VITAMIN D
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Vitamin D deficiency in children: a distant but re-emerging problem

Diego Peroni
Department of Clinical and Experimental Medicine, Paediatrics Section, University of Pisa; Director of the Paediatrics Unit, AOUP [Pisa University Hospital]

BACKGROUND, WHY THERE IS RISK

Vitamin D deficiency in children is a health problem with social implications that must be considered unresolved. Indeed, since vitamin D is a fundamental factor in development of the musculoskeletal system, it is at the core of children's growth. The primary action of vitamin D in childhood is to promote the proper formation of bone mass. Of note, 90-95% of vitamin D production is generated by exposure to sunlight, while only 5-10% comes from diet [1,2]. Thus, deficiencies can occur if exposure to sunlight is inadequate.

In this regard, a British study evaluating data on the prevalence of rachitis caused by vitamin D deficiency found that cases of rickets in the UK have risen, especially during the last decade [3]. This situation has been attributed to the fact that the ethnic component of the population living in the UK has probably undergone profound changes. Emergence of populations with darker skin tones has increased significantly, in which supplementation, even in the first year of life, has not been strongly recommended, which has brought about a greater risk of deficiency. In fact, darker phototypes do not allow complete absorption through exposure to sun and tend to require supplementation [3].

Vitamin D deficiency, however, is also possible in other countries such as Italy, where, although sun exposure is far more prevalent, the increase in the number of dark-skinned children has also been observed in the last decade. While some northern European countries often apply a policy of supplementing food with vitamin D (food fortification), resulting in a significant and widespread decrease in risk, lack of supplementation can increase the incidence of vitamin D deficiency. Therefore, in Italy as in other Mediterranean countries, lack of supplementation can also be a significant risk factor for vitamin D deficiency [4]. Considering this, several scientific societies have established recommended dosages and timing for vitamin D administration in children that allows for adequate bone growth [2]. However, during the first year of life even if administration is strongly recommended, there may be poor compliance, causing a marked increase in risk. Such risk may also be present at other stages of growth [2].

VITAMIN D DEFICIENCY: RISK FACTORS

The risk of vitamin D deficiency in children can be related to several factors:

1. Latitude: the further from the equator, the less sunlight there is to promote natural vitamin D production;
2. Ethnicity: darker skin is an obstacle to the formation of vitamin D by sunlight;
3. Cultural factors: for example, the extreme coverage of a mother's body with clothing for religious reasons during pregnancy is a risk factor for severe vitamin D deficiency;
4. Diet: this can play a role if intake or absorption of foods containing vitamin D is restricted.

During the first year of life, prophylaxis with 400 IU/day should be given, since supplementation is necessary for the prevention of rickets. An infant's vitamin D stores will be directly proportional to the mother's vitamin D status, which is often low: the newborn and nursing baby are exposed to minimal sunlight, while the infant's growth is expected to be high. Furthermore, breast milk and formula milk, often contain insufficient amounts of vitamin D. Although supplementation during the first year is highly recommended by paediatricians, mothers may interrupt it or be inconsistent in its administration. An study in the US showed that the reasons for discontinuation were often due to the fact that it was believed that vitamin D was also present in formula milk, that it would also be found in other foods introduced at weaning and that the child was considered to be old enough to not need it [4].

Situations of risk of vitamin D deficiency have also been reported for children over the age of 12 months [1], which is often due to inad-

Correspondence
Diego Peroni
diego.peroni@unipi.it

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equate dietary regimens. For example, a diet rich in phytates (mainly found in seeds, cereals, beans and legumes, and are considered an anti-nutrient since they reduce the absorption of calcium, magnesium and zinc during digestion, thus decreasing their assimilation by the human body) can hinder the absorption of vitamin D [2]. Increased risk can also be caused by chronic disorders such as liver disease or kidney disease, as well as obesity, which is another significant social and health issue. Since vitamin D is sequestered by fat tissue, it becomes unavailable, which significantly lowers serum concentrations in overweight individuals. This set of circumstances, which has been estimated to be present in 30% of the paediatric population, may constitute important risk factors for vitamin D deficiency. In addition, malabsorption disorders, such as cystic fibrosis, chronic inflammatory bowel disease, and undiagnosed coeliac disease, also hinder vitamin D absorption. Some drugs taken for chronic diseases such as antiepileptics, phenobarbital, phenytoin, systemic corticosteroids, antiretroviral drugs, and systemic antifungal agents can also represent risk factors for vitamin D deficiency. Finally, a number of other conditions such as prolonged immobilisation due to cerebral palsy or neuromuscular/neurodegenerative disorders, for example, are significant risk factors [2].

