might tip some mildly deficient children into clinical disease states [30], and genetic predisposition toward bigger bones might make some calcium-deprived children more susceptible to rickets. Specifically, children with rickets are more likely to carry the vitamin D receptor F allele which has been associated with stronger bones (and less risk of osteoporotic fractures) in adult women [48, 49]. Neither abnormalities in calcium absorption [50] nor lead exposure [51, 52] seem to be clinically relevant triggers to the development of rickets in areas of calcium insufficiency. It has also been suggested that high water fluoride concentrations are essential for low dietary calcium intakes to manifest with rickets and bone deformities [53]. Although the two factors do act synergistically to promote bone deformities and rickets, high water fluoride concentrations are not an essential component as low dietary calcium intakes have been shown to produce rickets in areas where water fluoride levels are low.

Typically, rickets associated primarily with vitamin D deficiency presents during the first year of life. Hypocalcemia is common, and tetany and seizures may occur. Muscle weakness and increased risk for respiratory infection are important aspects of rickets but might relate more to the actual vitamin D deficiency than to effects of altered calcium homeostasis. Rachitic children develop curved long bones when softened growth plates are involved in weight-bearing. Chests can become deformed, due to repeated stress on softened ribs from respiratory muscles and the pull of the negative intrapleural pressure. Fontanels have delayed closure, the skull bones are thin and soft (craniotabes), and developing teeth may have deficiencies of enamel.

Rickets primarily associated with dietary calcium deficiency usually presents after the first year of life. Hypocalcemia may be seen, but it is not usually so severe as to be associated with tetany. Bone pain and fractures are reported. Interestingly, elevations in parathyroid hormone concentrations are less marked in calcium deficiency rickets than vitamin D deficiency rickets, perhaps due to the presence of adequate circulating 1,25-dihydroxyvitamin D levels which modulate the parathyroid release in dietary calcium deficiency.

3.4 Non-skeletal complications of hypovitaminosis D

Increasingly, vitamin D has been linked to pathology beyond the skeletal system. Children with rickets are more likely to be ill with acute respiratory infection [54], a common cause of death in developing countries. Of particular concern in developing countries is the association of vitamin D deficiency with tuberculosis [55, 56].

Vitamin D deficiency is also linked to non-infectious complications. Vitamin D receptors are found in brain, prostate, breast, and colon tissues as well as in immune cells. These receptors respond to 1,25-dihydroxyvitamin D, and some of these tissues express a 1-alpha-hydroxylase that stimulates extra-renal 1-hydroxylation of 25-hydroxyvitamin D. Biologically active vitamin D affects cellular proliferation, differentiation, and apoptosis through its influences on the regulation of more than 200 genes, and topical 1,25-dihydroxyvitamin D is even useful in the treatment of psoriasis and ichthyosis [4, 31]. Low circulating levels of vitamin D have been associated with the incidence of and mortality from cancers of the colon, prostate, and breast [4]. Vitamin D receptors and vitamin D binding proteins are found in pancreatic tissue and relate to glucose tolerance and insulin secretion [57]. Low vitamin D levels are associated with cardiac failure and stroke as well as with cardiac risk factors such as hypertension and diabetes [58]. Immune-mediated diseases including systemic lupus erythematosus and multiple sclerosis have also been associated with relative vitamin D insufficiency [59]. In addition, schizophrenia and depression have been associated with vitamin D deficiency [4]. There is some evidence to suggest that supplementation with vitamin D in childhood mitigates the risk of subsequent development of diabetes [60], but it is not clear that pre-illness supplementation with vitamin D will alter the risk of these other diseases.

3.5 Research needs—better understanding of rickets

While much is known about the pathophysiology of disease conditions related to deficiencies of vitamin D and calcium, further research is clearly needed. Case-control studies

might further elucidate reasons why only some calcium-deprived children develop rickets in areas of the developing world where nutritional rickets is common. The amount of sun exposure required to maintain adequate vitamin D levels, particularly in dark-skinned populations, should be determined [3]. Modulating influences of calcium and vitamin D in children who are doubly deficient are not well understood. The relative values of vitamin D2 and vitamin D3 in pediatric bone health deserve further elucidation, especially as routine supplementation is increasingly proposed. The long-term pediatric effects of prenatal hypovitaminosis D should be clarified. Finally, better understanding of the pathophysiology of non-skeletal diseases related to adult and childhood vitamin D insufficiency could presumably lead directly to improved preventive interventions. The role that vitamin D deficiency plays in the high morbidity and mortality rates in infectious diseases in developing communities needs to be delineated.

