

.....

Consensus Development for the Supplementation of Vitamin D in Childhood and Adolescence

*Ze'ev Hochberg^a, Abdullah Bereket^b, Marsha Davenport^c,
Henriette A. Delemarre-Van de Waal^d, Jean De Schepper^e,
Michael A. Levine^f, Nicolas Shawg Eckhard Schoenau^h,
Silvia C. van Coeverden^d, Yosef Weismani Zvi Zadik^k, on behalf of the
European Society for Paediatric Endocrinology (ESPE) Bone Club*

^aMeyer Children Hospital, Haifa, Israel; ^bMarmara University, Istanbul, Turkey;
^cUniversity of North Carolina, Chapel Hill, N.C., USA; ^dVrije Universiteit,
Amsterdam, The Netherlands; ^eAcademic Hospital V.V.B., Brussels, Belgium;
^fJohns Hopkins University, Baltimore, Md., USA; ^gBirmingham Children's Hospital,
Birmingham, UK; ^hUniversitätskinderklinik, Cologne, Germany;
ⁱDana Children's Hospital, Tel Aviv, Israel; ^jKaplan Hospital Rehovot, Israel

Contents

The Consensus Process	260
Definitions	260
Nutritional Rickets and Treatment: An Overview	261
Nutritional Rickets in Developing Countries	263
Nutritional Rickets in Developed Countries: Racial and Ethnic Considerations	265
Nutritional Rickets in the USA	267
Fortification of Food with Vitamin D	268
Vitamin D and Preterm Infants	268
Vitamin D and Puberty	269
Vitamin D and Chronic Diseases	270
Vitamin D and Drug Therapy	272
Conclusions	274
Perspectives	275

The need for dietary supplementation of vitamin D during infancy has been widely accepted, yet rickets remains common even in the most affluent societies [1]. Several studies have suggested a relationship between childhood calcium and vitamin D intake and bone mineralization, fractures in adolescents, and osteoporosis in adulthood; but nutritional requirements and recommendations for supplementation are controversial. To insure that risk factors for vitamin D deficiency are well understood and that daily requirements for calcium and vitamin D for children are recognized, the Bone Club of the European Society for Paediatric Endocrinology (ESPE) convened a consensus development symposium on July 6, 2001.

The Consensus Process

The consensus development panel included pediatric endocrinologists from ten universities in Europe and the USA. Each of the participants reviewed the literature on a topic related to pediatric and adolescent vitamin D supplementation, and these reviews were presented at the consensus symposium. The reviews were then discussed by the panel and the symposium audience. The discussion was added to the reviews and the second draft was distributed to the panel members for comments. The final draft was presented as a consensus statement, and was approved by all panel members and the Board of the ESPE Bone Club. This statement is a consensus by the panel on the recommendations for prevention and treatment of vitamin D deficiency in the healthy pediatric population as well as at-risk pediatric populations such as infants and children during accelerated growth (puberty and catch-up from disease), with chronic diseases, on drug therapy, in developing countries, of a dark-skinned race and/or living away from the equator.

Definitions

Vitamin D is not a vitamin in the strict definition because it can be produced by exposure of the skin to sunlight. As such, humans do not have a dietary requirement for vitamin D when sufficient sunlight is available. However, nutritional vitamin D becomes essential when sunlight is insufficient to meet daily needs. This has become particularly acute as more people reside in urban centers where they are exposed to suboptimal levels of sunlight. Ultraviolet light from the sun is blocked by air pollution, clothes, tall buildings, indoor dwelling, and sunscreens, and these factors all reduce the ability of the skin to synthesize vitamin D₃. Moreover, people living far north (or south) of the equator obtain little purposeful ultraviolet radiation during the winter months. Under these

conditions, vitamin D (and its hormone derivative calcitriol) can be considered a bona fide vitamin in that it must be supplied in the diet [2].

The World Health Organization has defined the 'international unit' of vitamin D₃ as the activity of 0.025 µg of the international standard preparation of crystalline vitamin D₃. Thus, 1 IU of vitamin D₃ is 0.025 µg, or 65 pmol. The unit definition of the active metabolite calcitriol was set to be equivalent in molar terms to that of the parent vitamin D₃. Thus, 1 unit is 65 pmol of calcitriol, but as only a small fraction (<1/1,000) of vitamin D is converted to the active metabolite, a unit of calcitriol is over 1,000-fold more active than vitamin D itself. The vitamin D requirements for children or adults have not been precisely defined. Historically, it was defined on the basis of the vitamin D content in a teaspoon of fish oil, a quantity shown to be sufficient to prevent rickets. A more rigorous scientific definition is unavailable. The recommended dietary allowance (RDA) is the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals in each life stage and gender group. There is insufficient evidence to establish a RDA for vitamin D. Instead, an adequate intake (AI), a level of intake sufficient to maintain healthy blood levels of calcitriol, has been established. The 1998 AI's proposed by the Food and Nutrition Board of the Commission on Life Sciences of the National Research Council are 400 IU/day for infants, 200 IU/day up to the age of 50, 400 IU/day from age 51 to 70 and 600 IU/day over age 70 [3]. As vitamin D is endogenously produced and stored in adipose tissue for long periods of time, it is difficult to determine with exactness the dietary requirements. The daily requirement is also dependent on the dietary levels of calcium and phosphorus, age, sex and skin pigmentation, and exposure to sunshine (table 1).

Nutritional Rickets and Treatment: An Overview

Nutritional rickets can be classified according to the primary metabolic abnormality into disorders resulting from a decreased availability of vitamin D, calcium or phosphorus. Vitamin D deficiency rickets occurs most commonly during two periods in infancy, in the early months of life and during the toddler period. Vitamin D and 25-hydroxyvitamin D (25(OH)D), which cross the placenta during the last months of gestation, furnish the main vitamin D requirement of the newborn in its first months of life. Indeed, vitamin D deficiency rickets in early infancy is most prevalent in those infants whose mothers have poor vitamin D reserves due to inadequate diet, dark skin pigmentation, or religious dress codes that limit/prevent skin exposure. Vitamin D supplementation of 400 IU/day (10 µg) should be given to all pregnant women who are at high risk for vitamin D deficiency. It remains to be determined whether vitamin D

Table 1. Previous recommendations for calcium, phosphorus and vitamin D supplementation in premature infants

a European Society of Pediatric Gastroenterology and Nutrition			
	Breast-fed	Formula-fed (total amount per day)	
Calcium, mg/kg	up to 180 (milk + supplement)	80–180	
Phosphorus, mg/kg	up to 17 (added to milk)	up to 120	
Vitamin D, IU	800–1,600	800–1,600	

b American Academy of Pediatrics			
	Weight 800–1,200 g	1,200–1,800 g	
Calcium, mg/kg	210	185	
Phosphorus, mg/kg	140	75–120	
Vitamin D, IU	500	500	

c Canadian Pediatric Society			
	0–7 days	7 days – discharge from NICU	Discharge from NICU to 1 year of age
Calcium, mg/kg	60–80	160–240	250 (breast-fed)/day 370 (formula-fed)/day
Phosphorus, mg/kg	30–45	75–120	105 (breast-fed)/day 270 (formula-fed)/day
Vitamin D, IU	40–120 (birth weight <1,000 g) 40–260 (>1,000 g)	400 (800 for Blacks and Asians)	400

supplementation should be given to all pregnant women or only to high-risk subgroups. Thus, measurement of serum 25(OH)D levels during the last trimester of pregnancy is recommended in at-risk mothers.

Human milk is an inadequate source of vitamin D [4]. The total vitamin D and 25(OH)D in human milk equals approximately 12–60 IU/l, and thus will not provide the recommended AI of 400 IU/day for infants. To prevent postnatal rickets in breast-fed infants, especially those of high-risk mothers, vitamin D supplementation should be started in the neonatal period with a daily intake of 400 IU/day and continued at least until the age of 1 year. Whether supplemental of vitamin D is required beyond infancy and in older children is still controversial. It is complicated by the fact that mild vitamin D deficiency does not

manifest itself as clinical rickets but rather as undetected malabsorption of calcium, elevated parathyroid hormone levels and rapid bone remodeling. Thus, for at-risk children, the currently recommended dose of 200 IU/day would be less than half the estimated daily requirement to prevent vitamin D deficiency.

