How much vitamin D for children?

Ivana Pela

Department of Women’s and Children’s Health Sciences, University of Florence, Florence, Italy

Address for correspondence: Ivana Pela, MD
Associate Professor Department of Women’s and Children’s Health Sciences
University of Florence
Viale G. Pieraccini 24
50139 Florence, Italy
Phone: +39 055 5662536
Fax: +39 055 5662400
E-mail: ivana.pela@unifi.it

Summary

Recently a number of studies have reported worldwide recrudescence of biochemical and clinical rickets, despite continuous revisions of the experts about the adequate intake of vitamin D for infants and children to maintain an adequate 25-hydroxyvitamin D status and assure the achievement of peak bone mass during the growth. The aim of this review is to illustrate the current opinions and controversies about what should be considered the normal range for serum 25-hydroxyvitamin D concentrations and which doses of vitamin D supplements should be recommended in the various pediatric ages and in different contexts as climatic regions, colour of skin and sunlight exposure.

KEY WORDS: vitamin D, rickets, bone metabolism.

Introduction

Rickets was first recognized in human history in the 2nd century AD, but only since the 17th century it has been considered a significant health problem, mostly involving children living in industrialized cities of northern Europe. The peak age at which rickets is most prevalent is usually 3-18 months, and the characteristic clinical features of this metabolic bone disease include enlargement of the epiphyses of the long bones and rib cage, bowing of the legs, bending of the spine, and weak and toneless muscles. In the past, severe rickets entailed severe deforming and debilitating bone disease, and the high incidence of infant and maternal morbidity and mortality in young women with a deformed pelvis, led to the widespread practice of caesarean section in Great Britain (1, 2).

The relationship between exposure to sunlight and the cure of rickets was first reported in 1822 by a Polish researcher, and confirmed by an epidemiological study performed in Great Britain during the 18th and 19th centuries. Meanwhile, cod liver oil was used as a common folklore medicine for the prevention and cure of rickets, but only in the early 20th century its active principle was identified, the so-called antirachitic factor, later named vitamin D (1).

The biochemical characteristics and physiological mechanisms of vitamin D’s action are similar to steroid hormones, and human beings are in fact capable of producing "vitamin D" provided they receive sun exposure. However this is not always possible due to various setbacks such as insufficient sunlight above the 40th latitude and pollution in many areas. Food is another source of vitamin D, although it is only found naturally in very few foods. Therefore, after the 2nd World War the recommendation to fortify milk with a vitamin D supplement spread in Great Britain to ensure an adequate intake for infants and children. On the other hand, many severe cases of hypercalcaemia reported in the 1950s and blamed on vitamin D in fortified milk, revealed the risks related to excessive intake of this substance. As a result, after the 1960’s in USA and Western Europe, instead of fortified milk, all infants received a 400-IU vitamin D supplement, the same quantity as a tablespoon of cod liver oil. This practice led to the disappearance of rickets in infants and children.

However, although rickets was the first disease for which the preventive role of paediatric science was successful, recently a number of studies have reported worldwide recrudescence of biochemical and clinical rickets (3, 4). There are a variety of reasons for this phenomenon. Firstly, for many years the disappearance of rickets led to negligence by paediatricians in prescribing vitamin D supplements and/or poor compliance of the parents. Furthermore, since melanin is very efficient in absorbing the sun’s UVB rays and vitamin D synthesis is markedly reduced in cases of increased skin pigmentation, many recent articles report the high incidence of rickets in Afro-Americans and dark-skinned children from equatorial and subequatorial areas whose families immigrate to countries located at higher latitudes. A collaborative study performed in Great Britain reported 65 cases of rickets diagnosed from 1996 to 2001 in children aged 0-16 years and 63/65 were African or Asian (2).

Finally, although in a totally different context, the recommendation for white people to avoid all sun exposure and/or apply total UVB sunscreens due to the risk of skin cancer has a similar effect on the endogenous synthesis of vitamin D (3).