Table 1 Typical findings of rickets

	Primarily vitamin D deficiency	Primarily calcium insufficiency
History		
Age of onset	1st year of life	1–3 years of age
Seizures	Possible	Rare
Sun exposure	Limited	Normal
Calcium intake	Normal	Limited
Exam		
Curved legs	Rare	Common
Wide wrists	Common	Common
Rib beading	Common	Common
Craniotabes	Possible	Rare
Muscle weakness	Possible	Possible
Laboratory		
Serum calcium	Very low	Low to normal
25-OH D	Very low	Low to normal
1,25-di-OH D	Normal to slightly elevated	Very high
PTH	Very high	Normal to high

4 Diagnosis

4.1 Clinical diagnosis of rickets

In developed and in developing countries, the diagnosis of rickets is suggested by the clinical presentation. When a child presents during the first year of life with convulsions, especially when the Chvostek sign and craniotabes (ability to indent the skull with moderate finger pressure) are present or when the serum level of calcium or phosphorus are extremely low, a clinician should be suspicious of vitamin D deficiency rickets. When a child presents after the first couple of years of life with limb deformities, such as bow legs or knock knees or the combined windswept deformity, one should be suspicious of calcium deficiency rickets, especially when the ribs are palpably beaded and the wrists and ankles seem wide. While rickets can occur with mixed partial insufficiencies of both vitamin D and calcium, typical presenting features of primarily vitamin D deficiency rickets and of primarily calcium insufficiency rickets are noted in Table 1. Physical findings of rickets are shown in Fig. 2.

4.2 Laboratory and radiologic diagnosis of rickets

When suspicious of rickets and when confirmatory diagnostic testing is available, one should check for elevated serum alkaline phosphatase levels and radiographic evidence of bony changes (wrist and knee radiographs showing frayed, widened epiphyseal spaces, sometimes with cupping). Radiographs can be scored to document the severity of the radiographic rickets, which is useful in research studies [61]. The presence of an elevated alkaline phosphatase level and rachitic changes on radiographs indicates that the rickets is active. The finding of skeletal deformities typical of rickets in the absence of abnormal blood tests and X-rays suggests that the deformities are due to another condition and not related to rickets or that the active rickets has resolved but residual deformities remain. Skeletal changes improve over time with ongoing growth, but severe deformities in older children do not always resolve completely.

In Nigeria, rickets is common in some areas, but only about one third of children presenting with limb deformities actually had evidence of active rickets. Wrist enlargement and costochondral beading were the physical findings most associated with radiographic evidence of active rickets. Age less than 5 years, limb pain, and short stature were also somewhat predictive of active rickets in this group of children [62]. When alkaline phosphatase measurements and radiographs are not feasible in resource-limited areas, the presence of these other physical findings can be used to suggest a clinical diagnosis of rickets [63]. When individual children are found to have active rickets, it is also important to consider other causes of rickets, such as renal disease (elevated blood urea nitrogen and creatinine, electrolyte imbalances, normal 25-hydroxyvitamin D with very low 1,25-dihydroyvitamin D levels), familial hypophosphatemia, or medication use (anticonvulsants).

Even in developed countries, diagnostic proof of the etiology of rickets is not always sought [64], and there is evidence that some rickets attributed to vitamin D deficiency could have actually been due to calcium deficiency [22]. Typically, vitamin D deficiency rickets is associated with very low 25-hydroxyvitamin D (usually less than 12 nmol/L), variable (but incompletely elevated)