Overt vitamin D deficiency rickets can be safely and effectively treated by daily administration of 2,000–4,000 IU of vitamin D. Radiological signs of healing will usually be evident within 2–4 weeks, whereupon the vitamin D dose can be reduced to 400 IU/day. Another treatment approach to vitamin D deficiency rickets has been to administer vitamin D as a single, large dose, so-called ‘stoss therapy’. The European method in which a single or divided dose of up to 300,000 IU is administered orally or intramuscularly has been in use since the 1930s. Higher dose, or stoss therapy in well-nourished children, may be excessive and result in hypercalciuria and nephrocalcinosis [5].

Nutritional Rickets in Developing Countries

Nutritional rickets remains prevalent in developing regions of the world such as Africa, the Indian subcontinent, Asia and the Middle East. The prevalence of rickets is highly variable among these nations and even within different regions of the same country. Lack of large-scale, epidemiologic studies and heterogeneity with respect to genetic, nutritional, lifestyle and socioeconomic status accounts for this variability. Nevertheless, in these parts of the world, rickets is among the five most common diseases in children. In Nigeria, 2.4% of children under 5 had overt rickets and 14.9% had findings suggestive of rickets [6]. In Turkey, rickets was detected in 6% of children under age 3 who presented to an outpatient clinic for various reasons [7].

Rickets not only causes skeletal system problems but also leads to significant morbidity through affects on other systems. Children with rickets are 13 times more likely to get pneumonia (‘rachitic pneumopathy’) and almost twice as likely to die of it even after adjustment for family size, birth order, crowding and length of exclusive breast-feeding [8, 9].

It is unclear why rickets occurs so frequently in tropical countries with abundant sunlight [10]. Whereas genetic predisposition may contribute, lifestyle and the environment have been implicated to explain its occurrence. These include inadequate dietary vitamin D or calcium intake, darkly pigmented skin, inadequate exposure to sunlight due to excessive clothing, remaining indoors due to seasonal, cultural or religious reasons and air pollution.

Dietary calcium deficiency is a major factor contributing to development of rickets in Africa [11, 12] (table 2). The typical African diet is rich in grains that contain inhibitors of calcium absorption such as phytates, oxalate, tannates and

Table 2. Dietary calcium intake (mg/day): recommendations in the USA

Age	1997 NAS	1994 NIH
0–6 months	210	400
6 months to 1 year	270	600
1–3 years	500	800
4–8 years	800	800 (4–5 years) 800–1,200 (6–8 years)
9–13 years	1,300	800–1,200 (9–10 years) 1,200–1,500 (11–18 years)

phosphates. In a placebo-controlled trial, Nigerian children with rickets were found to have low intake of calcium and responded better to calcium or calcium plus vitamin D than to vitamin D alone [8]. Rickets due to dietary calcium deficiency has also been described in South Africa and Bangladesh [13–15].

In Nigeria, most rachitic children were moderately malnourished; their protein nutritional status and growth being better than those of severely malnourished children who grew slower and developed rickets less often [11]. This is consistent with the fundamental basis of rickets, being a disease of the growth plate and actively growing children are more likely to develop rickets than are children whose linear growth is impeded.

Additional risk factors that predispose to rickets in developing countries include insufficient exposure to sunlight, marasmus, prematurity, prolonged breast-feeding, no access to nutritional supplementation, type of residence and lower socioeconomic status. Maternal education level was found to be important in some but not all studies [16–19].

In many developing countries, rickets is not limited to infants. In Saudi Arabia the prevalence of symptomatic rickets is 68/100,000 children years at age 10–15 years [20] and all adolescents have an inadequate dietary calcium and vitamin D intake [21]. The median daily sun exposure was estimated at 15 min. Moreover, traditional clothing for women, which covers the entire body and the face, prevents exposure of the skin to sunlight and explains why more females develop vitamin D deficiency.

Maternal vitamin D deficiency is also more common in developing countries [22–24]. Severe vitamin D deficiency has been identified in 46–80% of pregnant women and nursing mothers in different regions of Turkey [25].

The dietary vitamin D intake of these women was far below the US AI and was associated with low socioeconomic status, covered clothing style and a low educational level. The most important risk factor for low serum 25(OH)D level in the newborn was low maternal level of 25(OH)D. Measurements of bone mineral

density revealed osteopenia in 40% of the women with a low serum 25(OH)D level. Women with osteopenia were from low socioeconomic class and 80% of them dressed in traditional attire that covered nearly all the skin. Concentrations of serum 25(OH)D were significantly related to the type of clothing [26].

Prevention of vitamin D deficiency, particularly in breast-fed infants, requires vitamin D supplementation during the first year of life, and calcium supplementation may also be necessary to achieve the recommended daily intake in certain children [27–30].

Breast milk calcium concentration is 340 mg/l compared to cow's milk calcium concentration of 1,339 mg/l. However, an average 55% of breast milk calcium is absorbed whereas only 38% of calcium in cow's milk or formula is absorbed. Thus, in general, breast milk is a good source of absorbable calcium. However, studies in Gambia have shown that breast milk of black mothers contains 22% less calcium than breast milk of white mothers [28]. Dietary calcium supplementation may influence gestational milk calcium content, but not during lactation [31]. Therefore, ensuring adequate dietary intake of calcium and vitamin D of pregnant women is essential.

Treatment of nutritional rickets in developing countries is essentially the same as that in developed countries [32]. Parenteral administration of vitamin D is also effective but is recommended only when diarrhea or malabsorption is present. Calcium supplementation should also be provided for the first 2 weeks of therapy to prevent hypocalcemia that can result from rapid skeletal mineralization, the so-called 'hungry bone syndrome'. Biochemical response, typically an elevation in serum phosphorus concentration, may be seen as early as 7 days and radiographic evidence of healing can be noted in 10–14 days.

In calcium deficiency rickets, 1,000 mg of oral elemental calcium is to be given daily for 6 months, in addition to vitamin D, which can be given as stoss therapy [11]. Regardless of the type of rickets, siblings of a patient with rickets should also be evaluated for the presence of subclinical vitamin D deficiency. Larger population-based studies are needed in each developing country to establish: (i) the true prevalence of rickets, hence the extent of the problem; (ii) specific local risk factors for rickets; (iii) the local intake of dietary vitamin D and calcium to prevent rickets, and (iv) easy, safe and inexpensive ways of providing adequate vitamin D and calcium.

Nutritional Rickets in Developed Countries: Racial and Ethnic Considerations

Children of immigrants who live in developed countries are also at increased risk for rickets [33]. 42% of Turkish and 23% of Moroccan children living in

The Hague, The Netherlands, had low serum levels of 25(OH)D, as compared to an indigenous reference population [34]. Likewise, in the USA, clinical rickets is common in children who are adopted from the former Soviet Union [35]. Vitamin D deficiency in Asians, whose ethnic origin is from India, Pakistan or Bangladesh, living in the UK was first reported nearly 30 years ago [36, 37]. Programs to improve life and social conditions, as well as public health initiatives to provide free vitamin D supplements, have led to declines in the prevalence of vitamin D deficiency in these ethnic groups [38]. To prevent vitamin D deficiency, the UK Committee on Medical Aspects of Food Policy (COMA) has recommended that all infants receive 400 IU of vitamin D daily either as part of a multivitamin preparation or contained in fortified infant formula milk. Furthermore, it recommends that all pregnant and lactating mothers should receive 400 IU of vitamin D daily [6, 39]. It also advises that Asian children should be encouraged to take vitamin D supplements throughout the first 5 years of life. In recent years there has been a resurgence of vitamin D deficiency in the UK among Asian children, however. In addition to skeletal rickets during the first 6–9 months of life, many infants also manifest symptomatic hypocalcemia, including seizures. Unlike other reports, which have implicated prolonged and exclusive breast-feeding [40], many of these infants have been formula fed and several have been receiving multivitamin supplements. These infants have evidence of severe vitamin D deficiency (serum concentrations of 25(OH)D <8 ng/ml), as have the majority of the mothers who have been tested. Most of these infants were born to mothers who were themselves born in the UK. These experiences have been mirrored by reports of severe vitamin D deficiency in infants [41], adults [42] and pregnant women [43]. The presentation of such cases and others [44] highlights the importance of maternal vitamin D stores to the developing fetus, as following birth the vitamin D status of an infant is 60–70% of measured maternal vitamin D levels [45].