Today we are able to calculate the serum dosage of vitamin D metabolites and other bone metabolism parameters, and have at our disposal facilities for studying the bone structure, so it is possible to determine the vitamin D status in different periods of growth and development and to correlate this with different physiological and pathological conditions such as puberty, pregnancy, feeding habits, physical activity, biochemical and/or clinical rickets, osteoporosis, inflammatory chronic intestinal diseases and obesity.

The steps towards defining vitamin D recommendations in the 20th century

Following the outbreak of hypercalcaemia due to the use of vitamin D-fortified milk in Great Britain in the 1950s, in 1963 the Committee on Nutrition of the American Academy of Pediatrics (AAP) established that the daily vitamin D requirement was 100-200 IU and recommended that all breastfed and formula-fed infants re-
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In short, according to the AAP, the daily intake of vitamin D should also be recommended for children living in Northern Europe and North and South America. In recent years, a valid aid for establishing the adequate intake of vitamin D has been the measurement of serum 25-hydroxyvitamin D. Therefore, in order to maintain an adequate 25-hydroxyvitamin D concentration in body fat and released during the winter months when vitamin D cannot be produced. Exposure to a minimal erythemal dose while wearing only a bathing suit is equivalent to ingestion of approximately 20000 IU of vitamin D. Therefore, in order to maintain an adequate 25-hydroxyvitamin D status, exposure of the arms and legs for 5-30 minutes (depending on the time of day, season, latitude, and skin pigmentation) between 10.00 am and 3.00 pm twice a week is often sufficient (14).

Conversely, it is difficult to assess just how much vitamin D will be converted through sunlight exposure in dark-skinned infants, children and adolescents living in North America or Europe; no relationship has been established between maternal vitamin D levels and the need for higher doses of vitamin D in dark-skinned infants, even though the need for maternal vitamin D supplementation has been demonstrated during pregnancy and lactation, but without an agreement on the daily dose being reached. Finally, no evidence-based information is available regarding the adequate dosage of vitamin D in this subset of people or even on the consequences of transitory vitamin D deficiency. In fact, the development of clinical rickets is dependent not only on the severity of the vitamin D deficiency, evaluated by measuring the circulating concentrations of 25-hydroxyvitamin D, but also on the duration of the deficiency, on the child’s growth rate, and on the dietary calcium content. Studies from Northern Europe and North and South America have highlighted the marked seasonal fluctuations in serum 25-hydroxyvitamin D concentrations, with values being lowest in late winter and highest in late summer or early autumn, without evident abnormalities of bone metabolism parameters (15, 16).

How can we assess the vitamin D status in infants and children?

In recent years, a valid aid for establishing the adequate intake of vitamin D has been provided by the measurement of serum 25-hydroxyvitamin D level as an index of vitamin D status: for this reason, since 2003, the request for a dosage of 25 OH D3 has increased 15 times at the Mayo Clinic of Rochester (3). In fact, it is now clear that the metabolite 25-hydroxyvitamin D has a half-life of about 3 weeks and therefore it is the most reliable indicator of the vitamin D status and total body stores. The metabolite 1,25 dihydroxyvitamin D should not be used because it may be...
increased by secondary hyperparathyroidism (17). In the past decade, considerable discussion has taken place among the experts regarding what should be considered the normal range for serum 25-hydroxyvitamin D concentrations and above all, the definition of vitamin D sufficiency (18, 19). In population studies, the term vitamin D insufficiency has been used to indicate serum 25-hydroxyvitamin D concentrations below those associated with actual and concrete scarcity of vitamin D, defined as vitamin D deficiency, and those considered to be optimal. On this basis, vitamin D deficiency was defined as a 25-hydroxyvitamin D level of less than 10 ng/mL and insufficiency as a 25-hydroxyvitamin D level of less than 20 ng/mL. On the other hand, available evidence indicates that the consequences of vitamin D deficiency occur at a higher level when circulating intact parathyroid hormone and 25-hydroxyvitamin D were measured in adult patients, and that vitamin D insufficiency is associated with mildly elevated parathyroid hormone concentrations, although values remain within the normal reference range (20). More specifically, secondary hyperparathyroidism occurs when serum 25-hydroxyvitamin D values fall below the range of 15-20 ng/mL and the 25-hydroxyvitamin D levels are inversely associated with the parathyroid hormone levels until the former reach 30 to 40 ng/mL, at which point the parathyroid hormone levels begin to level off. For this reason, most experts now agree that vitamin D deficiency in adults is defined as a 25-hydroxyvitamin D level of less than 20 ng/mL, and 25-hydroxyvitamin D levels between 21 and 29 ng/mL are thought to indicate a relative insufficiency; while levels higher than 30 ng/mL are considered sufficient.

