www.jpnim.com Open Access **eISSN: 2281-0692**
Journal of Pediatric and Neonatal Individualized Medicine 2022;11(1):e110137
doi: 10.7363/110137
Received: 2022 Mar 01; revised: 2022 Apr 12; accepted: 2022 Apr 12; published online: 2022 Apr 27

Editorial

Vitamin D: where we should go

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"An old story to be written in the near future"

Keywords

Vitamin D, deficiency, Italian data, immune system, intakes, toxicity.

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How to cite

Romagnoli C. Vitamin D: where we should go. J Pediatr Neonat Individual Med. 2022;11(1):e110137. doi: 10.7363/110137.

The problem of vitamin D deficiency

Vitamin D derives its name from being the fourth vitamin to be identified, as a factor that cures rickets, in 1922, while its structure was established by Askew et al. twenty years later from a mixture resulted from the irradiation of ergosterol [1, 2].

Known for its well-known effects on calcium and bone metabolism, vitamin D was added to common foods (such as bread, milk, dairy products and cereals), to prevent rickets and its use led to the disappearance of this disease starting in the 1930s. This practice was suspended after 1950 in many countries due to its alleged toxicity and that led to the current epidemiological deficit situation [1].

The hypovitaminosis D is becoming a notable health problem worldwide. The most recent data suggest that more than 50% of the population of each country has plasma concentrations of vitamin D compatible with the deficit definition (< 50 nmol/L – 20 ng/ml) [3]. A high incidence of vitamin D deficiency, greater than 45% and up to 80%, is also reported in two recent Italian studies [4, 5]. It is important to emphasise that the reported deficit does not concern populations with pathologies that can interfere with the normal vitamin D metabolism (malabsorption, some drugs, malnutrition, genetic polymorphisms, etc.), but concerns a paediatric low-risk population for which the deficiency results from a deficient production/assumption of vitamin D.

One of the emerging problems is whether the defined vitamin D deficit level, useful for skeletal diseases, is also suitable for all other well-known extra-skeletal functions. For this reason, the demand for measurement of vitamin D has significantly increased.

What are the extra-skeletal functions?

The biological functions of vitamin D are not limited to bone as suggested by evolution of life. Indeed, vitamin D was initially synthesized from algae to protect DNA from UVB and to defend against pathogens, and only with the passage of life from the sea to earth it assumed for tetrapods the role of absorption (intestine) and storage (bone) of calcium and its production was transferred to the skin [1].

The influence of vitamin D on the immune system is an essential element for the extra-skeletal actions of vitamin D. The genomic effects of vitamin D on the immune system induce the synthesis of anti-infective factors by macrophages and monocytes, the inhibition of the production of immunoglobulins by activated lymphocytes, and an immune tolerance by dendritic cells [6]. These actions justify the numerous associations between vitamin D deficiency and many disorders (infectious, allergic, autoimmune, endocrine), while the antioxidant and angiogenetic actions explain its effect on the cardiovascular system and on endothelial dysfunction [7, 8]. The influence of vitamin D on cellular growth and differentiation as well as on mechanisms of cellular apoptosis may explain its effects on cancer [9].

Despite the evidence of an association between vitamin D deficit and many diseases, the results of the randomized controlled trials (RCTs) on the treatment of these diseases with vitamin D have given inconsistent results [10]. Inconsistency of the results may depend on methodological problems, heterogeneity of the populations studied and individual susceptibility. The main methodological problem is that vitamin D is a nutrient and not a drug. Only deficient subjects who reach the state of sufficiency benefit from its action, which is missing if the deficient subjects remain deficient or if the nutrient is administered to non-deficient subjects. Treating all subjects studied in the same way can make the effect of the nutrient invisible. Another problem is the definition of threshold: bone health is guaranteed by 50 nmol/L of serum 25(OH)D (25-hydroxyvitamin D), while higher thresholds of serum 25(OH)D concentration are emerging for non-skeletal health benefits. A further problem is the standardization of the 25(OH)D dosing methods: the immunological method shows high variability (7-19%), while the use of HPLC-TMS (high-performance liquid chromatography – tandem mass spectrometry) offers levels of 3-6% higher. To these methodological problems must be added the heterogeneity of the populations studied and the variability of the individual response [10]. All that requires us to learn how to design RCTs able to give certain and scientifically sustainable answers about the role of vitamin D in extra-skeletal diseases.

In this field the future of research must consider identification of specific thresholds for the various pathologies and the setting of RCTs on a deficient population with doses of vitamin D to obtain the state of sufficiency. In the meantime, we should administer vitamin D to achieve the state of sufficiency in the whole child and adolescent population.

Why vitamin D deficiency is so widespread?

Vitamin D is produced about 80% on the skin by sun UVB rays, while the remaining 20% comes from the food intake. Exposure to the sun in a swimsuit

with up to a slight redness of the skin (minimum dose erythematous – 54 mJ/cm^2) for 15-20 minutes can produce up to 10,000 IU of vitamin D (250 μg). This effect decreases with increasing sun ray obliquity (time of day, season and latitude), increasing age and skin pigmentation, and using of sunscreen [11].