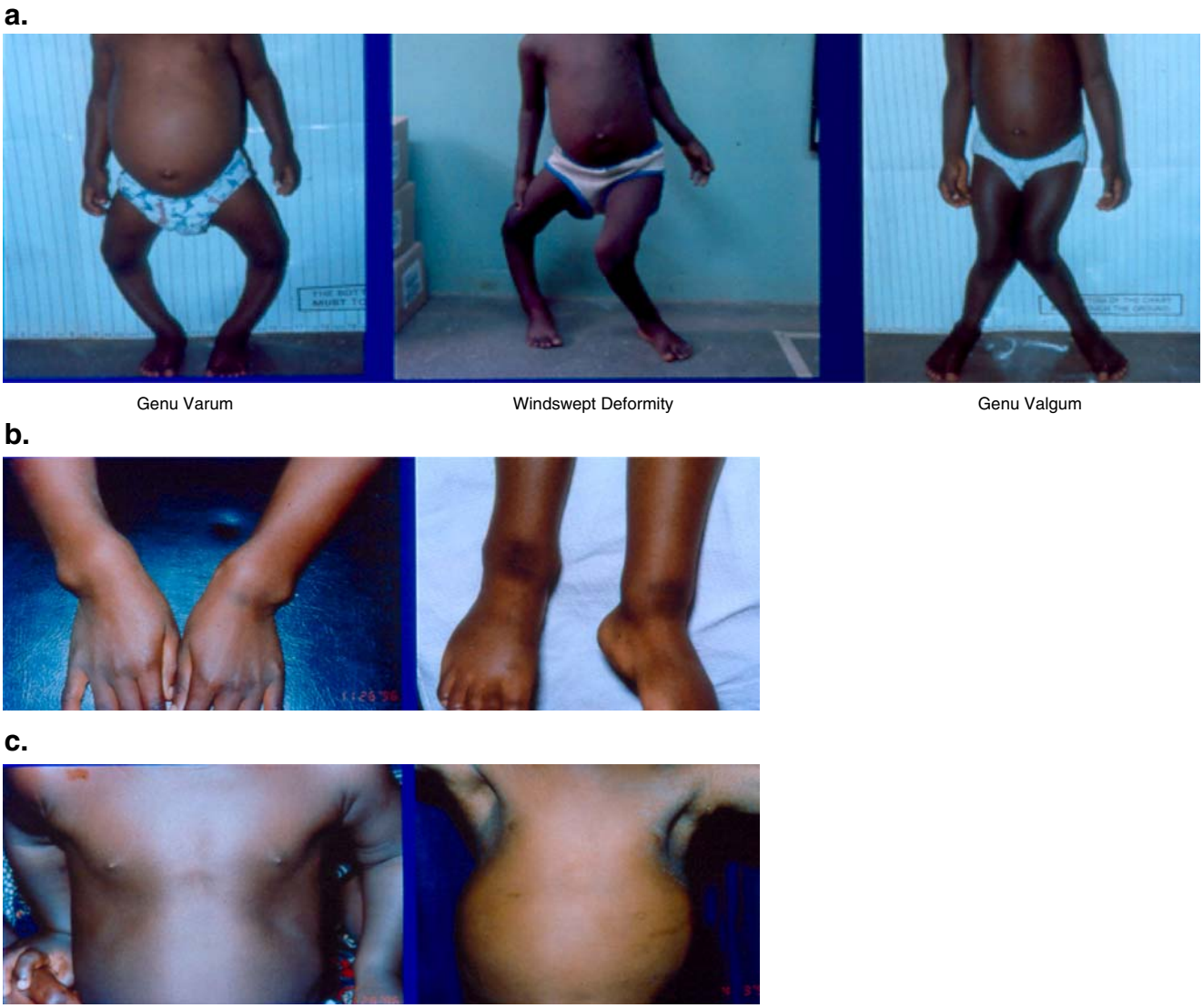

Fig. 2 Physical findings of rickets. **a** Limb deformities. **b** Widened wrists and ankles. **c** Chest deformity. **d** Beaded ribs. **e** Widened epiphyseal plates, frayed and cupped metaphyses

1,25-dihydroxyvitamin D, and elevated parathyroid hormone concentrations. With calcium deficiency rickets, serum calcium and 25-hydroxyvitamin D concentrations are normal to mildly low, while 1,25-dihydroxyvitamin D levels are extremely elevated, and parathyroid hormone values are variably elevated [19, 65].