VITAMIN D AND EXTRASKELETAL ACTIONS

Vitamin D, especially in children, has also been attributed a number of extraskeletal functions, which are the subject of ongoing discussion. Many authors view vitamin D as a pleiotropic hormone. This means that the presence of vitamin D and the activation of vitamin D receptors in different cells has homeostatic effects on different organs and systems. Vitamin D receptors are present in various cells that make up the immune system, which influences both its innate and adaptive components [5].

Although vitamin D is able to interact with monocytes, macrophages, and dendritic cells (innate immune system), it will also interact with T lymphocytes (adaptive immune system), thus modulating a child's immunological response. Vitamin D deficiency at different and successive times can expose a child, who may also have other risk factors, to the development of allergic sensitisation and bronchial asthma. Moreover, data from the literature has confirmed that there is a relationship between respiratory function and serum levels of vitamin D, which can be present during pregnancy. Mothers with low serum levels of vitamin D during gestation often give birth to children with reduced lung function. This represents an important risk factor for developing wheezing and bronchial obstruction in the first few months of life [6]. Vitamin D is also able to significantly modify the effect of unfavourable prognostic factors affecting lung function in newborns, such as exposure to cigarette smoke. If a mother smokes during pregnancy, adequate levels of vitamin D will act as a protective factor that appears to neutralise the negative effects of smoke exposure on lung development [7].

SUPPLEMENTATION AND EXTRASKELETAL EFFECTS

Conflicting data on the health effects of vitamin D supplementation has fuelled controversy over its extraskeletal role. A recently published review by endocrinologists concluded that vitamin D supplementation offers very few health benefits. No data has emerged in favour of supplementation for a number of diseases such as diabetes, cancer, autoimmune diseases, multiple sclerosis or asthma [8]. However, other meta-analyses on the effects of vitamin D supplementation on asthma during childhood have been published with more positive results. While vitamin D supplementation cannot reduce the number of exacerbations of asthma in all asthmatic children, the risk of having asthma may be reduced in children who habitually have particularly low levels of vitamin D, i.e. < 10 ng/mL [9]. In another very recent review that assessed the use of vitamin D for management of asthma, the authors found little evidence that the risk of exacerbations was reduced by vitamin D supplementation or its metabolites. However, it must be noted that, the patients most at risk, i.e. those with severe asthma and particularly low vitamin D levels, were poorly represented in the studies in that review.

From a practical standpoint, a child with asthma at higher risk (with moderate to severe asthma and risk factors for vitamin D deficiency) may benefit from vitamin D supplementation [10]. Supplementation during gestation does not appear to prevent asthma in school-age children: notwithstanding, evidence of a trend towards its efficacy has been seen in the prevention of wheezing and bronchospasms in pre-scholastic children. At the age of three years, a trend for greater protection from episodes of wheezing and bronchospasms was seen in the supplemented cohort. This finding was recently confirmed in an analysis of data from the same cohort, attributing it to the effect of vitamin D on lung function and the immune system as early as pregnancy [11].

VITAMIN D AND OBESITY

A clear relationship has been found between vitamin D and metabolic syndrome. In Italy, 30% of children are overweight and many of these are obese. Vitamin D deficiency appears to influence the development of metabolic syndrome and obesity. Serum levels acquired through vitamin D supplementation in children are influenced by body mass index (BMI). While supplementing a child of normal weight with a conventional dose may lead to adequate levels of vitamin D, the same may not be true when providing the same supplementation to a child who is overweight/obese. One study reported that BMI appeared to be associated with a reduced response to vitamin D supplementation [12]. In particular, children with obesity had greater resistance, in terms of non-response, to vitamin D supplementation. Furthermore, another study has shown that there is a conditioning effect determined by the association between BMI and vitamin D levels on respiratory mechanics in patients with mild asthma. Indeed, in patients whose weight is normal, adequate levels of vitamin D were associated with significantly better respiratory function, which was not evident in overweight patients [13].

