Vitamin D deficiency and low dietary calcium intakes act synergistically in increasing the prevalence of rickets in communities where both problems are present.

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Calcium and Vitamin D Metabolism in Children in Developing Countries

by John M. Pettifor

Key insights

An important role of vitamin D is to modulate the body's ability to adjust to changing calcium supply and demand. This is particularly important in developing countries, where calcium intakes are low. For dietary calcium, the consumption of dairy products was found to be a major source of this mineral. Although many children in developing countries do not meet the recommended daily intake of calcium, a large proportion of them are considered to have good bone status.

Current knowledge

Nutritional rickets is a global public health problem, affecting mainly infants and adolescents in developing countries. In some countries, vitamin D deficiency is the cause, resulting from social customs that limit sunlight exposure. In other countries where sunlight exposure is not a problem, low dietary calcium underlies the onset of rickets in older toddlers and children. The negative effects of calcium and vitamin D deficiency may have varying influences depending on genetic background and ethnic origin.

Practical implications

The factors that contribute to low vitamin D status in infants and children include overcrowding, atmospheric pollution, and clothing customs. The infant and adolescent age groups are at highest risk, particularly girls. Calcium homeostasis can effectively be adapted to low calcium intakes even with diets which are thought to impair intestinal calcium absorption. However, very low calcium intakes (below 200 mg/day) greatly increase the risk of rickets and osteomalacia. Calcium supplements

Nutritional rickets is a global health problem that affects mainly infants and adolescents in developing countries.

should be used with caution, as they do not appear to improve growth and may have adverse effects on height, although there are benefits on bone mass.

Recommended reading

Ray D, Goswami R, Gupta N, Tomar N, Singh N, Sreenivas V: Pre-disposition to vitamin D deficiency osteomalacia and rickets in females is linked to their 25(OH)D and calcium intake rather than vitamin D receptor gene polymorphism. Clin Endocrinol (Oxf) 2009;71:334–340.

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Key Messages

- In most developing countries, dietary calcium intakes of children and adolescents are approximately 1/3 to 1/2 of the recommended intakes for children living in developed countries, yet the majority of children adapt well to these lower intakes and appear to suffer no adverse effects.
- Nutritional rickets remains a public health problem among infants, young children, and adolescents in many developing countries, even in those lying within the tropical and subtropical regions of the world. Although vitamin D deficiency remains the commonest cause due to overcrowding, atmospheric pollution, and lack of sunlight exposure of lactating mothers and their infants, increasing evidence indicates that in some countries, children on very low calcium intakes may develop dietary calcium deficiency rickets.

Key Words

Dietary calcium · Vitamin D · Requirements · Children · Developing countries · Vitamin D deficiency · Rickets

Abstract

Low dietary calcium intakes and poor vitamin D status are common findings in children living in developing countries.

Despite many of the countries lying within the tropics and subtropics, overcrowding, atmospheric pollution, a lack of vitamin D-fortified foods, and social customs that limit skin exposure to sunlight are major factors in the development of vitamin D deficiency. Low dietary calcium intakes are typically observed as a consequence of a diet limited in dairy products and high in phytates and oxalates which reduce calcium bioavailability. Calcium intakes of many children are a third to a half of the recommended intakes for children living in developed countries, yet the consequences of these low intakes are poorly understood as there is limited research in this area. It appears that the body adapts very adequately to these low intakes through reducing renal calcium excretion and increasing fractional intestinal absorption. However, severe deficiencies of either calcium or vitamin D can result in nutritional rickets, and low dietary calcium intakes in association with vitamin D insufficiency act synergistically to exacerbate the development of rickets. Calcium supplementation in children from developing countries slightly increases bone mass, but the benefit is usually lost on withdrawal of the supplement. It is suggested that the major effect of calcium supplementation is on reducing the bone remodelling space rather than structurally increasing bone size or volumetric bone density. Limited evidence from one study raises concerns about the use of calcium supplements in children on habitually low calcium intakes as the previously supplemented group went through puberty earlier and had a final height several centimetres shorter than the controls.

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Introduction

In the osteoporosis literature, considerable emphasis has been placed on the importance of ensuring that peak bone mass is optimised in early adulthood so as to reduce the prevalence of low bone mass and osteoporotic fractures in the postmenopausal period in women and in elderly men. Until recently, this concept has been considered to be of importance only for high-income countries, where the proportion of elderly in the population has been increasing progressively and the cost of managing osteoporosis and its complications is an ever increasing burden on the health system, which in the USA was estimated to be 17 billion USD in direct costs in 2006 [1]. However, attention is now being drawn to the likely dramatic escalation of osteoporosis prevalence in low- and middle-income countries, where lifestyle and demographic changes will result in the proportion of all fractures rising from 50 to 75% from 1990 to 2050 [2].