A study of 25(OH)D levels in a resident nonpregnant adult population in the UK shows that in winter, 85% of Asians compared to 3.3% of non-Asians had 25(OH)D levels <8 ng/ml. Furthermore, even during summer 38% of the Asians had serum levels of 25(OH)D vitamin D that were <10 ng/ml; most (73%) of these vitamin-D-deficient subjects were women.

Previous studies have attributed vitamin D deficiency in Asian women to cultural and dietary habits and their infrequent use of vitamin D supplements. In these subjects, as well as others who do not use vitamin D on a routine basis, the primary source of vitamin D is skin that has been exposed to ultraviolet irradiation of the appropriate wavelength (290–310 nm). Importantly, this wavelength is not present in sunlight in Great Britain (and many other northern countries) from the end of October to the end of March.

Although inadequate sunlight exposure is not refuted, this is probably not the only factor. An interesting study undertaken in the USA [46] has shown

that altered vitamin D metabolism due to markedly increased 25(OH)D, 24-hydroxylase activity may contribute to low 25(OH)D levels in Asian subjects. Thus, it appears there may be a genetic predisposition to vitamin D deficiency in Asians. This suboptimal vitamin D status facilitates the occurrence of symptomatic vitamin D deficiency when there are increased requirements as in infancy, adolescence, pregnancy and lactation.

A recent study from Denmark of veiled Moslem women indicated that in the relative absence of sunlight exposure a dietary intake of 600 IU vitamin D per day is insufficient to maintain an adequate serum level of 25(OH)D, and suggested that 1,000 IU/day might be more appropriate for that group [47]. An alternative is to give 1,000 IU/day during the third trimester of pregnancy, which has been shown to produce normal serum levels of 25(OH)D in both mothers and infants at term [48]. An alternative proposal is to employ stoss therapy with administration of a single dose of 100,000–200,000 IU vitamin D during the 6th or 7th month of pregnancy, which provides sufficient vitamin D to meet maternal and fetal needs [49].

All Asian infants should be given 400 IU vitamin D daily whether breast or formula fed. Alternatively, if daily compliance is a problem an annual stoss therapy dose of 150,000 IU vitamin D at the beginning of autumn has been shown to provide protection against vitamin D deficiency without toxicity [50]. A new public health campaign to initiate these measures and raise the awareness of the risks of vitamin D deficiency amongst Asian, African and Middle Eastern families will be required.

Nutritional Rickets in the USA

Over the past decade, reports of vitamin D deficiency rickets in infants and toddlers living in the USA have increased [51–53]. The age at diagnosis for the 96 children described in these and other reports ranged from 3 to 25 months. All were breast fed and most were dark-skinned. Ninety were African-American or other dark-skinned individuals and 6 were Caucasian. Of the 6 Caucasians that developed rickets, 1 was kept exclusively indoors [54], 1 had ‘an unusual’ diet [55], and 1 had been switched to unfortified goats’ milk and received no vitamin D supplementation [56]. Another child received no milk after discontinuation of breast-feeding at 2 months of age [52].

The largest study described 30 children with nutritional rickets who had been evaluated during the 1990s at two academic institutions in North Carolina [57]. All children were African-American and had been breast fed (average duration = 12.5 months). The majority were diagnosed on the basis of skeletal abnormalities (bowed legs, flared wrists, rachitic rosary, fractures) and/or

failure to thrive. Others were diagnosed incidentally or during evaluations for seizures and developmental delays.

A principal cause for the increasing prevalence of rickets in the USA is decreased sunlight exposure, which results from increased time spent indoors, avoidance of direct sunlight, increased use of sunscreens, and air pollution. Dark-skinned individuals (both mothers and infants) require more sun exposure (about 6 times more) than light-skinned individuals to produce the same amount of vitamin D in their skin, and therefore, are at greater risk for vitamin D deficiency. Although recent increases in the number of African-American women who are breast-feeding is encouraging in many respects [58, 59], it also means that greater numbers of dark-skinned infants will be at risk of vitamin D deficiency. Regrettably, many physicians fail to prescribe vitamins for dark-skinned infants, and in one recent study, 16% did not prescribe vitamins for any breast-feeding infants [57].

Fortification of Food with Vitamin D

Cow's milk has been fortified with vitamin D in the USA and Canada since the 1930s, but is not fortified in most European countries [60]. Although infant formula is vitamin D-fortified, the recent resurgence of exclusive breast-feeding in these countries has led to an increased incidence of vitamin D deficiency rickets, especially in Black populations [52]. The content of vitamin D in fortified milk, is highly variable, however. No more than 20% of milk or its products contains the required 400–600 IU of vitamin D per quart, and 10.15% sampled milk does not contain any detectable levels. Several cases of vitamin D intoxication have been reported that apparently resulted from drinking milk that had been fortified with excessive amounts of vitamin D [61]. Lastly, the expense of fortification of food should be considered. It is uncertain, then, if the situation in countries that provide milk fortification is significantly better than in countries that provide none at all. Fortification of cow's milk with vitamin D should be standardized and monitored to ensure appropriate compliance.

Vitamin D and Preterm Infants

The rapid postnatal growth of premature infants requires attention to prevention of the metabolic bone disease of prematurity. The daily requirements of vitamin D for the very low birth weight infant have not established by experimental approach. The main etiological factor is inadequate mineral intake rather than vitamin D deficiency [62]. Even though, a previous European

recommendation prescribes a very high vitamin D dose in relation to those infant's weight [63]. The European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) recommended a dose of 800–1,600 IU/day, while the American Academy of Pediatrics (AAP) and the Canadian Pediatric Society recommended 400 IU/day [64, 65]. Several studies indicate that a daily vitamin D intake of up to 400 IU maintains normal skeletal development and vitamin D status, while higher dosages may have a potential risk for hypocalcaemia and subsequent complications [66–68]. A randomized study showed that 200 up to 400 IU vitamin D per day and 960 IU/day intake (vitamin D content of used formula plus supplementation) have no different influence on bone mineral accretion in preterm infants [69].

There are no data on vitamin D supplementation in 'extreme' preterm infants (birth weight <700 g). The ideal vitamin dose is still controversial. But a total vitamin D intake of 200 up to 400 IU/day seems to be sufficient for a normal skeletal development in the premature infant, provided that calcium and phosphorus intake is adequate.

Vitamin D and Puberty

Although osteoporosis primarily affects the aging population, there is now a general agreement that failure to achieve peak bone mass at the end of adolescence can increase the risk of osteoporosis later in life. Thus, senile osteoporosis can be regarded, in part, as a paediatric disease. Moreover, bone mineral density and structural strength of bones relate to the risk for fracture at all ages, including the pediatric age [70]. The balance between the peak bone mass achieved in the first two decades of life and the subsequent bone loss that occurs later in life determines osteopenia in the elderly. More than 85% of the eventual peak skeletal mass is present by the age of 18 years, making childhood and adolescent bone growth and mineral accretion a critical process [71]. Failure to achieve an appropriate peak bone mass during this critical growth period results in increased risk of osteopenia and fractures later in life.

During puberty, the rate of longitudinal bone growth exceeds the rate of bone mass accumulation [72, 73]. This tends to produce a transient but a critical period of increased bone fragility [74–76] and the incidence of fractures, particularly in the forearm, increases sharply during puberty.

Factors that may have an effect on bone mass accumulation during puberty are nutrition, hormones and physical activity. In many studies, variations in pediatric dietary calcium intake have been shown to have a lifelong effect on bone mass [75, 77]. A positive relationship was found between milk consumption in childhood and bone mineral density of adult women [78–80]. Among

other factors, the bioavailability of calcium in food products has to be taken into consideration [81, 82]. In addition, genetic polymorphisms of the vitamin D receptor may also influence the response of bone mass to calcium intake [83]. During adolescence, a 'calcium threshold' may apply, indicating that intake below this threshold affects bone accumulation, but a calcium surplus, above this threshold, does not accelerate the constant accumulation of bone [84, 85]. On the other hand, an increase of bone retention of calcium was reported for adolescent girls with a high calcium intake [86].