The same ranges are also considered valid for newborns, infants, children and adolescents, but few studies have been conducted among paediatric subjects to determine whether these limits are valid (21, 22). One study by Zeghoud et al. performed in young infants revealed that the concentration of the parathyroid hormone only increased when 25-hydroxyvitamin D concentrations were in the vitamin D-deficient range, and in another study, Docio et al. suggest that among prepubertal children, perturbations in calcium homeostasis occur when 25-hydroxyvitamin D concentrations are below 12 and 20 ng/mL. Studies performed in adolescents showed that parathyroid hormone concentrations increased when 25-hydroxyvitamin D concentrations dropped below 12-16 ng/mL (23-26).

However further studies are necessary to verify whether the set levels of serum 25-hydroxyvitamin D concentrations have been accurately established for children and adolescents (27). The possibility of using the dosage of the 25-hydroxyvitamin D concentrations, has allowed for correlating the daily amount of vitamin D ingested with the serum 25-hydroxyvitamin D level. In a recent study performed in Turkey, 148 fully breastfed healthy children aged 2-24 months were evaluated by screening serum 25-hydroxyvitamin D concentrations. Three groups were formed according to age (2-6, 6-12, 12-24 months) with three subgroups in each age group according to vitamin D intakes of ≤300 IU/day, 400 IU/day and 600 IU/day during the first year of life. The clothing worn by mothers and vitamin D supplements during pregnancy were recorded and the serum 25-hydroxyvitamin D concentration cut-off was 40 ng/mL. The study demonstrated that 300 IU/day of vitamin D is insufficient for preventing vitamin D deficiency in all children, while 400-600 IU/day are insufficient in 50% of children. The authors concluded that in developing countries lack of vitamin-D fortified food and religious and social customs imposing veiling of mothers with no vitamin D supplements during pregnancy, result in insufficient serum vitamin D concentrations in 80% of cases, and cause inadequate vitamin D status in their offspring (28). This study, although geographically very limited, and traditionally and culturally circumscribed, emphasizes the difficulty of evaluating the adequacy of vitamin D intake because of the numerous variables involved and above all it concludes that 400 IU/day of vitamin D are insufficient even in very sunny countries.

The dosage of 400 IU/day also appears to be inadequate in adolescents and adults with minimal solar exposure when assessed via serial checking of serum 25-hydroxyvitamin D concentrations (29).

Besides the lack of vitamin D, dietary calcium deficiency occurring before epiphyseal fusion can also play an important role in causing bone disease. Greer et al. demonstrated that most children over 8 and adolescents in the United States do not achieve the recommended daily intake of calcium, even though an adequate dietary supply of calcium is strictly necessary for the development of peak bone mass (30). The recommended dietary calcium intake in the United States is of 210-270 mg/day in infants; 500 mg/day in children 1-3 years of age; 800 mg/day in children 4-8 years of age; 1000 mg/day in children and adolescents 9-18 years of age, however mostly in teenagers, the replacement of milk with soft drinks causes an insufficient supply of calcium for bone mineral accretion (30). The importance of dietary calcium is also evident in the study of Pettifor et al. in South Africa, which suggests that rickets among rural children was attributable to low dietary calcium intakes and not to vitamin D deficiency. In particular, these children had active rickets between the ages of 4 and 16 y (31). Low calcium intake is mostly frequent in African communities such as Egypt and Nigeria where little cow’s milk is consumed and the diet is based on a limited variety of cereals. In these situations, calcium supplements alone are able to heal bone disease (32, 33).