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Although genetics plays an important role in determining peak bone mass, environmental factors, such as nutrition [3] and physical exercise (especially in late childhood and early puberty) [4], are considered to be important modulators of an individual's genetic potential. In countries where malnutrition is prevalent, it is clear that many factors, such as impaired growth, and nutrient deficiencies, such as protein and trace element deficiencies, also play important roles in determining bone mass and health in children [5]. Many researchers, however, believe that overall dietary calcium intake and vitamin D status are the two major nutritional factors influencing optimal bone development in childhood and adolescence [6]. In this review, I shall summarise the physiology and synergy between vitamin D and calcium, and discuss vitamin D status and dietary calcium intakes in developing countries and the effects of low vitamin D status and calcium intake on child health and development.

The Physiology of Vitamin D and Calcium

Vitamin D

Although vitamin D is considered to be a major player in bone development and homeostasis, it has other physiological roles as well. Over the past few decades, researchers have suggested that vitamin D may have other actions besides those associated with bone and mineral homeostasis. These non-classical actions of vitamin D include possible roles in immune function, autoimmune diseases, and allergy, certain cancers, such as breast, colon, and prostate, cardiovascular and metabolic diseases, and neurological disorders, such as multiple sclerosis [7]. Although these possible roles have created much excitement, a number of researchers and committees have cautioned that, although the results are of interest, empirical research to support these claims is limited [8, 9]. I shall thus not discuss these possible roles any further.

Clinical and animal studies have highlighted the central role that vitamin D plays in the physiology of mineral homeostasis by maintaining normocalcaemia through optimising intestinal calcium absorption, even at the expense of skeletal mineralisation [10]. In vitamin D-replete children and adolescents on adequate calcium intakes, approximately one third of the dietary calcium intake is absorbed, although the variation is large [11]. In vitamin D deficiency, calcium absorption has been reported to be reduced to 10–15% [12], but is not negated completely. Vitamin D-dependent intestinal calcium absorption is an important process when calcium intakes are low, as absorption is mainly transcellular and dependent on active transport involving vitamin D-dependent TRPV6 and calmodulin- D_{9k} in intestinal mucosal cells [13]. Passive paracellular calcium transport plays a major role in calcium absorption when calcium intakes are high, and probably in early neonatal life as well. The mechanism for the increased intestinal calcium absorption that occurs during pregnancy appears to be independent of vitamin D, but possibly dependent on oestrogen [13].

Thus, vitamin D status is a key factor influencing the body's ability to adjust to changing calcium supply and demand, as for example may occur at the time of weaning when dietary calcium intake may fall or during the adolescent growth spurt when calcium accretion rates into bone are maximal. This role of vitamin D is of particular importance in developing countries where calcium intakes are characteristically low and of reduced bioavailability (see later).

The Assessment of Vitamin D Status

The last 20 years have seen considerable discussion around the definitions of vitamin D sufficiency and deficiency. There is general agreement that serum 25-hydroxyvitamin D (25-OHD) concentrations are an appropriate reflection of both dietary intake and cutaneous synthesis of vitamin D, but there is still only limited consensus as to what should be considered an appropriate cutoff of 25-OHD to differentiate an adequate vitamin D status from an inadequate one. Much of the dissention centres round whether or not the cutoff should take into consideration the possible non-classical actions of vitamin D. In 2011, the Institute of Medicine of the National Academy of Sciences in the USA released its Committee's report on the dietary reference intakes for vitamin D and calcium, in which vitamin D sufficiency was defined as a 25-OHD concentration of >50 nmol/l, while the risk of vitamin D deficiency was considered to increase when 25-OHD was <30 nmol/l [9, 14]. In the same year, the Endocrine Society issued its clinical guideline for the evaluation of vitamin D deficiency [15], in which it defined 25-OHD <50 nmol/l as deficient and ≥ 75 nmol/l as optimal. A number of specific paediatric guidelines have also been published. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition has highlighted the difficulty in defining a cut-point for vitamin D deficiency but recommends 25-OHD >50 nmol/l as indicative of sufficiency and <25 nmol/l as indicative of severe deficiency [16]. The American Academy of Pediatrics has defined deficiency as 25-OHD ≤ 37.5 nmol/l and sufficiency as 50–250 nmol/l [17]. From a paediatric bone health perspective, it is frequently considered that 25-OHD of <25 or 30 nmol/l is necessary before disturbances in bone health are seen [18].