It is possible that the unfavorable effect of suboptimal calcium intake on bone mass during puberty is masked by the dominant effect of pubertal hormones and physical activity. A multiple regression analysis demonstrated that pubertal stage and exercise have a greater value in the regression equation than does nutritional calcium intake [87].

Vitamin D and Chronic Diseases

Because several organs are involved in the synthesis, absorption, activation and storage of vitamin D, many chronic skin, intestinal, liver and renal diseases are associated with defective vitamin D supply, activation, or action [88, 89]. Children with chronic diseases – even those that affect organs not directly involved in vitamin D metabolism – are at increased risk of functional vitamin D deficiency. Poor dietary intake, a limited sunlight exposure, and reduced adipose tissue reserves all play a role in the development of vitamin D deficiency in chronically ill children [90].

Great variability in the frequency of hypovitaminosis D has been reported in several chronic diseases, such as cystic fibrosis and anorexia nervosa [91–96]. Differences in patient characteristics (age, nutritional status, physical function and activity, severity of disease, compliance with supplementation) and differences in methodological details (season of study, the selected cut-off values and type of 25(OH)D assays), in part explain the great disparity of reported prevalence of vitamin D deficiency in chronic disease [97–99]. Beside ethnic (dark skin pigmentation, genetic) and geographical factors (northern latitude), differences in clothing, customs and food consumption (i.e. some foods may be vitamin D fortified or naturally rich in vitamin D) contribute to the differences observed between countries.

Although overt rachitic bone disease or symptomatic hypocalcemia is seldom reported in children with chronic diseases, clinical findings related to a mild defects in mineral metabolism such as muscle weakness, bone pain and impaired mobility, may be present but overlooked in chronically ill patients. Non-ambulatory patients with neurological diseases and patients with fat malabsorption

origin appear at highest risk for symptomatic vitamin D deficiency, while infancy and adolescence appear the critical periods for developing symptomatic vitamin D deficiency in the chronically ill child [100, 101]. Lack of sun exposure is an important factor contributing to the development of low circulating levels of 25(OH)D. Ileal resection in children with inflammatory bowel disease, and cholestasis (rather than the parenchymal cell disease) in children with chronic liver disease, are major risk factors for hypovitaminosis D [102, 103]. Vitamin D deficiency has been reported in several other chronic diseases without malabsorption, such as type 1 diabetes, juvenile rheumatic diseases or malignancy, but the precise predisposing factors have not been identified [104–106].

Although hypovitaminosis D is a concern in children who must restrict dietary fat, such as familial hypercholesterolemia, or in adolescents with anorexia nervosa, a condition of self-imposed severe dietary restriction, low serum concentrations of 25(OH)D are not a consistent findings [107].

The biochemical profile of subclinical hypovitaminosis D in patients with chronic diseases is variable, both within and between diseases. A serum level of 25(OH)D that is <25 ng/ml is considered low by most experts, and levels that are <11 ng/ml are clearly abnormal. Serum levels of calcitriol may be normal, decreased or even increased in patients with vitamin D deficiency. PTH concentrations are generally high in patients with low 25(OH)D concentrations [108], but a 'normal' PTH level may be elevated for a specific patient.

Universal vitamin D supplementation for chronically ill children remains controversial, in part because clinical rickets is rare. Vitamin D supplementation must not be regarded as only a treatment for symptomatic rickets, but rather should be considered as a means to optimize bone mineralization during childhood and adolescence. This is particularly true for children with a variety of chronic diseases that predispose to vitamin D deficiency, in whom circulating levels of 25(OH)D remain low despite routine vitamin D supplementation. Thus, current guidelines (and compliance) for vitamin D supplementation appear to be inadequate. Nevertheless, in some studies no relationship between the vitamin D status and the degree of bone mineralization could be established [109]. These studies highlight the need to determine the relative relationships of vitamin D deficiency and other, as yet unknown factors, to the development of defective bone mineralization in children with chronic diseases.

There have been no controlled trials of vitamin D supplementation in the majority of chronic diseases associated with vitamin D deficiency to establish the efficacy and safety of a specific supplementation regimen. Furthermore, it may not be possible to develop a single, standardized vitamin D supplementation regimen for all children with chronic diseases as environmental, genetic and behavioral factors might differ widely between individuals. It is thus difficult to provide a general evidence-based management plan for most of these chronic conditions.

In children with a chronic disease that interferes with normal vitamin D absorption or synthesis, it is reasonable to provide oral vitamin D supplements at 2–3 times the locally established RDA values. This can be accomplished with 1,200 IU daily or 100,000 IU monthly, but levels of serum 25(OH)D should be monitored regularly to confirm compliance and to guide adjustment of the dose of vitamin D supplement. The optimal target level of serum 25(OH)D has not been established, and it might vary for different patients and with different medical disorders. Administration of vitamin D metabolites [e.g. 25(OH)D or parenteral vitamin D] may be appropriate for selected patients who are unable to maintain normal serum vitamin D levels with oral vitamin D [110]. The question of whether calcitriol [1,25(OH)₂D] supplementation has some/any advantage over vitamin D supplementation in patients with nonrenal diseases remains to be determined. The value of measuring serum bone markers in the short term or bone mineral density in the long term is for assessing the beneficial effects on bone metabolism of the vitamin D supplementation, since several factors influence bone mineralization in patients with chronic disease. Standard vitamin D supplementation (400 IU daily or 25,000 IU monthly) might be considered in the wintertime for all children with a chronic disease associated with impaired bone mineralization or treated with a medication that can interfere with vitamin D metabolism [111].

Finally, in addition to vitamin D supplementation, it is important to ensure adequate intake of calcium in order to prevent or reverse bone mineral loss (table 3).

Vitamin D and Drug Therapy

Corticosteroids impair bone formation directly through the inhibition of osteoblast activity [112] and indirectly by decreasing sex steroid secretion [113], decreasing intestinal calcium absorption [114], increasing urinary calcium excretion [115] and promoting bone resorption due to secondary hyperparathyroidism [116]. Prevention of corticosteroid-induced osteoporosis can be primary, at the onset of corticosteroid therapy, or secondary, after low bone density has developed. In adults as well as in children, there is little evidence to support the use of high-dose vitamin D in either prevention or treatment of corticosteroid-induced osteoporosis [117]. Management measures recommended by the Consensus Group for children requiring long-term corticosteroids can be summarized as follows: (i) a minimal effective dose of corticosteroids should be used; (ii) prescribe inhaled or topical steroids where possible; (iii) deflazacort is less damaging to the bone than prednisolone; (iv) assure adequate daily intake of calcium, vitamin D and proteins; (v) encourage normal physical activity, and (vi) bone damage is

Table 3. ESPE Bone Club recommendations for daily requirements of calcium, phosphorus and vitamin D in childhood and adolescence

	Calcium mg	Phosphorus mg	Vitamin D IU
Third trimester pregnancy + lactation	1,500	1,500 ^a	400–1,000 ^b
Premature infants	180/kg	140/kg	200–400 ^b
Term – first year	400	300 ^a	200–800 ^b
Childhood	800	800 ^a	0–400 ^c
Adolescence	1,200	1,200 ^a	0–1,000 ^c
Chronic disease	800–1,200	800–1,200 ^a	400 ^{c,d}
Drug therapy	800–1,200	800–1,200 ^a	0–1,000 ^c

^aPhosphate is present in all food composed of plant or animal cells. In a normal diet there is no need for supplementation.

^bThe higher dose is recommended for dark skin complexion and when sun exposure is limited.

^cDuring childhood and adolescence, vitamin D requirement change with physical activity, geographical and cultural sun exposure and skin complexion. In all ages, stoss therapy, using the right dose, is an option.

^dAn initial dose of 1,200 IU is recommended for malabsorption, to be monitored by serum 25(OH)D levels.

worst during the initial months of corticosteroid therapy. Consider bisphosphonate treatment in cases before severe osteoporosis develops [118].