Vitamin D status in pregnant women and bone metabolism in early childhood

In their study in Finland, Viljakainen et al. reported that during pregnancy, 69% of women and 37% of newborns at birth were vitamin-D deficient with consequences on bone mineral accrual and size during the intrauterine period which cannot be totally reverted by postnatal vitamin D supplementation (34). It is now known that 25-hydroxyvitamin D passes easily through the placental barrier and the concentration of placental-vein 25-hydroxyvitamin D correlates with the concentration found in the maternal circulation, therefore the vitamin D pool of the foetus depends on that of the mother. Conversely, investigations on the trans-placental passage of 1,25-hydroxyvitamin D have provided contrasting results, although foetal synthesis of 1,25-hydroxyvitamin D has been demonstrated (35). With use of dual-energy X-ray absorptiometry, it has also been observed that serum 25-hydroxyvitamin D levels in pregnant women are highest in the third trimester and many studies, performed in various countries with different nutritional, sunlight exposure, and clothing habits, have demonstrated a correlation between the vitamin D concentration in the mother during pregnancy and the bone mineral content in the newborn. Furthermore, it is interesting to note that a very low serum-vitamin D concentration in mothers and their newborns can also clinically manifest with elevated alkaline phosphatase bone isoenzyme activity, and sometimes in infants with symptomatic hypocalcaemia and larger fontanelles (36). In addition, it has been demonstrated how the administration of supplementary vitamin D during pregnancy, besides improving foetal calcium and bone metabolism, also reduces the numbers of infants classified as growth-retarded for both weight and length (35). As regards the adequate amount of vitamin D supplement, the belief that 400 IU/day are sufficient in all pregnant women has been contradicted by many studies (13, 35). Salle et al. suggest a vitamin D supplement throughout the entire pregnancy with an intake of 400 IU/day in well-nourished women with adequate sunlight exposure, and 1000 IU/day in women without vitamin D fortified foods or living in countries where sunlight exposure is low (35). Also confirming this, Hollis demonstrated that mothers who were vitamin-D deficient at the beginning of pregnancy, were still deficient at the end of pregnancy.
Despite daily supplements of 800-1600 IU throughout the entire pregnancy (37). Human milk contains approximately 20 IU per litre of vitamin D, which is a very small concentration of vitamin D, so many studies with varying amounts of vitamin D supplements (400 IU/day; 1000 IU/day; 2000 IU/day; 4000 IU/day) have been conducted in lactating mothers and their offspring to establish the vitamin D requirements. The results have shown that a relatively high dose of maternal vitamin D supplements, equal to 2000 IU/day are needed to increase maternal breast milk concentrations to levels capable of maintaining the optimal vitamin D status of the breast-fed infant (38). On the other hand, Specker et al. demonstrated that the vitamin D status is also correlated in breastfed infants with sunlight exposure rather than with the vitamin D content of maternal breast milk (39).

Ultimately, even if further studies are required to define the vitamin D requirements of lactating mothers, a daily intake of vitamin D of 2000 or 4000 IU is considered necessary by most researchers. In particular, Hollis and Wagner state that the daily intake of 4000 IU of vitamin D in lactating mothers increases the circulating 25-hydroxyvitamin D concentrations in their infants until reaching the normal range after only 3 months of breastfeeding thanks to the transfer of vitamin D into the mother’s milk, which would make vitamin D supplements for these infants superfluous (40). On the other hand, since there is no consensus regarding infants, at present the AAP indications are largely accepted despite not being exhaustive.