A number of studies have estimated the prevalence of vitamin D deficiency in different countries around the world using a variety of different cutoffs for 25-OHD to diagnose deficiency [6, 18–20]. Prentice's [18] paper highlights the effect of using different 25-OHD cutoffs on the prevalence of vitamin D deficiency in the UK. Across adults' and children's age ranges, the prevalence varied between 20 and 50% if a cutoff of 50 nmol/l was used, while the prevalence was 5–20% if 25 nmol/l was used. Utilising 50 nmol/l as the cutoff globally, it has been estimated that over 1 billion people would be classified as being vitamin D deficient, and would result in the majority

of countries having a large proportion of their populations being classified as such [20]. However, there is little information on vitamin D status from most developing countries. Arabi et al. [19], looking specifically at data from developing countries, were only able to find information on 23 of 144 such countries. Despite many of the developing countries lying within the tropical and subtropical zones and thus being exposed to UV radiation around the year, the authors concluded that hypovitaminosis D (varying cut-points were used, but the major-

ity of studies used <37.5 or <25 nmol/l) was prevalent in most areas of the world, especially in the Middle East and North Africa, China and South Asia (India, Pakistan, and Bangladesh). There are, however, a number of caveats

that must be highlighted, the most important of which being that the studies only represented a small proportion of all developing countries and, therefore, may not typify the picture in all such countries and that the paediatric age ranges were generally poorly covered. Very few studies have been conducted among children in Africa, but studies from the Gambia [18] and Nigeria [21] on the west coast and South Africa [22] have indicated that vitamin D deficiency is uncommon in ambulatory children and adolescents, but information on early infancy is limited. Studies from Ethiopia [23] and Sudan [24] suggest that infantile rickets due to vitamin D deficiency is not uncommon and is associated with malnutrition, limited sunlight exposure, and prolonged breastfeeding. Traditional indigenous ethnic groups within Tanzania were found to be vitamin D replete with 25-OHD concentrations well above 50 nmol/l [25]. In general, the factors responsible for a low vitamin D status among infants and children in developing countries reflect inadequate skin exposure to UV radiation as a consequence of overcrowding, atmospheric pollution, little opportunity to play out of doors, and clothing customs, ensuring extensive skin coverage.

If reports on vitamin D deficiency rickets/osteomalacia are used as a guide to assess the age groups at risk of vitamin D deficiency, then in most countries, it is the infant and adolescent age groups who are most at risk. In the adolescent age group in many developing countries, it is girls who are most prone to vitamin D deficiency due to cultural practices which see greater skin coverage by clothing and reduced outside activities by girls. Children in most developing countries are almost exclusively de-

Utilising 50 nmol/l as the cutoff globally, it has been estimated that over 1 billion people would be classified as being vitamin D deficient.

Table 1. Calcium intakes in children in a number of developing countries around the world

Country	Age, years	Calcium intake, mg/day ¹	Ref.
Kenya (rural)	7	316	29
South Africa (rural)	3–5	282±144	30
	8–10	338±170	
	13–16	378±279	
Bangladesh (rural)	2–4	142	31
India (urban)	2–4	172	32
	10–18	314±194 (low SES)	33
		713±241 (high SES)	
China	<5	123–130	34
China	10±0.4	433±170	35
Brazil	1–6	728–763	36

SES = Socioeconomic status. ¹ Calcium intakes are given as the mean, with or without the standard deviation. If a range is shown, it implies that there was a range of means for the age group quoted.

pendent on the cutaneous synthesis of vitamin D rather than on dietary intake, as very few available foods (besides oily fish) in these regions naturally contain significant amounts of vitamin D or are vitamin D fortified. Breast-fed infants in developing countries are also largely dependent on UV radiation to ensure their vitamin D status, as the vitamin D status of pregnant and lactating women is frequently poor resulting in low 25-OHD concentrations in the neonate and low vitamin D content in breast milk [26]. Studies have suggested that lactating mothers may need vitamin D supplements as high as 6,400 IU/day for sufficient vitamin D to cross in breast milk to ensure infant 25-OHD concentrations equivalent to those obtained if the infant was supplemented with 400 IU/day directly [27]. Supplements with doses as high as those given to the lactating mothers in the above study are not recommended until they have been shown to be safe in large clinical trials.