HOW SHOULD VITAMIN D BE SUPPLEMENTED IN CHILDREN?

Proposed dosages vary widely. Therefore, it is important to refer to the doses recommended by national and international guidelines [2,14]. Only supplementation or food fortification can achieve and maintain adequate levels of vitamin D, especially in children at risk. Exposure to sunlight alone has often been found to not be sufficient at all paediatric ages. A study in 2018 found that only supplementation significantly and effectively increased vitamin D levels in the paediatric population and in pregnant women [15]. A significant aspect that has now been clarified is that dose should be taken daily, and not as a monthly or weekly bolus. A biologically plausible explanation for this is the fact that

TABLE I.
Recommended daily vitamin D requirements at ages between 1-18 years (from Peroni, 2022) [14].

Age	IOM 2011 and AAP 2012			LARN 2012			Endocrine Society 2011	
	EAR, UI/day	RDA, UI/day	UL, UI/day	EAR, UI/day	RDA, UI/day	UL, UI/day	Daily Requirements, UI/day	UL, UI/day
1-3 years	400	600	2,500	400	600	2,000	600-1,000	4,000
4-8 years	400	600	3,000	400	600	2,000 (4-10 years)	600-1,000	4,000
9-18 years	400	600	4,000	400	600	4,000 (11-18 years)	600-1,000	4,000

EAR: Estimate Average Requirement (estimated intake to cover the needs of 50% of the population); RDA: Recommended Dietary Allowances (recommended intake for the population: intake estimated to cover the needs of more than 97.5% of the population); UL: Tolerable Upper Intake (intake above which adverse events may occur). * Recommended requirements for individuals at risk of vitamin D deficiency.

high single bolus doses may induce the long-term expression of enzymes involved in the catabolism of vitamin D, which inactivate the vitamin when it is administered in large quantities [16]. Thus, it is important to supplement daily. This was highlighted in a review of the literature published in 2013, where the risk for development of respiratory tract disease in children was more significantly reduced in subjects receiving vitamin D as a daily dose and not as a bolus [17,18].

WHAT DOSES CAN BE USED FOR SUPPLEMENTATION?

One must first consider that supplementation is important to achieve adequate serum levels (Tab. I). Vitamin D is relevant to the development of appropriate bone mass, also because osteoporosis is a disease that many believe begins in childhood. Therefore, it is essential to ensure adequate intake of vitamin D and calcium early in life, which will build up bone mass. Nevertheless, to achieve levels of vitamin D levels that are effective on extraskeletal functions, it will probably be necessary to achieve higher serum levels than that what are considered beneficial for bone health. All children should receive adequate supplementation during the first 12 months, and probably for 24 months: 400 and 600 units of vitamin D, respectively. In middle and late childhood, it is also important to give vitamin D to children and pre-adolescents who have risk factors for vitamin D deficiency. Lifestyle also makes a difference. In children and adolescents who are frequently outdoors and eat a broad variety of foods, exposure to sunlight and diet should ensure good vitamin D absorption. During winter months, vitamin D supplementation is worthwhile, while considering the presence of risk factors such as lack of exposure to sunlight and overweight/obesity. Daily intake should be 400 units/day during the first year of life, which should then vary between 600 and 1000 units/day. A child who presents with very low levels of vitamin D, and with a clinically evident deficiency, will need higher levels of supplementation 2.

CONCLUSIONS

Levels of vitamin D may be low at all paediatric ages, especially in the presence of certain risk factors. Food fortification, a situation that, at the level of the entire population in countries where vitamin D levels have traditionally been low, for example due to inadequate exposure to sunlight, has helped overcome health problems such as rickets [17,18]. However, the problem is not yet solved. Food fortification, together with daily supplementation, must be considered because, as risk factors have changed, with more dark-skinned children, and as lifestyles have evolved, the likelihood of vitamin D deficiency has tended to increase. In Italy, the number of at-risk and vulnerable children has also increased notably in recent years. Therefore, the benefits of vitamin D supplementation should be acknowledged and thus recommended.

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