Specific problems affect premature infants. The vitamin D requirements of preterm infants are influenced by body storage at birth, which in turn depends on the length of gestation and maternal stores; however it is recommended that all premature infants fed with formula milk, receive 400 IU/day of vitamin D irrespective of the content in low-birth-weight formulas, and 1000 IU/day when breastfed. Conversely, Hollis and Wagner observed that the dose of 400 IU/day for 4 months is capable of increasing the serum 25-hydroxyvitamin D concentration to within the normal range both in term and preterm infants (40). Despite vitamin D supplements, osteopenia is common in premature infants, mostly due to low calcium and phosphorus intake for prolonged periods of parenteral feeding, steroid treatment and diet deficiency.

How can we evaluate the toxic serum concentrations in infants and children?

The amount of circulating 25-hydroxyvitamin D that induces toxicity should be higher than 100-150 ng/mL, which corresponds to a daily vitamin D intake in adults well in excess of 10000 IU/day for several months (13). The daily dose-limit of vitamin D in infancy in order to exclude toxicity is still undetermined however (40). The clinical symptoms of the toxic effects of vitamin D are hypercalcemia and hypercalciuria, and its consequences include anorexia, nausea/vomiting, weakness, fatigue, lassitude, polyuria/polydipsia, nocturia and extraskeletal calcifications. As mentioned above, this clinical picture developed after the administration of 2000-3000 IU/day of vitamin D for long periods in infants and children in Great Britain in the 1950’s; and in a subset of these, toxicity appeared with even much lower doses of vitamin D, revealing the risk of indiscriminate supplementation of vitamin D in milk and other foods. Many reports have caused alarm, with the attributing of infantile idiopathic hypercalcaemia and the supravalvular aortic stenosis syndrome to an excessive intake of vitamin D in pregnant women (41). On the other hand it is worrying to note that in the past the recommended intake of vitamin D for infants in Finland was 4000-5000 IU/day, later reduced to 2000 IU, and finally to 1000 IU/day; neither idiopathic infantile hypercalcaemia nor any other health problems have ever been described even with higher doses (42). It is likely that the toxic dose of vitamin D is influenced by individual characteristics or sensitivity and also that no definitive indications could derive from studies and reports taking place in a period prior to the possibility of dosing serum 25-hydroxyvitamin D levels and correlating them with the other calcium metabolism parameters.

For this reason, when high intakes of vitamin D are prescribed, in addition to the detecting of the serum concentration of 25-hydroxyvitamin D, monitoring of urinary calcium excretion is also a reliable means for establishing the safest amount of vitamin D to be administered to children. The mechanisms giving rise to vitamin D toxicity are still unclear. It has been emphasized how the level of 1,25 dihydroxyvitamin D can be within the normal range also in the presence of high levels of 25-hydroxyvitamin D and hypercalcaemia; the explanation advanced is that a high concentration of 25-hydroxyvitamin D and other vitamin D metabolites displaces the free 1,25-hydroxyvitamin D from the vitamin D binding protein, allowing an intracellular action on gene transcription and the priming of its biochemical effects (43).

How to evaluate the status of vitamin D and bone metabolism?

An important question which still remains unresolved at the paediatric age concerns the methods for evaluating the optimal status of vitamin D in relation to the accretion of new bone mass. In fact, bone metabolism is influenced by various correlated and interdependent factors, which work over a long period of time, therefore, biochemical parameters for assessing the vitamin D status and calcium metabolism may not be adequate for verifying good bone development. For this reason it is necessary to perform longitudinal studies including biochemical and instrumental investigations to establish the optimal intake of vitamin D and calcium, in relation to age, sex, growth velocity, weather, and sunlight exposure (27).