Calcium

In most populations, dietary calcium intakes are largely dependent on dairy product consumption. In 1990, the Food and Agriculture Organisation (FAO) estimated that the average per capita calcium intake in developed countries was 850 mg/day compared to 344 mg/day in developing countries. The major nutrient difference responsible for the markedly lower calcium intakes in developing countries was the proportion of calcium derived from animal (dairy) sources [28]. The FAO-estimated per capita

consumption in developing countries is very similar to the average calcium intakes of children who have been assessed by food frequency questionnaires and 24-hour dietary assessments in a number of different countries (table 1). Thus, many children have intakes of 300–400 mg/day, which are mainly derived from vegetable sources, as dairy product consumption is limited once weaning occurs, except possibly in more affluent communities [37].

Recommended dietary calcium intakes vary between different countries, but using the recent recommendations from the Institute of Medicine of the National Academy of Sciences, USA, as a guideline, its recommended daily allowance (RDA) for children increased between the ages of 1 year and 18 years from 700 to 1,300 mg/day and its estimated average requirement increased from 500 to 1,100 mg/day [38]. Clearly, many children in developing countries do not meet these recommendations, yet the majority would be considered healthy, as far as bone status is concerned.

How Do Children Adapt to Low Calcium Content of Diets?

As mentioned earlier, calcium homeostasis is maintained mainly by controlling the gastrointestinal absorption of calcium. Typically, calcium absorption at recommended intakes is an active process, dependent on an adequate vitamin D status and intact renal and parathyroid function. Fractional calcium absorption is inversely proportional to calcium intake, but is also greater in African-American than in white American pre- and postmenarchal girls (39 vs. 30 and 44 vs. 25%, respectively, at intakes of approximately 900 mg/day) [39]. A few absorption studies have been conducted in children in developing countries, where calcium intakes are less than half those of children living in developed countries. In Nigeria, Thacher and Abrams [40] found a mean fractional absorption of 61% in children between 2 and 14 years of age with a mean calcium intake of 227 mg/day. This fractional absorption is very similar to that of 63.1% reported for Chinese children on low calcium intakes of 359 mg/day [41]. These values are thus approximately double those of children on calcium intakes close to the RDA. Children on low calcium intakes also reduce their renal excretion of calcium, but the obligatory loss of calcium from the gastrointestinal tract is similar in those on normal and low calcium intakes. It thus appears that children on habitually low dietary calcium intakes adapt very effectively to these lower intakes, probably through stimulation of renal CYP27B1 (1- α hydroxylase) and increased produc-

tion of 1,25-(OH)₂D. What is not known, however, is whether this is only achieved at higher circulating 25-OHD concentrations than are required by children on higher calcium intakes. Further, it is unclear at what level of calcium intake bone mass becomes negatively affected, and if it does, whether it is more likely to occur when bone accretion is maximal during the period of peak height velocity during puberty. Although calcium supplementation of diets has been shown to increase bone mass marginally in children, the effects are marginal and generally only maintained during supplementation [42]. This effective adaptation of calcium homeostasis to low calcium intakes is achieved on diets frequently high in phytates and oxalates which are thought to impair intestinal calcium absorption in humans [43].

Nutritional Rickets in Developing Countries

As discussed earlier, nutritional rickets is a major public health problem affecting mainly infants and adolescents in many developing countries, even among those living within tropical or subtropical regions. In a number of these countries, such as Algeria, Egypt, Turkey, and the Middle East, vitamin D deficiency has been clearly established as the cause, resulting from social customs which limit skin exposure to sunlight and UV radiation of both the mother and her breastfed infant, and of adolescent girls, in particular.

In other countries, such as India [44], Bangladesh, Nigeria, and South Africa, reports have highlighted the role that low dietary calcium intakes play in the pathogenesis of rickets in generally older toddlers and children, in whom sunlight exposure is not limited. In all four countries, calcium intakes of those with rickets have been estimated to be approximately 200 mg/day. Although serum 25-OHD concentrations in affected children are lower than those in control subjects, the mean values are generally above 30 nmol/l, which is higher than those found in typical vitamin D deficiency. Another characteristic biochemical feature is the marked elevation of 1,25-(OH)₂D concentrations prior to treatment (fig. 1). Concentrations are generally 1.5–2 times higher than those found in age-matched community controls [45]. In a randomised controlled trial from Nigeria, children with rickets suspected of being due to dietary calcium deficiency responded better to calcium alone or to calcium and vitamin D supplements than to vitamin D alone [46]. In India, the response of children with active rickets to calcium supplements has been mixed, suggesting that both vitamin D and calcium deficiency are causes of rickets on the subcontinent [44, 47].