Anticonvulsants increase the rate vitamin D turnover by the liver and thereby can induce a relative deficiency of vitamin D. In one recent study of children and adolescents with cerebral palsy and epilepsy who were receiving high doses of anticonvulsants, children who were treated with 0.25 µg calcitriol and 500 mg calcium per day showed a significantly increased bone mineral density of the lumbar spine as compared to a control untreated group [119]. Recommended measures include periodic monitoring of serum 25(OH)D, initiation of vitamin D supplementation with 400 IU/day and subsequent adjustment of dosage according to serum level of 25(OH)D and provision of adequate dietary calcium.

Chemotherapy diminishes bone mineral density in some children [120]. Serum levels of osteocalcin, a marker for bone formation, are frequently below the normal range for age in children with cancer at the beginning of chemotherapy, and increase into the normal range at 6 months of therapy [121–123]. Levels of carboxy-terminal telopeptide of type 1 collagen (1CTP), a marker of bone resorption, are elevated [121], normal [122], or low [123] compared with controls at the start of chemotherapy, and increase significantly during 2 years of chemotherapy. Serum calcitriol was below the normal range at diagnosis and throughout 2 years

of chemotherapy in a number of children [121–123]. Reduced serum levels of calcitriol could result from an accelerated rate of cell turnover due to chemotherapy, leading to increased utilization of vitamin D, or impaired synthesis due to corticosteroids [119, 123]. Normal osteocalcin levels in combination with a low serum calcitriol during chemotherapy indicate appropriate bone formation with ineffective mineralization, while bone resorption seems to be elevated [124].

Only one intervention study has evaluated vitamin D requirements of children treated with high doses of anticonvulsants, and it showed a positive effect of vitamin D therapy in combination with calcium. Intervention studies with calcitriol supplementation are not available in children treated with chemotherapy. Considering the reduced levels of calcitriol in those children, supplementation might seem a logical step. On the other hand, bone mineral density is not reduced in all children treated with chemotherapy, and if there is a reduction it is not always associated with a low calcitriol levels. Therefore, supplementation of vitamin D should be considered individually. Prospective controlled trials will be necessary to determine whether vitamin D supplementation can prevent disturbances in bone mineralization in children on chronic drug treatment.

Conclusions

Having entered the 21st century, there is a consensus that breast-fed infants and toddlers are at risk for vitamin D deficiency. There is also panel consensus that *all* breast-fed infants, regardless of skin color or latitude, should receive 400 IU of supplemental vitamin D per day from birth until they are receiving adequate formula or vitamin D-fortified cow's milk to provide 400 IU of vitamin D per day. Although nutritional rickets occurs most frequently in dark-skinned individuals, it is clear that many light-skinned individuals are also at risk of vitamin D deficiency. As it is difficult to predict whether vitamin D supplies are adequate based on complexion, lifestyle and estimated sun exposure [125], given the safety of 400 IU of vitamin D per day, it seems reasonable to recommend vitamin D supplementation to all of these children.

It is apparent that vitamin D obtained through formula feeds or given as a standard supplement of 400 IU/day is inadequate to overcome the impact of maternal vitamin D deficiency. It is important to ensure that fetal stores are optimized by supplementation of at-risk mothers with a daily dose of 400 IU vitamin D, which should theoretically result in normal maternal concentrations of 25(OH)D and calcitriol.

The following recommendations are made for prevention of nutritional rickets. (i) Pregnant women should be encouraged to use sun exposure (hands and face 15–20 min/day, at least 3 times per week) or fortified dairy products

to ensure an adequate supply of vitamin D. (ii) Vitamin D 1,000 IU daily or 100,000 IU as single dose should be given at the last trimester of pregnancy to women with a history of insufficient dietary vitamin D and sunshine exposure [30, 46]. (iii) In developing countries, breast-feeding is encouraged up to 18 months especially in calcium deficiency areas to provide enough calcium. (iv) An adequate calcium intake must be ensured and inexpensive, locally acceptable food sources of calcium should be provided during weaning period and thereafter. (v) All infants should receive supplemental vitamin D 400 IU/ day during the first year of life regardless of the type of feeding. All infants, children and adolescents should have adequate sunshine (30 min/week clothed only in a diaper or 2 h/week fully clothed but no hat – dark-skinned children will require longer exposures for infants). (vi) Dietary calcium and vitamin D intake of children and adolescents should be raised to suggested guidelines by consuming fortified food or supplements. (vii) Vitamin D should be administered directly into the mouth and not added to the milk. Vitamin D is a fat-soluble vitamin and can adhere on the surface of feeding tubes and bottles.

Measurement of circulating 25(OH)D is the best biochemical parameter for vitamin D status. The target levels of 25(OH)D for starting and modifying supplementation need further study; serum levels <11 ng/ml are generally considered subnormal, but levels <25–30 ng/ml may not be adequate to ensure optimal vitamin D action.

Fortification of milk with vitamin D should be regulated and supervised to ensure that all milk products (whole milk or reduced fat milk) contains the recommended 400 IU per quart. Food fortification is not recommended, unless it can be enforced upon all producers.

Perspectives

There are many open questions regarding vitamin D deficiency. The most controversial question continues to be whether all or only selected breast-fed infants should receive supplementation. Some of the research and actions that need to take place are listed below. (1) The prevalence and scope of vitamin D deficiency in breast-fed infants and toddlers needs to be determined. It has been assumed that the cases diagnosed clinically (e.g. significant skeletal deformities, failure to thrive and/or seizures) are the ‘tip of the iceberg’ and that the majority of children with vitamin D deficiency have a relatively subtle phenotype and, consequently, are not identified. (2) A palatable, inexpensive liquid preparation delivering the recommended daily intake of vitamin D [126] needs to be developed. (3) The effectiveness of this daily therapy needs to be documented. (4) Health policy should be developed to make vitamin D available to

all breast-feeding mothers, and to ensure analysis of its utilization. (5) Guidelines will need to be developed that directly and experimentally address the optimal vitamin D requirements for pregnant women and very low birth weight infants. (6) Finally, a public health plan to educate the public and physicians about the effects of vitamin D deficiency and the rationale for supplementation should be developed. Careful research will be needed to determine the effects of different educational initiatives on practice policies and the number of women breast-feeding.

Finally, more studies are required to understand the effect of vitamin D, not only on the skeletal mineralization and bone strength, but also on muscle strength, the immune system, gonadal function and the glucose tolerance [127–129].

References

- 1 Hochberg Z: Rickets: It's not just vitamin D deficiency. *Curr Opin Endocrinol Diabetes* 2001; 8:23–28.
- 2 Utiger RD: The need for more vitamin D. *N Engl J Med* 1998;228:828–829.
- 3 Subcommittee on the Tenth Edition of the RDAs, Food & Nutrition Board, Commission on Life Sciences and National Research Council. *Recommended Dietary Allowances*. Washington, National Academy Press, 1989, pp 1–285.
- 4 Weisman Y, Bawnik JC, Eisenberg Z, Spirer Z: Vitamin D metabolites in human milk. *J Pediatr* 1982;100:745–748.
- 5 Markestad T, Hesse V, Siebenhuner M, et al: Intermittent high-dose vitamin D prophylaxis during infancy: Effect on vitamin D metabolites, calcium and phosphorus. *Am J Clin Nutr* 1987;46:652–658.
- 6 Akpede GO, Omotara BA, Ambe JP: Rickets and deprivation: A Nigerian study. *J R Soc Health* 1999;119:216–222.
- 7 Ozkan B, Buyukavci M, Aksoy H, Tan H, Akdağ R: Incidence of rickets among 0- to 3-year-old children in Erzurum. *Cocuk Sağlığı ve Hastalıkları Dergisi* 1999;42:389–396.
- 8 Muhe L, Lulseged S, Mason KE, Simoes EA: Case-control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children. *Lancet* 1997;349:1801–1804.
- 9 Banajeh SM, al-Sunbali NN, al-Sanahani SH: Clinical characteristics and outcome of children aged 5 years hospitalized with severe pneumonia in Yemen. *Ann Trop Paediatr* 1997;17:321–326.
- 10 Walker AR: Etiology of nutritional rickets: Geographic variations. *J Pediatr* 1998;132:187–189.
- 11 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;19:563–568.
- 12 Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Isichei CO, Chan GM: Case-control study of factors associated with nutritional rickets in Nigerian children. *J Pediatr* 2000;137:367–373.
- 13 Fischer PR, Rahman A, Cimma JP, Kyaw-Myint TO, et al: Nutritional rickets without vitamin D deficiency in Bangladesh. *J Trop Paediatr* 1999;45:291–293.
- 14 Bhimma R, Pettifor JM, Coovadia HM, Moodley M, Adhikari M: Rickets in black children beyond infancy in Natal. *S Afr Med J* 1995;85:668–672.
- 15 Bishop N: Rickets today – Children still need milk and sunshine. *N Engl J Med* 1999;341:602–603.
- 16 Lulseged S, Fitwi G: Vitamin D deficiency rickets: Socio-demographic and clinical risk factors in children seen at a referral hospital in Addis Ababa. *East Afr Med J* 1999;76:457–461.
- 17 Ekanem EE, Bassey DE, Eyong M: Nutritional rickets in Calabar, Nigeria. *Ann Trop Paediatr* 1995;15:303–306.
- 18 Nyakundi PM, Kinuthia DW, Orinda DA: Clinical aspects and causes of rickets in a Kenyan population. *East Afr Med J* 1994;71:536–542.

