VITAMIN D
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UPDATE ON VITAMIN D IN PEDIATRIC PATIENTS

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INTRODUCTION

Vitamin D is essential for humans. In addition to its recognized roles in calcium and phosphorus metabolism and bone mineralization, vitamin D is also known for its activity at the extra-skeletal level, as many cells throughout the body express the vitamin D receptor and the 1α-hydroxylase enzyme. Extra-skeletal actions of vitamin D are significant in pediatric patients because they have an impact on the normal processes of a child's development, including those of the immune system, thus promoting good health.

In a review which I prepared in 2017, these were the conclusions I drew on vitamin D in pediatric patients:

- the action of vitamin D may have beneficial effects in the prevention and cure of chronic diseases;
- vitamin D can play a synergic role in the maintaining and developing a child's immune system;
- it is crucial to maintain normal vitamin D serum levels for clinical efficiency apart from those required for bone metabolism. Even if roughly one-third of the population of western countries, Italy included, has insufficient levels of vitamin D (serum levels < 20 ng/nL - 50 nmol/L), it has been suggested that efficient levels needed to sustain an appropriate response of the immune system should be higher (equal to or higher than 30-40 ng/m - 75-100 nmol/L) (Fig. 1).

Note that these statements are all hypothetical ("can", "it is possible", etc.). The aim is to establish the role of vitamin D in chronic diseases, a very controversial and debated topic for which we find contrasting and equivocal data in the literature. Observational studies in adults affected by various pathologic conditions have shown that these diseases are more severe in those subjects with low vitamin D levels. However, very often studies on vitamin D supplementation have produced negative and controversial results and have even provided documented evidence on the inefficiency of vitamin D supplementation in subjects with cardiovascular and oncological diseases. The Vitamin D and OmegA-3 TriaL (VITAL), which investigated whether taking supplements of vitamin D (2.000 IU/day) and omega-3 fatty acids (1 gram/day) would reduce the incidence of cancers or cardiovascular diseases over 5 years, showed that there was no difference between subjects taking the supplement and those taking the placebo. This study suggests a difference between association data compared to those obtained by supplementation [1,2].

The aim of this review is, first, to provide a reasoned update of what the literature tells us about the role of vitamin D in pediatric patients; second, to show that levels of dietary vitamin D intake are almost always insufficient at all ages [3]; and, third, to show that supplementation is the way to obtain adequate levels of vitamin D. It is yet not clear, though, whether achieving adequate levels of vitamin D is associated with a significant clinical improvement.

The recent *Nota 96*, issued by the Italian Medicine Agency (AIFA) to introduce new regulatory criteria on whether the National Health Service (SSN) will reimburse vitamin D costs for the adult population, does not apply to patients of pediatric age (0-18 years old). For these subjects, reimbursement of vitamin D continues to be completely covered by the SSN (*Nota 96, Gazzetta Ufficiale*, general series no. 252, 26 Oct. 2019). This regulation could be explained by the higher vulnerability of children with insufficient vitamin D status, a circumstance that necessitates greater elasticity in coverage criteria.

ACTION ON BONE TISSUE

Let me begin by discussing new developments with regard to bone metabolism. In pediatrics, it is necessary to consider the primary role played by vitamin D in bone mass formation immediately from birth. Vitamin D can

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Conflict of interest
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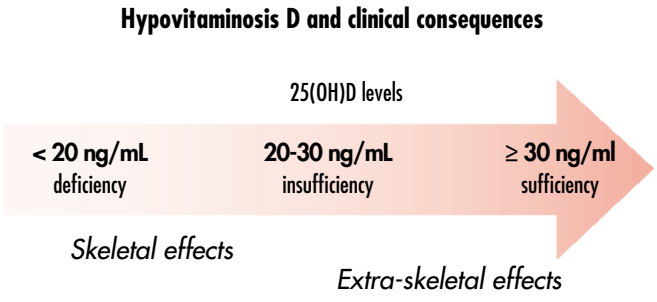

FIGURE 1.
Vitamin D values.

cause hypercalcemia that starts at the intestinal level, where it triggers calcium (Ca) and phosphorous (P) absorption, increasing the expression of Ca channels on the surface of enterocytes. Vitamin D deficiency is associated with an increase in parathormone (PTH), which in turn causes an increase in bone turnover and a reduction in bone density. This action favors the onset of both rickets during childhood and osteomalacia during adolescence and adulthood [4]. In this regard, an English article from 2018 warns about the increased incidence of cases of rickets where neonatal and infantile vitamin D supplementation is not mandatory [5]. Moreover, the increase in these cases in the UK is due to the fact that fortified dietary intake of vitamin D alone does not completely protect against significant vitamin D deficiency. This circumstance, associated with risk factors for hypovitaminosis, such as ethnicity, dark skin color, religious practices, and lifestyles, entails increased risks that need to be taken into account, leading these authors to urge changes to current preventive health policies [5].