Newer tests, though not currently readily available in most developing country settings, could potentially further identify the pathologic abnormalities of children presenting with bone disease. Bone specific alkaline phosphatase detects just the alkaline phosphatase of bone origin and overcomes the possible confounding factor of concurrent hepatobiliary disease, thus serving to measure osteoblast function. Osteocalcin is synthesized by mature osteoblasts and serves as another measure of bone formation, but is not useful in rickets [66]. Amino- and carboxy-terminal procollagen propeptides of type I collagen (PICP and PINP, respectively) are measures of both bone and collagen formation. The degree of bone resorption may be quantified by measuring hydroxyproline in the urine but interpretation may be confounded if there are other non-bone-related collagens being broken down. The pyridium crosslinks pyridinoline (PYD) and deoxypyridinoline (DPD) stabilize skeletal collagen. DPD is a more specific serum marker of bone resorption than PYD. Fasting levels of crosslinked telopeptides are both blood and urine measures of collagen degradation. Bone sialoprotein is a non-collagenous phosphoprotein in bone; increased serum levels suggest increased bone resorption [67]. These tests could be useful in basic research studies but are generally not needed to

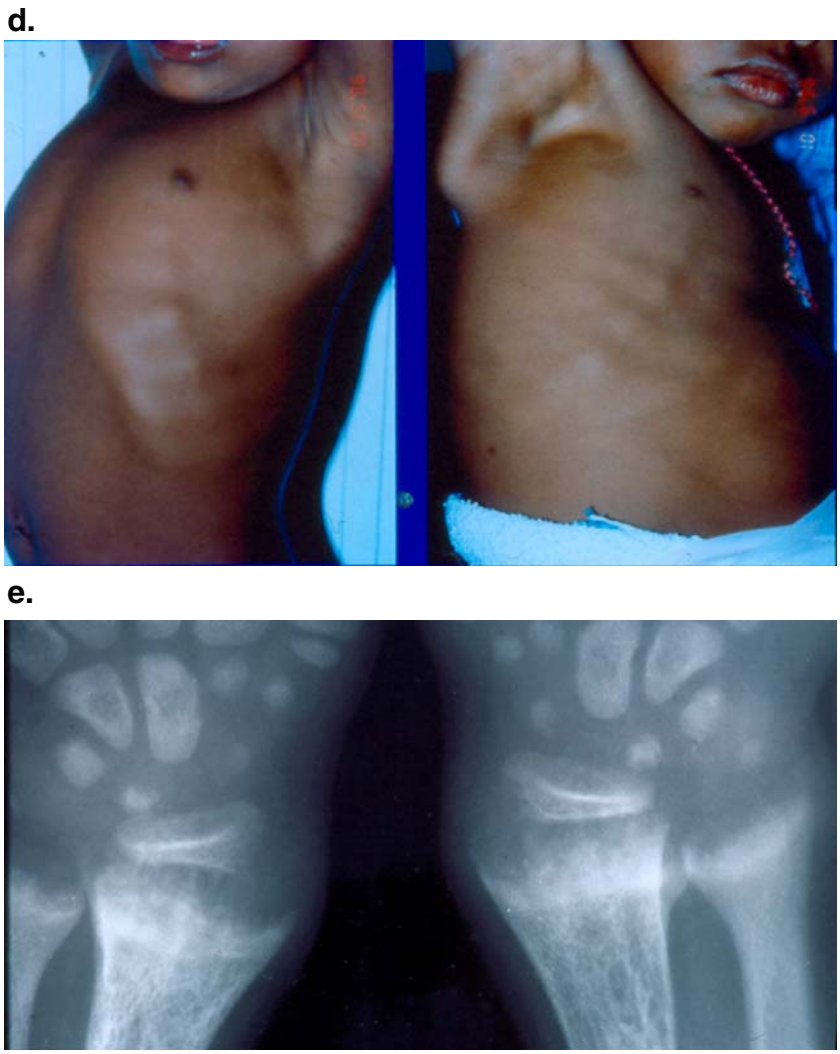

Fig. 2 (continued)

determine appropriate treatment regimens in vitamin D-deficient or calcium-deficient children.

4.3 Research needs—improved diagnosis of rickets

What further research would help with diagnostic determination for children with possible rickets in developing countries? Research applications of radiographic scoring have been useful for studies of children after the first year or two of life [61], and further determination of the clinical value of simple X-ray scoring in children would be helpful. Similarly, correlation of serum and radiographic evidence of rickets with clinical features in younger children with, predominantly, vitamin D deficiency could help clinicians better approach these children when diagnostic testing is not readily available. Identification of a simple test for a serum or urine marker of rickets would also be useful when other testing is not feasible.