- 19 el-Hag A, Karrar ZA: Nutritional vitamin D deficiency rickets in Sudanese children. *Ann Trop Paediatr* 1995;15:69–76.
- 20 Narchi H, El Jamil M, Kulaylat N: Symptomatic rickets in adolescence. *Arch Dis Child* 2001;84:501–503.
- 21 American Academy of Pediatrics Committee on Nutrition: Calcium requirements of infants, children, and adolescents. *Pediatrics* 1999;104:1152–1157.
- 22 Gullu S, Erdogan MF, Uysal AR, Baskal N, Kamel AN, Erdogan G: A potential risk for osteomalacia due to sociocultural lifestyle in Turkish women. *Endocr J* 1998;45:675–678.
- 23 el-Sonbaty MR, Abdul-Ghaffar NU: Vitamin D deficiency in veiled Kuwaiti women. *Eur J Clin Nutr* 1996;50:315–318.
- 24 Alagol F, Shihadeh Y, Boztepe H, Tanakol R, Yarman S, Azizlerli H, Sandalci O: Sunlight exposure and vitamin D deficiency in Turkish women. *J Endocrinol Invest* 2000;23:173–177.
- 25 Andiran N, Yordam N, Ozon A: The risk factors for vitamin D deficiency in breast-fed newborns and their mothers. *ESPE 39th Annual Meeting*, P3–425, Brussels, 2000.
- 26 Ozkan B, Buyukavci M, Energin M, Dirican ME, Alp H, Akdag R: Nutritional rickets: Comparison of three different therapeutic approaches. *Cocuk Sağlığı ve Hastalıkları Dergisi* 2000;43:30–35.
- 27 Specker BL, Tsang RC, Hollis BW: Effect of race and diet on human milk vitamin D and 25-hydroxyvitamin D. *Am J Dis Child* 1985;139:1134–1137.
- 28 Pitkin RM: Calcium metabolism in pregnancy and the perinatal period: A review. *Am J Obstet Gynecol* 1985;151:99–101.
- 29 Cross NA, Hillman LS, Allen SH, Krause GF, Vieira NE: Calcium homeostasis and bone metabolism during pregnancy, lactation and post weaning: A longitudinal study. *Am J Clin Nutr* 1995;61:514–523.
- 30 Prentice A, Jarjou LMA, Cole TJ, Stirling DM, et al: Calcium requirements of lactating Gambian mothers: Effects of a calcium supplement on breast milk calcium concentration maternal bone mineral content and urinary calcium excretion. *Am J Clin Nutr* 1995;62:58–67.
- 31 Feeley RM, Etienmiller RR, Benton-Jones J, Barnhart H: Calcium, phosphorus and magnesium contents of human milk during early lactation. *J Pediatr Gastroenterol Nutr* 1983;2:262–267.
- 32 Shah B, Finberg L: Single-day therapy for nutritional vitamin D deficiency rickets: A preferred method. *J Pediatr* 1994;125:487–490.
- 33 Brunvand L, Brunvate R: Health problems among immigrant children in Norway. *Tidsskr Nor Laegeforen* 2001;28:121:715–718.
- 34 Meulmeester JF, van den Berg H, Wedel M, et al: Vitamin D status, parathyroid hormone and sunlight in Turkish, Moroccan and Caucasian children in The Netherlands. *Eur J Clin Nutr* 1990;44:461–470.
- 35 Reeves GD, Bachrach S, Carpenter TO, Mackenzie WG: Vitamin D deficiency rickets in adopted children from the former Soviet Union: An uncommon problem with unusual clinical and biochemical features. *Pediatrics* 2000;106:1484–1488.
- 36 Ford JA, Colhoun EM, McIntosh WB, Dunnigan MG: Rickets and osteomalacia in the Glasgow Pakistani community, 1961–1971. *Br Med J* 1972;ii:677–680.
- 37 Ford JA, McIntosh WV, Butterfield R, et al: Clinical and subclinical vitamin D deficiency in Bradford children. *Arch Dis Child* 1976;51:939–943.
- 38 Dunnigan MG, Glekin BM, Henderson JB, et al: Prevention of rickets in Asian children: Assessment of the Glasgow campaign. *Br Med J (Clin Res Ed)* 1985;291:239–242.
- 39 Department of Health: Dietary reference values for food energy and nutrients for the United Kingdom. Report on Health & Social Subjects, 41. London, HMSO, 1991.
- 40 Mughal MZ, Salama H, Greenaway T, Laing I, Mawer EB: Florid rickets associated with prolonged breast-feeding without vitamin D supplementation. *BMJ* 1999;318:39–40.
- 41 Lawson M, Thomas M: Vitamin D concentrations in Asian children aged 2 years living in England: Population survey. *BMJ* 1999;318:28.
- 42 Iqbal SJ, Kaddam I, Wassif W, Nichol F, Walls J: Continuing clinically severe vitamin D deficiency in Asians in the UK (Leicester). *Postgrad Med J* 1994;70:708–714.
- 43 Alfaham M, Woodhead S, Pask G, Davies D: Vitamin D deficiency: A concern in pregnant Asian women. *Br J Nutr* 1995;73:881–887.