VITAMIN D DURING PREGNANCY AND LACTATION

More and more scientific evidence indicates the importance of adequate levels of vitamin D during pregnancy and lactation, for mothers, fetuses, and newborns.
Nota 96, published by the AIFA in October 2019, introduced new regulatory criteria regarding reimbursement of vitamin D costs by the SSN for the adult population and officially recognized the importance of vitamin D during pregnancy and lactation, assuring the reimbursement of its costs by the SSN regardless of 25(OH)D level.
During pregnancy, vitamin D metabolism is modified in response to the increased Ca needs required for fetal skeletal mineralization, leading to an increase in 1,25(OH)2D levels in maternal plasma. Calcitriol plays a fundamental role in the modulation of calcium-phosphorus homeostasis in both the mother and the fetus, increasing intestinal Ca absorption [4]. The fetus is almost completely dependent on the mother for its 25(OH)D levels. In fact, maternal and fetal 25(OH)D levels are strictly related, as shown by the positive association between maternal 25(OH)D levels evaluated during pregnancy or near term and those in the fetal cord or the newborn. A high incidence of hypovitaminosis D in pregnant women is very common. An Italian study [4] evaluated 25(OH)D plasma levels in pregnant Italian women at term and found that roughly 60% had vitamin D plasma levels < 20 ng/mL.
Regarding breast feeding, maternal milk certainly represents the best food for the baby. However, as we know, it contains low quantities of vitamin D (< 50 IU/L), levels which are not in line with those recommended by the International Scientific Society for this age range (400 IU/day) (Table I). Furthermore, the literature has highlighted that vitamin D levels in maternal milk are directly related to those of the mother, with the same seasonal trends (high levels in summer, influenced by the mother's exposure to the sun) [6]. These results confirm the importance of promoting adequate levels of vitamin D not only in infants but also in mothers during the period of breastfeeding.
In this regard, a study showed that a mother who is breastfeeding has a fourfold higher risk of being vitamin D deficient compared to women who are not, especially during winter and spring [7].
In addition, women who breastfeed have a high risk of bone fragility fractures because of the loss of bone mass. During lactation, some hormonal variations, independent of calcium absorption, can cause the loss of about 5-10% of bone mineral content in order to ensure calcium intake in the mother's milk [8]. Indeed, women who breastfeed secrete about 210 mg of Ca/day into their milk and experience long periods of postpartum amenorrhea, during which plasma estrogen levels are drastically reduced. During breastfeeding, therefore, important metabolic changes occur at the maternal skeletal level, both because calcium is passed onto the baby and because of high bone turnover due to a drastic decrease of postpartum estrogens.

EXTRA-SKELETAL EFFECTS

In the last few years, many effects of vitamin D at the extra-skeletal level have been identified. Among these, an important role is played by the regulation of immune system response. For many years, it has been known that vitamin D carries out important functions on many cells of the innate and adaptive immune system: it produces defensins and cathelicidin, which contribute to providing children with immediate defenses; it provides dendritic cells (DC) with greater tolerance; it has an anti-inflammatory effect, suppressing Th lymphocytes and increasing the number of the regulatory T cells (TREG); it reduces the production of the pro inflammatory cytokines from Th1 lymphocytes; and it is able to regulate the intestinal barrier, which is still immature in the newborn, by increasing the development of epithelial cells, triggering the formation of tight-junctions, and developing immune system cells present in the intestine.

THE ROLE OF VITAMIN D IN INFECTIONS

Many studies have shown a relationship between vitamin D levels and respiratory infections. Specifically, a higher incidence of respiratory infections in children with rickets has been observed. Camargo et al. found a higher risk of respiratory infections at three months after birth for infants with vitamin D values < 10 ng/mL in their cord blood compared to those with values > 30ng/mL [9]. Belderbos et al. reached the same conclusions regarding a higher incidence of bronchiolitis in babies with vitamin D deficiency [10].