In the 1600s the industrial revolution impacted the environment increasing air pollution (due to increased use of coal burning) and reducing sun exposure with the impairment of production of vitamin D. A significant increase in rickets ensued. Nowadays the reduction of the ozone layer in the atmosphere due to environmental pollution has increased the penetration of sunlight with negative consequences for skin health. Hence the need to use skin protection systems from the sun that interfere with the production of vitamin D results in an insufficient production of vitamin D, which contributed to the vitamin D deficiency not only for people living far from the equator, but also in our country (Italy). For these reasons, the dietary intake of vitamin D has become more and more important. The first unconscious dietary administration of vitamin D was made using cod liver oil, which was later used first as a therapy then as a prevention of rickets [1, 2]. A teaspoon of cod liver oil contains about 400 IU of vitamin D: this is the dose still recommended today to prevent rickets, but perhaps it is not enough to avoid the state of insufficiency.

The dietary intake of vitamin D is very variable and difficult to identify except for foods in which it is added. In Italy, few foods are fortified with enough vitamin D and therefore infants, children and adolescent are at high risk of deficiency.

A recent paper suggests that, despite the well-known differences between types of food products and taking as standard the results obtained from pork (raised outdoors and fed with vitamin D supplemented foods), it can be estimated that in Danish children the food intake of vitamin D accounts for less than 25% of the total daily requirement [12].

In the UK, also, most foods provide less than 20% of the vitamin D expected intake [13].

Italian data on this subject are missing, but we can hypothesize quantities not exceeding those reported in the Danish study, and that makes it mandatory the vitamin D supplementation.

How much vitamin D should be given?

The definition of vitamin D and calcium intakes made so far is based on scientific data (meta-analyses, RCTs, case-control studies, etc.) and is related to the bone health (absence of rickets or similar lesions) and not to the possible extra-skeletal effects of vitamin D. The suggested intakes are aimed at obtaining plasma concentrations of 20 ng/ml or 50 nmol/L which are considered "sufficient", being 100 ng/ml or 250 nmol/L the limit of "excess". Some international recommendations insist on doses of 400-600 IU/day, while in many other countries the administration of higher doses is suggested: 800 IU/day in Canada, Australia, and Germany, up to 1,600 IU/day in Finland [14, 15].

Only a few data are available in this regard for the Italian paediatric population. Stagi et al. studied 365 infants/adolescents with hypovitaminosis D who were divided into two arms: the control group (160 subjects) was informed about the possibility of improving endogenous production and nutritional intake of vitamin D (outdoor physical activity, non-use of sunscreen, adequate nutrition, etc.), while the treated group (205 subjects) received 400 IU/day of cholecalciferol. Follow-up was prolonged for 12 months. At enrolment the study groups were similar for all variables able to modify the status for vitamin D and similar was the number of subjects with vitamin D insufficiency or deficiency. At the end of the follow-up year, only 29.7% of the vitamin D group and 20.6% of the control group had a sufficient status, while insufficiency was found in 42.0% of treated and 34.4% of control subjects and a deficiency was still found in 28.3% of treated and 45.0% of control infants, respectively. The conclusion of the study was that neither the setting of lifestyles nor the administration of 400 IU/day of cholecalciferol can significantly improve the status for vitamin D in an Italian infant and adolescent population [4]. More indicative data are reported by Mazzoleni et al. who enrolled in Padua (Northern Italy) 203 patients, aged between 2 and 15 years, divided into a treatment group (82 subjects) who received 1,500 IU/day of vitamin D from November to April and a control group (121 subjects) who did not receive vitamin D supplementation. The results showed that, despite the significant increase of vitamin D plasma concentration, a part of subjects remained deficient even in the treatment group. The Authors concluded that a more prolonged treatment (throughout the year), also with higher doses is indicated, especially in adolescents and dark-skinned subjects [5].

Is there a maximum dose that can be administered?

Vitamin D toxicity is very rare and can be caused by accidental or deliberate ingestion of excessive

doses of the vitamin. Incongruous administration may result from inappropriate administration or error in formulation or from unlicensed and uncontrolled products. Doses of 10,000 IU/day for 5 months do not cause toxicity [16], and absence of toxicity has also been found for administration of doses > 30,000 IU/day over long periods with plasma concentrations < 500 nmol/L (< 200 ng/ml) [17].

Literature data about accepted upper limits of vitamin D administration are scarce since the case reports or studies on small cases are prevalent, but, considering the most reliable ones, it can be concluded that doses up to 4,000 IU/day for long periods can be considered free of toxicity [18].

The analysis of epidemiological data and of possible toxicity could suggest the dose of 1,000-2,000 IU/day of vitamin D to be administered preventively without seasonal variations. Regardless of the dose, administration should be individualized with the determination of the plasma concentration of $25(OH)D_3$ to avoid possibly harmful levels, maintaining plasma levels between 75 nmol/L (30 ng/ml) and 250 nmol/L (100 ng/ml). As for the doses to be administered in non-skeletal diseases, mainly for cancer, the literature seems to suggest much higher doses. To avoid side effects from high doses of vitamin D, modern technology is studying the possible use of vitamin D analogues with higher effects on immune system than on calcium metabolism [9].

Conclusions

It is time to reconsider the dose of vitamin D to be administered to Italian children/adolescents to avoid hypovitaminosis D as well as to set up study methodologies that do not have the limits highlighted so far with the aim to have statistically valid answers about the efficacy of vitamin D also in non-skeletal diseases.

Declaration of interest

The Author declares that there is no conflict of interest.

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