In the past, rickets or osteomalacia were associated with serum 25-hydroxyvitamin D concentrations below 10 ng/mL. Apart from the concept of vitamin D deficiency, vitamin insufficiency was also proposed, encompassing values below 20 ng/mL. On the other hand, a precise definition of vitamin D deficiency or insufficiency depending on 25-hydroxyvitamin D values is still a matter of debate, and many patients with a diagnosis of vitamin deficiency or insufficiency, even at lower values, show no evidence of bone disease (44). Nevertheless, the limits recently proposed by experts for defining the different vitamin D status are increased to <20 ng/mL for deficient, 21-29 ng/mL for insufficient, and >30 ng/mL for adequate due to the demonstration in adults that vitamin D levels higher than 30 ng/mL are associated with maximal suppression of parathyroid hormone secretion. Nonetheless, this vitamin D status classification is the result of a theoretical-scientific consensus and not of perspective studies aimed at evaluating the consequences on bone development, above all in subjects of paediatric age (45). In fact, the application of a vitamin D status classification in children and adolescents established on the parathyroid hormone level criterion is limited by the observation that at that age an elevated parathyroid hormone does not necessarily indicate an inadequate vitamin D status, but rather, increased calcium absorption due to the stimulation of periosteal bone formation and greater bone accrual during growth (44). Despite these considerations, Cheng et al., by selecting a cut-off of 20 ng/mL for deficient and 40 ng/mL for insufficient serum vitamin D concentrations demonstrated a significant relationship between deficient and insufficient serum levels of 25-hydroxyvitamin D, hyperparathyroidism and low cortical bone density, and that there are negative effects on bone structure even with greater vitamin D concentrations than those considered adequate (46).
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Conversely, the recent study by Bowden et al. conducted on children referred to a paediatric metabolic bone clinic with osteopenia or osteoporosis, revealed a 21.1% prevalence of vitamin D deficiency defined as serum 25-hydroxyvitamin D < 20 ng/ml and an 80.0% prevalence of vitamin D insufficiency defined as serum 25-hydroxyvitamin D < 30 ng/ml. Furthermore, low serum 25-hydroxyvitamin D concentration was positively correlated with 1,25 dihydroxyvitamin D, parathyroid hormone, alkaline phosphatase, and urine markers for bone turnover (47). Finally, to determine the effectiveness of vitamin D supplementation for improving bone mineral density in children and adolescents and the influence of vitamin D status, Winzeberg et al. performed a meta-analysis on published studies; their conclusion has been that it is unlikely that vitamin D supplements are beneficial in children and adolescents with normal vitamin D levels (48).

Childhood obesity and vitamin D

Vitamin D deficiency or insufficiency have been reported among a high percent of healthy obese and overweight children and adolescents worldwide (49). The study performed by Cizmeciglu et al., besides confirming that the mean level of 25-hydroxyvitamin D was deficient or insufficient in 65% of children, and significantly lower in girls than boys, also showed a significantly negative correlation between serum 25-hydroxyvitamin D levels and BMI in obese and overweight subjects (50). Furthermore it has also been demonstrated that a 1% increase in BMI percentile results in a 5% decrease in serum 25-hydroxyvitamin D level. This phenomenon is attributed to increased adipose tissue, which decreases vitamin D bioavailability via sequestration in body fat. For this reason, some authors suggest a vitamin D supplementation of 1000-2000 IU/day to prevent vitamin D deficiency in obese people (51).

Conclusion

Longitudinal studies considering the influence of different factors involved in bone metabolism in children and adolescents, such as doses of vitamin D, serum 25-hydroxyvitamin D levels, calcium intake and its correlations with bone metabolism parameters, are necessary to establish the relationship between all the variables and the careful vitamin D intake in the different contests (48). Besides this, another important observation regards the development of paediatric sciences. In fact, as of the 1960s paediatric science consisting above all of nursing science, changed to a more complex discipline and became internal childhood medicine for promoting the survival of children previously destined to a short lifespan and/or death. Thus the prevalence of infants and children with chronic diseases affecting the synthesis and absorption of calcium and vitamin D has dropped dramatically, opening up another field for investigation regarding the vitamin D status and the possible consequences of its deficiency. In addition, a number of studies have revealed an association between vitamin D deficiency and the risk of insulin-dependent mellitus diabetes, autoimmune diseases, and some types of cancer following the discovery that vitamin D is a hormone that regulates numerous cellular functions (4, 52). Consequently the research on the implications of vitamin D status for individual health is still open to exploration.

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