- 44 Blond MH, Gold F, Pierre F, et al: Nutritional fetal rickets. A case report. *J Gynecol Obstet Biol Reprod* 1997;26:834–836.
- 45 Waiters B, Godel JC, Basu TK: Perinatal vitamin D and calcium status of northern Canadian mothers and their newborn infants. *J Am Coll Nutr* 1999;18:122–126.
- 46 Awumey EM, Mitra DA, Hollis BW, Kumar R, Bell NH: Vitamin D metabolism is altered in Asian Indians in the southern United States: A clinical research center study. *J Clin Endocrinol Metab* 1998;83:169–173.
- 47 Glerup H, Mikkelsen K, Poulsen L, et al: Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. *J Intern Med* 2000;247:260–268.
- 48 Brooke OG, Brown IR, Bone CD, et al: Vitamin D supplements in pregnant Asian women: Effects on calcium status and fetal growth. *Br Med J* 1980;280:751–754.
- 49 Hellouin de Menibus C, Mallet E, Henocq A, Lemeur H, L'Hostis C: Neonatal hypocalcemia. Results of vitamin D supplement in the mother. Study on 13,377 newborn infants. *Bull Acad Natl Med* 1990;174:1051–1060.
- 50 Oliveri B, Cassinelli H, Mautalen C, Ayala M: Vitamin D prophylaxis in children with a single dose of 150,000 IU of vitamin D. *Eur J Clin Nutr* 1996;50:807–810.
- 51 Feldman KW, Marcuse EK, Springer DA: Nutritional rickets. *Am Fam Physician* 1990;42:1311–1318.
- 52 Bhowmick SK, Johnson KR, Rettig KR: Rickets caused by vitamin D deficiency in breastfed infants in the southern United States. *Am J Dis Child* 1991;145:127–130.
- 53 Herman MJ, Bulthuis DB: Incidental diagnosis of nutritional rickets after clavicle fracture. *Orthopedics* 1999;22:254–255.
- 54 Pugliese MT, Blumberg DL, Hludzinski J, Kay S: Nutritional rickets in suburbia. *J Am Coll Nutr* 1998;17:637–641.
- 55 Kaper BP, Romness MJ, Urbanek PJ: Nutritional rickets: Report of four cases diagnosed at orthopedic evaluation. *Am J Orthop* 2000;29:214–218.
- 56 Eugster EA, Sane KS, Brown DM: Minnesota rickets. Need for a policy change to support vitamin D supplementation. *Minn Med* 1996;79:29–32.
- 57 Kreiter SR, Schwartz RP, Kirkman HN Jr, Charlton PA, Calikoglu AS, Davenport ML: Nutritional rickets in African-American breastfed infants. *J Pediatr* 2000;137:153–157.
- 58 Wright A, Schanler R: The resurgence of breast-feeding at the end of the second millennium. *J Nutr* 2001;131:421S–425S.
- 59 Markovic V, Jelic T, Wardlaw GM, Ilich J, Goel PK, Wright JK, et al: Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. *J Clin Invest* 1994;93:199–208.
- 60 Pietrek J, Preece MA, Windo J, O'Riordan JL, Dunnigan MG, McIntosh WB, Ford JA: Prevention of vitamin D deficiency in Asian infants. *Lancet* 1976;7970:1145–1148.
- 61 Jacobus CH, Holick MF, Shao Q, Chen TC, Holm IA, Kolodny JM, Fuleihan GE, Seely EV: Hypervitaminosis D associated with drinking milk. *N Engl J Med* 1992;326:1213–1215.
- 62 Koo WW, Sherman R, Succop P, Ho M, Buckley D, Tsang RC: Serum vitamin D metabolites in very low birth weight infants with and without rickets and fractures. *J Pediatr* 1989;114:1017–1022.
- 63 European Society of Paediatric Gastroenterology and Nutrition. *Acta Paediatr Scand Suppl* 1987;336:1–14.
- 64 American Academy of Pediatrics: Nutritional needs of low-birth-weight infants. *Pediatrics* 1985;75:976–986.
- 65 Canadian Pediatric Society: Nutrient needs and feeding of premature infants. *Can Med Assoc J* 1995;152:1765–1785.
- 66 Cooke R, Hollis B, Conner C, Watson D, Werkman S, Chesney R: Vitamin D and mineral metabolism in the very low birth weight infant receiving 400 IU of vitamin D. *J Pediatr* 1990;116:423–428.
- 67 Koo WW, Krug-Wispe S, Neylan M, Succop P, Oestreich AE, Tsang RC: Effect of three levels of vitamin D intake in preterm infants receiving high mineral-containing milk. *J Pediatr Gastroenterol Nutr* 1995;21:182–189.
- 68 Pittard WB 3rd, Geddes KM, Hulsey TC, Hollis BW: How much vitamin D for neonates? *Am J Dis Child* 1991;145:1147–1149.

- 69 Backstroem MC, Maki R, Kuusela AL, et al: Randomised controlled trial of vitamin D supplementation on bone density and biochemical indices in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1999;80:F161–F166.
- 70 Goulding A, Cannan R, Williams SM, Gold EJ, Taylor RW, Lewis-Bamed NJ: Bone mineral density in girls with forearm fractures. *J Bone Miner Res* 1998;13:143–148.
- 71 Bonjour JP, Theintz G, Buchs B, Slosman D, Rizzoli R: Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. *J Clin Endocrinol Metab* 1991;73:555–563.
- 72 Lappe JM, Stegman M, Davies KM, Barber S, Recker RR: A prospective study of quantitative ultrasound in children and adolescents. *J Clin Densitom* 2000;3:167–175.
- 73 Rupich RC, Specker BC, Lieu AFAM, Ho M: Gender and race differences in bone mass during infancy. *Calcif Tissue Int* 1996;58:395–397.
- 74 Alfram PA, Bauer GCH: Epidemiology fractures of the forearm. *J Bone Joint Surg Am* 1962;44:105–114.
- 75 Landin L, Nilsson BE: Bone mineral content in children with fractures. *Clin Orthop* 1983;178:292–296.
- 76 Bailey DA, Wedge JH, McCulloch RG, Martin AD, Bernhardson SC: Epidemiology of fractures of the distal end of the radius in children as associated with growth. *J Bone Joint Surg Am* 1989;71:1225–1231.
- 77 Hu JF, Zhao XH, Jia JB, Parpia B, Campbell TC: Dietary calcium and bone density among middle-aged and elderly women in China. *Am J Clin Nutr* 1993;58:219–227.
- 78 Halioua L, Anderson JJ: Lifetime calcium intake and physical activity habits: Independent and combined effects on the radial bone of healthy premenopausal Caucasian women. *Am J Clin Nutr* 1989;49:534–541.
- 79 Murphy S, Khaw KT, May H, Compston JE: Milk consumption and bone mineral density in middle-aged and elderly women. *BMJ* 1994;308:939–941.
- 80 Soroko S, Holbrook TL, Edelstein S, Barrett-Connor E: Lifetime milk consumption and bone mineral density in older women. *Am J Public Health* 1994;84:1319–1322.
- 81 Forbes RM, Weingartner KE, Parker HM, Bell RR, Erdman JW Jr: Bioavailability to rats of zinc, magnesium and calcium in casein-, egg- and soy protein-containing diets. *J Nutr* 1979;109:1652–1660.
- 82 Forbes RM, Erdman JW Jr: Bioavailability of trace mineral elements. *Annu Rev Nutr* 1983;3:213–221.
- 83 Fischer PR, Thacher TD, Pettifor JM, Jorde LB, Eccleshall TR, Feldman D: Vitamin D receptor polymorphisms and nutritional rickets in Nigerian children. *J Bone Miner Res* 2000;15:2206–2210.
- 84 Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, Weaver C: Peak bone mass. *Osteoporos Int* 2000;11:985–1009.
- 85 Jackman LA, Millane SS, Martin BR, Wood OB, McCabe GP, Peacock M, Weaver CM: Calcium retention in relation to calcium intake and postmenarcheal age in adolescent females. *Am J Clin Nutr* 1997;66:327–333.
- 86 Wastney ME, Martin BR, Peacock M, Smith D, Jiang XY, Jackman LA, Weaver CM: Changes in calcium kinetics in adolescent girls induced by high calcium intake. *J Clin Endocrinol Metab* 2000;85:4470–4475.
- 87 Maggiolini M, Bonofiglio D, Giorno A, Catalano S, Marsico S, Aquila S, Ando S: The effect of dietary calcium intake on bone mineral density in healthy adolescent girls and young women in southern Italy. *Int J Epidemiol* 1999;28:479–484.
- 88 Blecker U, Mehta DI, du Pont AI, Davis R, Sothorn MS, Suskind RM: Fat-soluble vitamin deficiencies. *Pediatr Rev* 1999;20:394–395.
- 89 Chesney RW: Metabolic bone diseases. *Pediatr Rev* 1984;5:227–237.
- 90 Thompson GN: Determinants of serum vitamin D levels in preadolescent cystic fibrosis children. *Acta Paediatr Scand* 1987;76:962–965.
- 91 Hahn TJ, Squires AE, Halstead LR, Strominger DB: Reduced serum 25-hydroxyvitamin D concentration and disordered mineral metabolism in patients with cystic fibrosis. *J Pediatr* 1979;94:38–42.