Fig. 1. Schematic representation of the pathogenesis of vitamin D deficiency and dietary calcium deficiency rickets. + = Stimulatory effect; - = suppressive effect; Ca = calcium; iCa = ionized calcium; Pi = inorganic phosphate; PTH = parathyroid hormone; Vit D = vitamin D.

Bone Mass in Children Living in Developing Countries

A question of considerable importance to children and adolescents living in developing countries who have habitually low dietary calcium intakes is: 'Is there any evidence of deleterious consequences of these low calcium intakes on bone mass accrual during childhood and adolescence and therefore on peak bone mass attained in early adulthood?', as poor bone growth and impaired peak bone mass might influence the incidence of fractures during childhood and of osteoporosis and fragility fractures in later life. As discussed in the previous section, there is now good evidence that very low calcium intakes of approximately 200 mg/day may be associated with impaired

mineralisation and rickets, but is there evidence that children whose intakes are above these very low values but below the RDA have reduced bone mass?

The interpretation of bone mass measurements during childhood is difficult because of the close relationship that the measured bone mass variables of bone area, bone mineral density (BMD), and bone mineral content (BMC) have with body height, weight, and pubertal development [48]. Thus, during the assessment and interpretation of bone mass in children and adolescents, these variables need to be taken into consideration. Because of marked differences in growth rates and pubertal development in children living in developing communities compared to those in more affluent societies, reference data generated in developed countries need to be used and interpreted with caution when assessing bone mass of children and adolescents in developing communities. Numerous environmental and genetic factors play roles in determining bone mass in a growing child.

In South Africa, studies have consistently shown ethnic differences in bone mass between black and white children and pre- and postmenopausal women. Black children and women have greater bone mass at the femoral neck than their white peers, despite calcium intakes of the black participants being approximately half those of whites, nutrition in general being poorer in the black groups, and the black participants being shorter than their white peers [49, 50]. Bone mass at the lumbar spine and whole body was found to be similar in blacks and whites after adjusting for differences in body size. These results differ from those reported for African-American and non-black children in the USA, where African-American children have greater bone area and BMC at all measured sites (lumbar spine, hip, radius, and whole body) than non-black children [48]. In South Africa, despite the lower calcium intakes and the poorer growth of black children, they have a fracture incidence approximately half that of white children even though X-ray absorptiometry-measured bone mass is similar at most skeletal sites [51].

In the Gambia, calcium supplementation (1,000 mg/day for 5 days a week) of pre- or early-pubertal children, who had habitual calcium intakes of approximately 340 mg/day, resulted in a 4–5% greater increase in radial BMC than in controls over 12 months [52]. The authors concluded that this rise was a result of a reduction in bone remodelling space rather than an actual increase in bone

size or a correction of the effects of dietary calcium deficiency. The calcium supplements had no effect on growth during the period of administration, but on follow-up, after stopping the supplementation, previously supplemented boys had advanced mid-adolescent height growth and an earlier peak height velocity. The net effect was an earlier cessation of growth in the previously supplemented boys, who at 23 years of age were 3 cm shorter than their non-supplemented peers [53]. No long-term effects on growth or pubertal development were noted in girls. Although these findings have not yet been confirmed in other studies, they do raise concern that altering habitual intakes through supplementation may have unintended adverse consequences.

Paediatric reference values for BMC and BMD have been published from a number of developing countries, including India [54] and China [55]. Total body BMC and

Altering habitual intakes through supplementation may have unintended adverse consequences.

BMD were found to be lower at most ages in Indian and Chinese children than in Caucasians from Europe, even after correcting for differences in height. The Indian participants had normal growth pa-

rameters (using Indian growth references) and had been carefully selected from private schools, thus excluding children from poorer communities who were more likely to be more undernourished, have poorer vitamin D status, and have lower dietary calcium intakes. A number of supplementation studies using both calcium and/or vitamin D have been conducted in children from India, where vitamin D deficiency is a frequent finding. Groups receiving calcium and vitamin D had greater increases in bone mass than those receiving vitamin D alone [33, 56]. In China, calcium supplementation in children, who had habitually low calcium intakes of 280 mg/day, resulted in an increase in appendicular bone mass [57] similar to that reported from supplementation studies of children on much higher calcium intakes. As has been reported from a number of other calcium supplementation studies, the bone mass advantage was lost within 18 months of stopping the supplement [58]. The calcium supplements had no effect on growth.