5 Treatment

5.1 Prevention

Prevention of vitamin D and calcium deficiencies and thus the prevention of rickets should be a priority of pediatric nutrition. No growing child should be deprived of adequate vitamin D and calcium. There are challenges, however, in determining necessary doses and in delivering adequate preventive interventions.

Young children without certainty of sun exposure to the head for at least 60 min per week and ambulatory children without at least 60 min of sun exposure to the head and extremities each week would be candidates for vitamin D supplementation, especially if they have pigmented skin or live far from the equator. Breastmilk from unsupplemented mothers contains about 25 IU vitamin D per liter, a quantity that does not meet infant requirements [68]. In some areas,

it is suggested that all children receive supplemental vitamin D—either by pharmacologic supplements or by using fortified beverages. Current recommendations in the United States suggest that all infants, children, and adolescents receive at least 200 IU of oral vitamin D per day; this may come either as a supplement or by ingesting at least 500 mL of vitamin D-fortified beverage [68]. Others have suggested that a higher supplemental dose might be needed [8], and recommendations for vitamin D intake vary widely between countries [41]. In many developing countries, however, vitamin D supplements are not easily provided to the entire pediatric population, and providers might well suggest that children be adequately exposed to sunshine.

Calcium requirements vary as bone growth changes over time in children. Expert groups have provided recommendations that vary from 210 to 400 mg per day during the first 6 months of life, 270 to 600 mg per day during the second 6 months of life, 500 to 800 mg per day during the second through fourth years, 800 to 1,200 mg per day in preadolescents, and 1,300 to 1,500 mg per day during adolescence [13]. As mentioned earlier, these recommendations pertain to Caucasian children with typical western diets and lifestyles. Whether they apply to children in developing countries with very different dietary patterns and lifestyles is not known. It does appear however that African-American and African blacks conserve dietary calcium better than their Caucasian peers and thus may require lower calcium intakes [69, 70].

It is important to remember that these daily requirements refer to the amount of elemental calcium since the actual amount of calcium differs between various calcium salts. (13% of calcium lactate is elemental calcium, for instance, compared to 40% of calcium carbonate). Dairy products easily provide calcium for growing children. Mixing ground dried fish (ground with the bones included) or calcium salts (limestone, a widely available form of calcium carbonate) with the diet represent possible sources of dietary calcium. Vegetables contain varying amounts of calcium, with kale and collard greens being rich sources of bioavailable calcium. In Cambodia and Bangladesh, small indigenous fish serve as an important source of dietary calcium [71]. Dietary fortification has been proposed as a means of improving calcium nutrition in southeast Asia as well [72].

Internationally, there have been efforts to test interventions in the prevention of rickets. In China, community education about rickets was associated with a significant decrease in the incidence of rickets; interestingly, however, no specific preventive behaviors changed following the education [73]. In a Bangladeshi study using historical controls, the provision of even small amounts of calcium seemed to prevent rickets in a high incidence area [74]. In Nigeria, dietary supplements of calcium (using dried ground fish) and daily pharmaceutic calcium supplements were more effective than placebo in increasing bone density and in decreasing the risk of rickets during the second and third years of life.(TD Thacher, unpublished data)