THE ROLE OF VITAMIN D IN WHEEZING AND ASTHMA

Regarding the prevention of these diseases, Danish studies showed that high doses of vitamin D starting from the 24th week of gestation were not associated with a reduction in the risk of asthma in children at 6 years of age [11]. On the other hand, other studies have observed a positive effect of vitamin D supplementation on pulmonary functionality in newborns. Many studies have shown that

TABLE I.
Treatment recommended by International Scientific Organizations for prevention and treatment of vitamin D deficiency.

	Prophylaxis with D_3 or D_2	Treatment with D_3 or D_2
0-12 months	400-1,000 IU/day regardless of type of feeding	2,000 IU/day for 6 weeks or 50,000 IU/week for 6 weeks < 1 month: 1,000 IU/day for 1-3 months 1-12 months: 1,000-3,000 IU/day (depending on weight) for 1-3 months
Preterm with net weight < 1,500 g	200-400 IU/day	
Preterm with net weight > 1,500 g	400-600 IU/day	
1-18 years	600-1,000 IU/day, at least during months with low exposure to sun; double or triple doses are recommended for patients with risk factors	2,000 IU/day for 6-8 weeks or 50,000 IU/week for 6-8 weeks
1-18 years with risk factors: obesity, liver pathology, malabsorption syndrome [inflammatory bowel disease (IBD), celiac disease, cystic fibrosis], treatment with anticonvulsants, corticosteroids, antiretroviral or antifungal medications	1,000-1,500 IU/day, at least during months with low exposure to sun	4,000-6,000 IU/day

vitamin D deficiency in pediatric patients is linked to a higher number of respiratory infections and therefore to more hospital visits, more hospitalizations, and greater use of oral cycles of corticosteroid therapy [12]. Other trials, such as the current DIVA study, will probably be able to clarify whether high doses of vitamin D supplementation can reduce the frequency of asthma exacerbations and lead to better control of the pathology [12]. DIVA is a multicentric, placebo-controlled Canadian study: preschool aged children affected by wheezing caused by viral infections will receive two high doses of vitamin D (100,000 IU) at an interval of two months, followed by a daily dose of 400 IU during the winter.
Currently available evidence shows that vitamin D supplementation decreased the risk of exacerbations (fewer systemic steroids and fewer visits to the ER) but was less effective in reducing the severity of the asthma [13]. According to a meta-analysis, the greatest benefit is achieved in patients with very low baseline 25(OH)D levels (< 10 ng/mL) and in those who followed therapy with daily or weekly doses of vitamin D [14]. However, these effects are less evident in children between 1 and 5 years of age, probably because the obstructive respiratory disease is characterized by different causes and a different physiopathology.

THE ROLE OF VITAMIN D IN AUTOIMMUNE DISEASES

Many studies have shown a correlation between hypovitaminosis D and the risk of developing such autoimmune diseases as diabetes mellitus type 1 (DM1), Crohn's disease and Rheumatoid Arthritis (RA). In fact, an adequate supply of vitamin D in the first years of life is associated with a reduction in the risk of developing DM1 in the following years. This reduced risk is directly proportional to the administered dosage of vitamin D [15, 16]. In particular, the protective effect was measured at 27% in the U.K. However, other studies did not find the same positive effects in terms of protection against the risk of developing these diseases, whether supplementation was given during pregnancy or during infancy. It should be noted, though, that very few controlled randomized studies have been conducted.
RA mainly increases in cases of hypovitaminosis D. However, results on vitamin D supplementation are still very controversial: supplementation could have an impact on the severity of the disease especially when vitamin D levels are low. Again, more studies need to be carried out in this field.

OBESITY AND METABOLIC SYNDROME

Available data show an association between obesity and hypovitaminosis D (insufficient levels > 50% in obese children). On the other hand, the biological effect of vitamin D deficiency on insulin resistance, hypertension, hyperlipidemia, and progression to Type 2 Diabetes is probably of little relevance, which could explain why results on vitamin D supplementation are mixed [3].

CONCLUSIONS

In conclusion, vitamin D has biological effects that go far beyond skeletal ones. While it is important to maintain adequate levels of vitamin D for healthy bone structure, the same recommendation may also apply to a variety of systems and organs.
However, intervention studies conducted to evaluate the effect on the prevention or improvement of pathologies attributed to vitamin D deficiency are often contradictory, at least for the moment. More research data need to be collected to determine the dosages, therapy duration and serum vitamin D levels which are optimal for obtaining positive clinical and biological outcomes.

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