Conclusions

Following weaning, children living in the majority of developing countries have habitual dietary calcium intakes between one third and a half of the recommended intakes for children in the developed world. For the ma-

jority of these children, there is little evidence to suggest that their mineral balance or bone mass is adversely affected by these low intakes, provided their vitamin D status is not compromised as well. There is, however, evidence that children on very low calcium intakes of approximately 200 mg/day or less may develop rickets and osteomalacia, which responds to treatment with calcium supplements alone. Further research is required to elucidate the various factors predisposing these children to rickets. Calcium supplementation in children from developing countries does not appear to improve growth and may in fact have adverse effects on final height. Bone mass increases during calcium supplementation, but most studies have found that the benefit is lost following cessation of the supplement.

Poor vitamin D status remains a major public health problem among infants, young children, and adolescents in many developing countries despite adequate sunshine

and UV radiation. Overcrowding, atmospheric pollution, the lack of vitamin D-fortified food, and social customs which reduce sunlight exposure are major factors responsible for the high prevalence. Vitamin D deficiency and low dietary calcium intakes act synergistically in increasing the prevalence of rickets in communities where both problems are present.

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References

- Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A: Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res* 2007;22:465–475.
- Cooper C, Campion G, Melton LJ III: Hip fractures in the elderly: a world-wide projection. *Osteoporos Int* 1992;2:285–289.
- Greer FR, Krebs NF; American Academy of Pediatrics Committee on Nutrition: Optimizing bone health and calcium intakes of infants, children, and adolescents. *Pediatrics* 2006;117:578–585.
- Gunter KB, Almstedt HC, Janz KF: Physical activity in childhood may be the key to optimizing lifespan skeletal health. *Exerc Sport Sci Rev* 2012;40:13–21.
- Prentice A, Schoenmakers I, Laskey MA, de Bono S, Ginty F, Goldberg GR: Nutrition and bone growth and development. *Proc Nutr Soc* 2006;65:348–360.
- Fischer PR, Thacher TD, Pettifor JM: Pediatric vitamin D and calcium nutrition in developing countries. *Rev Endocr Metab Disord* 2008;9:181–192.
- Rosen CJ, Adams JS, Bikle DD, Black DM, Demay MB, Manson JE, Murad MH, Kovacs CS: The nonskeletal effects of vitamin D: an Endocrine Society scientific statement. *Endocr Rev* 2012;33:456–492.
- Rosen CJ, Taylor CL: Common misconceptions about vitamin D – implications for clinicians. *Nat Rev Endocrinol* 2013;9:434–438.
- Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA: The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011;96:53–58.
- Lieben L, Masuyama R, Torrekens S, Van Looveren R, Schrooten J, Baatsen P, Lafage-Proust MH, Dresselaers T, Feng JQ, Bone-wald LF, Meyer MB, Pike JW, Bouillon R, Carmeliet G: Normocalcemia is maintained in mice under conditions of calcium malabsorption by vitamin D-induced inhibition of bone mineralization. *J Clin Invest* 2012;122:1803–1815.
- Abrams SA, Griffin IJ, Hawthorne KM, Gunn SK, Gundberg CM, Carpenter TO: Relationships among vitamin D levels, parathyroid hormone, and calcium absorption in young adolescents. *J Clin Endocrinol Metab* 2005;90:5576–5581.
- Dimitri P, Bishop N: Rickets. *Paediatr Child Health* 2007;17:279–287.
- Christakos S, Lieben L, Masuyama R, Carmeliet G: Vitamin D endocrine system and the intestine. *BoneKey Rep* 2014, DOI: 10.1038/bonekey.2013.230.
- Aloia JF: The 2011 report on dietary reference intake for vitamin D: where do we go from here? *J Clin Endocrinol Metab* 2011;96:2987–2996.
- Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM, Endocrine S: Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96:1911–1930.
- Braegger C, Campoy C, Colomb V, Decsi T, Domellof M, Fewtrell M, Hojsak I, Mihatsch W, Molgaard C, Shamir R, Turck D, van Goudoever J: Vitamin D in the healthy European paediatric population. *J Pediatr Gastroenterol Nutr* 2013;56:692–701.
- Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M; Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society: Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics* 2008;122:398–417.
- Prentice A: Vitamin D deficiency: a global perspective. *Nutr Rev* 2008;66:S153–S164.
- Arabi A, El Rassi R, El-Hajj Fuleihan G: Hypovitaminosis D in developing countries – prevalence, risk factors and outcomes. *Nat Rev Endocrinol* 2010;6:550–561.
- van Schoor NM, Lips P: Worldwide vitamin D status. *Best Pract Res Clin Endocrinol Metab* 2011;25:671–680.
- Pfützner MA, Thacher TD, Pettifor JM, Zoumakis AI, Lawson JO, Isichei CO, Fischer PR: Absence of vitamin D deficiency in young Nigerian children. *J Pediatr* 1998;133:740–744.