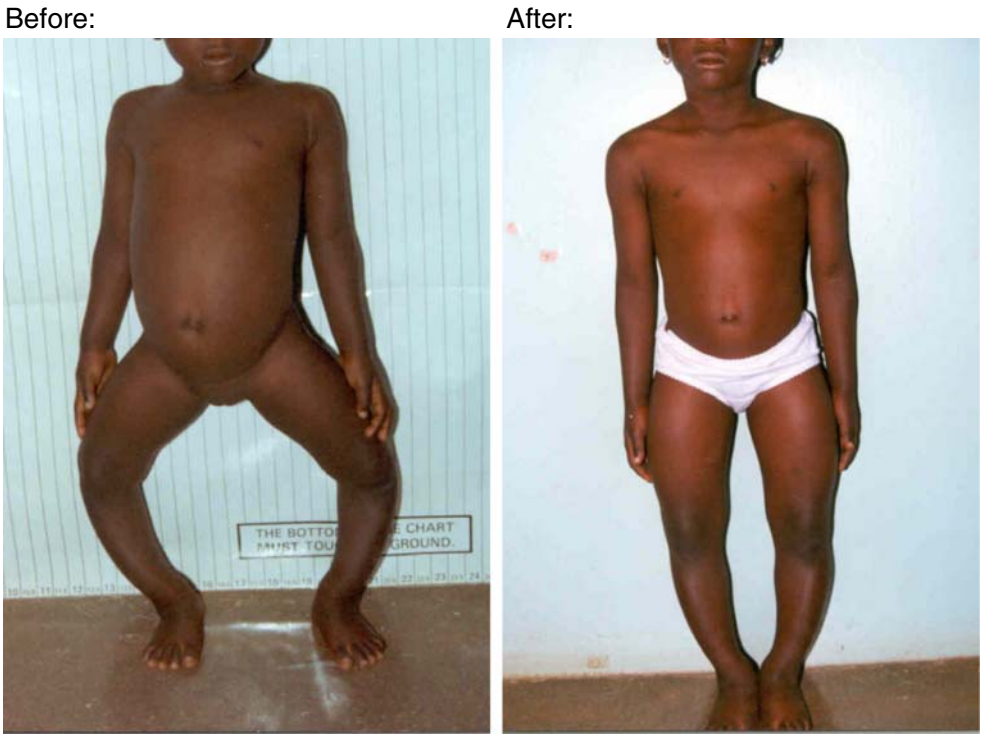

Fig. 3 Results with calcium treatment and 3 years of growth

5.2 Treatment of rickets

Whether rickets is caused primarily by either a vitamin D or a calcium deficiency or by a combination of the two deficiencies, all children with nutritional rickets need adequate vitamin D and calcium to facilitate healing. Dosing recommendations vary for the treatment of vitamin D deficiency rickets, and comparative trials have not been done. When compliance with daily treatment is uncertain, a single injection of 150,000 to 600,000 IU vitamin D in oil provides adequate vitamin D for 3 to 6 months, and the lower doses do not carry the risk of secondary hypercalcemia [41]. Otherwise, daily administration of 5,000 IU vitamin D for 2 months is usually adequate. Whatever the dosing of acute treatment, however, the child must be ensured adequate ongoing vitamin D supply, either through ensuring adequate sunlight exposure or dietary supplementation.

When rickets is primarily due to calcium deficiency, administration of 1,000 mg of supplemental daily elemental calcium for 6 months is curative [45]. For ongoing health, the child should be receiving the age-appropriate recommended daily intake of calcium. There is emerging evidence that nutritional advice alone is effective in leading to the cure of rickets with mild deformities [75].

With time and resolution of medically active rickets, rachitic deformities undergo significant spontaneous correction. (Fig. 3) When surgery is necessary for severe deformities, it should be delayed until rickets is no longer active (normalization of alkaline phosphatase and resolution of radiographic changes). Bracing (or splinting) has not been well studied but might represent a useful adjunct to medical treatment to prevent worsening deformities while initial therapy is underway [76].

5.3 Needs for further research

Further studies should help identify which populations and patients need supplemental vitamin D and/or calcium to prevent rickets [77]. Then, comparative studies could be done comparing dietary changes and various calcium supplements in preventing rickets in areas where dietary calcium insufficiency is common. The effectiveness of dietary modification in treating rickets should be carefully tested in additional studies. The dosing and duration of calcium and vitamin D treatment should be evaluated in randomized, blinded, controlled therapeutic trials. Finally, the effectiveness of bracing (splinting) of deformities should be tested.

6 Concluding summary

Rickets is the proverbial “tip of the iceberg” and represents the most obvious problem stemming from inadequate vitamin D and calcium intake. In recent years, not only has rickets re-emerged as a common problem in many areas around the planet, but the importance of dietary insufficiency of calcium has also been confirmed as a major etiologic factor in the pathophysiology of rickets [78]. In developing countries where careful diagnostic testing is incompletely available, careful clinical diagnoses can be made based on the patterns of presentation of rickets. Treatment is effective, even though further research is needed to better specify details of a “best” therapeutic regimen. Beyond rickets, deficiencies of vitamin D potentially put growing children at risk of subsequent cardiovascular, metabolic, infectious, and neoplasic disorders. Even without overt rickets, calcium insufficiency in childhood possibly represents a significant risk factor for osteoporosis and fractures during adult life. Fortunately, the coupling of implementation of new knowledge and the discovery of additional knowledge will help obviate the scourge that rickets still represents.

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