- 92 Congden PJ, Bruce G, Rothburn MM, Clarke PC, Littlewood JM, Kelleher J, Losowsky MS: Vitamin status in treated patients with cystic fibrosis. *Arch Dis Child* 1981;56:708–714.
- 93 Henderson RC, Lester G: Vitamin D levels in children with cystic fibrosis. *South Med J* 1997;90:378–383.
- 94 Aarskog D, Aksnes L, Markestad T, Trygstad O: Plasma concentrations of vitamin D metabolites in pubertal girls with anorexia nervosa. *Acta Endocrinol Suppl (Copenh)* 1986;279:458–467.
- 95 Grey V, Lands L, Pall H, Drury D: Monitoring of 25-OH vitamin D levels in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2000;30:314–319.
- 96 Fonseca VA, D'Souza V, Houlter S, Thomas M, Wakeling A, Dandona P: Vitamin D deficiency and low osteocalcin concentrations in anorexia nervosa. *J Clin Pathol* 1988;41:195–197.
- 97 Davies PSW, Bates CJ, Cole TJ, Prentice A, Clarke PC: Vitamin D: Seasonal and regional differences in preschool children in Great Britain. *Eur J Clin Nutr* 1999;53:195–198.
- 98 Docio S, Riancho JA, Perez A, Olmos JM, Amado JA, Gonzalez-Macias J: Seasonal deficiency of vitamin D in children: A potential target for osteoporosis-preventing strategies? *J Bone Miner Res* 1998;13:544–548.
- 99 Vieth R, Carter G: Difficulties with vitamin D nutrition research: Objective targets of adequacy and assays for 25-hydroxyvitamin D. *Eur J Clin Nutr* 2001;55:221–222.
- 100 Baer MT, Kozlowski BW, Blyler EM, Trahms CM, Taylor ML, Hogan MP: Vitamin D, calcium and bone status in children with developmental delay in relation to anticonvulsant use and ambulatory status. *Am J Clin Nutr* 1997;65:1042–1051.
- 101 Kooh SW, Jones G, Reilly BJ, Fraser D: Pathogenesis of rickets in chronic hepatobiliary disease in children. *Pediatrics* 1979;94:870–874.
- 102 Tokita A, Nittono H, Mori T, Maruyama T, Hayashi M, Obinata K, Watanabe T, Yabuta K, Miyano T: Vitamin D metabolism in preoperative extrahepatic biliary atresia. *Acta Paediatr Scand* 1991;80:634–639.
- 103 Driscoll RH, Meredith SC, Sitrin M, Rosenberg IH: Vitamin D deficiency and bone disease in patients with Crohn's disease. *Gastroenterology* 1982;83:1252–1258.
- 104 Arreola F, Paniagua R, Diaz-Bensussen S, Urquieta B, Lopez-Montano E, Partida-Hernandez G, Villalpando S: Bone mineral content, 25-hydroxycalciferol and zinc serum levels in insulin-dependent (type 1) diabetes patients. *Arch Invest Med (Mex)* 1990;21:195–199.
- 105 Arikoski P, Kroger H, Riikonen P, Parviainen M, Voutilainen R, Komulainen J: Disturbance in bone turnover in children with a malignancy at completion of chemotherapy. *Med Pediatr Oncol* 1999;33:455–461.
- 106 Reed A, Haugen M, Pachman LM, Langman CB: 25-Hydroxyvitamin D therapy in children with active juvenile rheumatoid arthritis: Short-term effects on serum osteocalcin levels and bone mineral density. *Pediatrics* 1991;119:657–660.
- 107 Tonstad S, Aksnes L: Fat-soluble vitamin levels in familial hypercholesterolemia. *J Pediatr* 1997;130:274–280.
- 108 Issa S, Rothauwe HW, Burmeister W: 25-Hydroxyvitamin D and vitamin E absorption in healthy children and children with chronic intrahepatic cholestasis. *Eur J Pediatr* 1989;148:605–609.
- 109 Bhudhikanok GS, Lim J, Marcus R, Harkins A, Moss RB, Bachrach LK: Correlates of osteopenia in patients with cystic fibrosis. *Pediatrics* 1996;97:103–111.
- 110 Heubi JE, Hollis BW, Tsang RC: Bone disease in chronic childhood cholestasis. II. Better absorption of 25-OH vitamin D than vitamin D in extrahepatic biliary atresia. *Pediatr Res* 1990;27:26–31.
- 111 Rajantie J, Lamberg-Allardt C, Wilska M: Does carbamazepine treatment lead to a need of extra vitamin D in some mentally retarded children? *Acta Paediatr Scand* 1984;73:325–328.
- 112 Bressot C, Meunier PJ, Chapuy MC, Lejeune E, Edouard C, Darby AJ: Histomorphometric profile, pathophysiology and reversibility of corticosteroid-induced osteoporosis. *Metab Bone Relat Res* 1979;1:303–311.
- 113 Sambrook PN, Eisman JA, Champion GD, Pocock NA: Sex hormone status and osteoporosis in postmenopausal women with rheumatoid arthritis. *Arthritis Rheum* 1988;31:973–978.
- 114 Hahn TJ, Halstead LR, Baran DT: Effects of short term glucocorticoid administration on intestinal calcium absorption and circulating vitamin D metabolite concentrations in man. *J Clin Endocrinol Metab* 1981;52:111–115.

- 115 Reid IR, Ibbertson HK: Evidence of decreased tubular reabsorption of calcium in glucocorticoid-treated asthmatics. *Horm Res* 1987;27:200–204.
- 116 Sambrook P, Birmingham J, Kelly P, et al: Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol and calcitonin. *N Engl J Med* 1993;328:1747–1752.
- 117 Eastell R, Reid DM, Compston J, et al: A UK consensus group on management of glucocorticoid-induced osteoporosis: An update. *J Intern Med* 1998;244:271–292.
- 118 Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. *Arthritis Rheum* 2001;44:1496–1503.
- 119 Jekovec-Vrhovsek M, Kocijancic A, Prezelj J: Effect of vitamin D and calcium on bone mineral density in children with CP and epilepsy in full-time care. *Dev Med Child Neurol* 2000;42:403–405.
- 120 Henderson RC, Madsen CD, Davis C, Gold SH: Longitudinal evaluation of bone mineral density in children receiving chemotherapy. *J Pediatr Hematol Oncol* 1998;20:322–326.
- 121 Halton JM, Atkinson SA, Fraher L, et al: Altered mineral metabolism and bone mass in children during treatment for acute lymphoblastic leukemia. *J Bone Miner Res* 1996;11:1774–1783.
- 122 Arikoski P, Komulainen JJ, Riikonen P, Voutilainen R, Knip M, Kroger H: Alterations in bone turnover and impaired development of bone mineral density in newly diagnosed children with cancer: A 1-year prospective study. *J Clin Endocrinol Metab* 1999;84:3174–3181.
- 123 Boot AM, van den Heuvel-Eibrink MM, Hahlen K, Krenning EP, de Muinck Keizer-Schrama SMPF: Bone mineral density in children with acute lymphoblastic leukaemia. *Eur J Cancer* 1999;35:1693–1697.
- 124 Atkinson SA, Fraher L, Gundberg CM, Andrew M, Pai M, Barr RD: Mineral homeostasis and bone mass in children treated for acute lymphoblastic leukemia. *J Pediatr* 1989;114:793–800.
- 125 Specker BL, Valaris B, Hertzberg V: Sunshine exposure and serum 25-hydroxyvitamin D concentration in exclusively breast-fed infants. *J Pediatr* 1985;107:372–376.
- 126 Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride. Washington, National Academy Press, 1997.
- 127 Bischoff HA, Stahelin HB, Urscheler N, Ehrensam R, Vonthein R, Perrig-Chiello P, Tyndall A, Theiler R: Muscle strength in the elderly: Its relation to vitamin D metabolites. *Arch Phys Med Rehabil* 1999;80:54–58.
- 128 Boucher BJ: Inadequate vitamin D status: Does it contribute to the disorders comprising syndrome 'X'? *Br J Nutr* 1998;79:315–327.
- 129 Kinuta K, Tanaka H, Moriwake T, Aya K, Kato S, Seino Y: Vitamin D is an important factor in estrogen biosynthesis of both female and male gonads. *Endocrinology* 2000;141:1317–1324.

Ze'ev Hochberg, MD, DSc
 Pediatric Endocrinology
 Meyer Children's Hospital, Rambam Medical Center
 POB 9602, Haifa 31096 (Israel)
 Tel./Fax +972 4 8542157, E-Mail z_hochberg@rambam.health.gov.il