- 22 Poopedi MA, Norris SA, Pettifor JM: Factors influencing the vitamin D status of 10-year-old urban South African children. *Public Health Nutr* 2011;14:334–339.
- 23 Wondale Y, Shiferaw F, Lulseged S: A systematic review of nutritional rickets in Ethiopia: status and prospects. *Ethiop Med J* 2005;43:203–210.
- 24 el Hag AI, Karrar ZA: Nutritional vitamin D deficiency rickets in Sudanese children. *Ann Trop Paediatr* 1995;15:69–76.
- 25 Luxwolda M, Kuipers R, Kema I, Veer E, Dijk-Brouwer DAJ, Muskiet FJ: Vitamin D status indicators in indigenous populations in East Africa. *Eur J Nutr* 2013;52:1115–1125.
- 26 Dawodu A, Wagner CL: Prevention of vitamin D deficiency in mothers and infants worldwide – a paradigm shift. *Paediatr Int Child Health* 2012;32:3–13.
- 27 Wagner CL, Hulse TC, Fanning D, Ebeling M, Hollis BW: High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeed Med* 2006;1:59–70.
- 28 Food and Agriculture Organization of the United Nations: *Production Yearbook Vol 44*. Rome, FAO, 1990.
- 29 Grillenberger M, Neumann CG, Murphy SP, Bwibo NO, Weiss RE, Jiang L, Hautvast JG, West CE: Intake of micronutrients high in animal-source foods is associated with better growth in rural Kenyan school children. *Br J Nutr* 2006;95:379–390.
- 30 Eyberg C, Pettifor JM, Moodley G: Dietary calcium intake in rural black South African children. The relationship between calcium intake and calcium nutritional status. *Hum Nutr Clin Nutr* 1986;40C:69–74.
- 31 Arsenault JE, Yakes EA, Islam MM, Hossain MB, Ahmed T, Hotz C, Lewis B, Rahman AS, Jamil KM, Brown KH: Very low adequacy of micronutrient intakes by young children and women in rural Bangladesh is primarily explained by low food intake and limited diversity. *J Nutr* 2013;143:197–203.
- 32 Ekbote VH, Khadilkar AV, Chiplonkar SA, Hanumante NM, Khadilkar VV, Mughal MZ: A pilot randomized controlled trial of oral calcium and vitamin D supplementation using fortified laddoos in underprivileged Indian toddlers. *Eur J Clin Nutr* 2011;65:440–446.
- 33 Bhatia V: Dietary calcium intake – a critical reappraisal. *Indian J Med Res* 2008;127:269–273.
- 34 Willows ND, Barbarich BN, Wang LC, Olstad DL, Clandinin MT: Dietary inadequacy is associated with anemia and suboptimal growth among preschool-aged children in Yunnan Province, China. *Nutr Res* 2011;31:88–96.
- 35 Zhang Q, Ma G, Greenfield H, Zhu K, Du X, Foo LH, Hu X, Fraser DR: The association between dietary protein intake and bone mass accretion in pubertal girls with low calcium intakes. *Br J Nutr* 2010;103:714–723.
- 36 de Castro MA, Verly E Jr, Fisberg M, Fisberg RM: Children's nutrient intake variability is affected by age and body weight status according to results from a Brazilian multicenter study. *Nutr Res* 2014;34:74–84.
- 37 Marwaha RK, Tandon N, Reddy DR, Aggarwal R, Singh R, Sawhney RC, Saluja B, Ganie MA, Singh S: Vitamin D and bone mineral density status of healthy schoolchildren in northern India. *Am J Clin Nutr* 2005;82:477–482.
- 38 Institute of Medicine: *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, National Academies Press, 2011.
- 39 Abrams SA, O'Brien KO, Liang LK, Stuff JE: Differences in calcium absorption and kinetics between black and white girls aged 5–16 years. *J Bone Miner Res* 1995;10:829–833.
- 40 Thacher TD, Abrams SA: Relationship of calcium absorption with 25(OH)D and calcium intake in children with rickets. *Nutr Rev* 2010;68:682–688.
- 41 Lee WT, Leung SS, Fairweather-Tait SJ, Leung DM, Tsang HS, Eagles J, Fox T, Wang SH, Xu YC, Zeng WP, et al: True fractional calcium absorption in Chinese children measured with stable isotopes (^{42}Ca and ^{44}Ca). *Br J Nutr* 1994;72:883–897.
- 42 Winzenberg T, Shaw K, Fryer J, Jones G: Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. *BMJ* 2006;333:775.
- 43 Gibson RS, Bailey KB, Gibbs M, Ferguson EL: A review of phytate, iron, zinc, and calcium concentrations in plant-based complementary foods used in low-income countries and implications for bioavailability. *Food Nutr Bull* 2010;31:S134–S146.
- 44 Aggarwal V, Seth A, Aneja S, Sharma B, Sonkar P, Singh S, Marwaha RK: Role of calcium deficiency in development of nutritional rickets in Indian children: a case control study. *J Clin Endocrinol Metab* 2012;97:3461–3466.
- 45 Glorieux FH, Pettifor JM: Vitamin D/dietary calcium deficiency rickets and pseudo-vitamin D deficiency rickets. *BoneKey Rep* 2014, DOI: 10.1038/bonekey.2014.1019.
- 46 Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Isichei CO, Reading JC, Chan GM: A comparison of calcium, vitamin D, or both for nutritional rickets in Nigerian children. *N Engl J Med* 1999;341:563–568.
- 47 Balasubramanian K, Rajeswari J, Gulab, Govil YC, Agarwal AK, Kumar A, Bhatia V: Varying role of vitamin D deficiency in the etiology of rickets in young children versus adolescents in northern India. *J Trop Pediatr* 2003;49:201–206.
- 48 Zemel BS, Kalkwarf HJ, Gilsanz V, Lappe JM, Oberfield S, Shepherd JA, Frederick MM, Huang X, Lu M, Mahboubi S, Hangartner T, Winer KK: Revised reference curves for bone mineral content and areal bone mineral density according to age and sex for black and non-black children: results of the bone mineral density in childhood study. *J Clin Endocrinol Metab* 2011;96:3160–3169.
- 49 Daniels ED, Pettifor JM, Schnitzler CM, Russell SW, Patel DN: Ethnic differences in bone density in female South African nurses. *J Bone Miner Res* 1995;10:359–367.
- 50 Vidulich L, Norris SA, Cameron N, Pettifor JM: Differences in bone size and bone mass between black and white 10-year-old South African children. *Osteoporos Int* 2006;17:433–440.
- 51 Thandrayen K, Norris SA, Micklesfield LK, Pettifor JM: Heterogeneity of fracture pathogenesis in urban South African children: the birth to twenty cohort. *J Bone Miner Res* 2011;26:2834–2842.
- 52 Dibba B, Prentice A, Ceesay M, Stirling DM, Cole TJ, Poskitt EM: Effect of calcium supplementation on bone mineral accretion in Gambian children accustomed to a low-calcium diet. *Am J Clin Nutr* 2000;71:544–549.
- 53 Prentice A, Dibba B, Sawo Y, Cole TJ: The effect of prepubertal calcium carbonate supplementation on the age of peak height velocity in Gambian adolescents. *Am J Clin Nutr* 2012;96:1042–1050.
- 54 Khadilkar AV, Sanwalka NJ, Chiplonkar SA, Khadilkar VV, Mughal MZ: Normative data and percentile curves for dual energy X-ray absorptiometry in healthy Indian girls and boys aged 5–17 years. *Bone* 2011;48:810–819.
- 55 Guo B, Xu Y, Gong J, Tang Y, Xu H: Age trends of bone mineral density and percentile curves in healthy Chinese children and adolescents. *J Bone Miner Metab* 2013;31:304–314.
- 56 Khadilkar A, Kadam N, Chiplonkar S, Fischer PR, Khadilkar V: School-based calcium-vitamin D with micronutrient supplementation enhances bone mass in underprivileged Indian premenarchal girls. *Bone* 2012;51:1–7.
- 57 Lee WT, Leung SS, Wang SH, Xu YC, Zeng WP, Lau J, Oppenheimer SJ, Cheng JC: Double-blind, controlled calcium supplementation and bone mineral accretion in children accustomed to a low-calcium diet. *Am J Clin Nutr* 1994;60:744–750.
- 58 Lee WT, Leung SS, Leung DM, Cheng JC: A follow-up study on the effects of calcium-supplement withdrawal and puberty on bone acquisition of children. *Am J Clin Nutr* 1996;64:71–77.