VITAMIN D
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Update on the role of vitamin D in the prevention of osteoporosis

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In recent years the possible multiple positive effects of vitamin D (antineoplastic, cardioprotective, immunomodulatory, etc.) have aroused growing interest and an increase in scientific (and non-scientific) publications on the subject. However, uncertainties about its usefulness in the prevention of osteoporosis have also been raised, following discordant results in the literature, beyond any reasonable doubt on extra-skeletal effects.

Osteoporosis has a burdensome impact on the healthcare system: in Italy approximately 3.5 million women and 1 million men are affected by the disease. Incidence increases with age (the steady ageing of the population leads to more cases). From age 50, the incidence of fragility fractures increases progressively, becoming comparable to that of stroke and breast cancer [1]. Annual costs attributable to such fractures (acute management and long-term disability) grow with the ageing of the population. What is needed is an acceptable prevention strategy that makes the best use of available resources.

NOTE 96

AIFA's recent Note 96 regulates the prescription of compounds with the indication "prevention and treatment of vitamin D deficiency" in adults, charged to the National Health Service (NHS), in an effort to reconcile the need to achieve sufficient vitamin D levels with the need to contain the cost of prescribing vitamin D based products.

AIFA's June 2021 update of the Note [2] (20 months after its introduction), which monitors consumption trends, shows a 25% containment of the expenditure for drugs included in the Note incurred by the NHS compared to previous periods, with insignificant increases in the consumption of and expenditure for vitamin D analogues not in the Note. These are general and preliminary assessments. Considering the diversified "pre-Note" situation in the different Regions of Italy along with the equally disparate "post-Note" response, specific, long-term in-depth studies are clearly necessary. In all age groups (except 0-10 years) there was a reduction in consumption (even among young adults, which was probably excessive). Nevertheless, the greatest reduction was in the 40-60 age group, especially among women, but also in the 60-80 age group (Table I). Both of these age groups are at risk of hypovitaminosis D and osteoporosis, for which correct supplementation is especially important, along with any anti-fracture therapies, whose clinical efficacy depends on the correction of hypovitaminosis D as a prerequisite, as specified in Note 96 and in the literature [3].

VITAMIN D AND BONE HOMOEOSTASIS

Vitamin D is a fat-soluble compound that acts as a steroid hormone. Its main source (with some coming from the diet) is the conversion of pro-vitamin D (7-dehydrocholesterol) in the deep layers of the epidermis, by exposure to UVB radiation, into vitamin D_3 (cholecalciferol), the inactive precursor. Cholecalciferol undergoes an obligatory two- step hydroxylation. The first is in the liver where it turns into 25(OH)D or calcifediol, the compound with the longest half-life, which is used for the dosage of serum vitamin D levels. The second, which is in the kidney, gives rise to the biologically active form, $1,25(OH)_2D$ or calcitriol (Fig. 1). By binding to the vitamin D receptor (VDR), calcitriol induces its biological effects, first of all on phosphocalcic metabolism [stimulation of calcium and phosphate absorption in the small intestine, inhibition of parathormone (PTH) synthesis and secretion, activation of the RANKL/RANK system and consequent osteoclastogenesis by induction of RANKL expression on osteoblasts], regulating serum calcium and phosphorus levels and bone mineralisation (Fig. 2) [4]. It follows that subnormal levels of this nutrient can alter the balance described. Namely, 25(OH)D levels at < 30 ng/mL reduce intestinal calcium absorption (which increases in a linear manner with 25(OH)D levels reaching a *plateau* at 32 ng/mL) [5] and increases PTH secretion,

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Conflict of interest
The authors state that there are no conflicts of interest.

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TABLE I.
AIFA Note 96 monitoring of vitamin D consumption trends. Preliminary analysis of the 20 months after the introduction of the Note (November 2019 - June 2021). Data by age group - ATC in Note 96. Figures below the national average are in red.[2] NB Gender and age information was not available for 0.5% of packages (https://www.aifa.gov.it/documents/20142/1030827/NOTA_96_20mesi_22.10.2021.pdf).

	Packages females	Delta % packages previous period	Gross females	Delta % packages previous period	Packages males	Delta % expenditure previous period	Gross males	Delta % expenditure previous period
Total Italy	42,295,282	-27.1	337,593,955	-24.7	8,230,373	-19.3	64,113,376	-17.5
Age groups								
0-10	400,521	1.7	2,070,124	1.4	431,335	1.6	2,220,819	1.4
10-20	269,051	-11.6	1,891,416	-14.3	198,484	-9.5	1,353,184	-11.9
20-30	427,089	-23.9	3,459,222	-23.0	186,544	-19.6	1,515,270	-18.1
30-40	787,504	-26.5	6,334,166	-25.7	232,703	-22.8	1,875,888	-20.9
40-50	2,298,338	-34.1	18,748,999	-32.7	470,127	-26.0	3,749,088	-24.2
50-60	6,839,559	-35.1	55,733,820	-33.2	981,648	-21.1	7,812,630	-19.3
60-70	10,043,108	-30.2	81,406,064	-27.5	1,572,989	-21.7	12,588,757	-19.7
70–80	11,762,214	-26.2	94,008,595	-23.1	2,251,209	-21.8	17,946,285	-19.3
> 80	9,467,898	-16.7	73,941,548	-13.3	1,905,334	-15.4	15,051,454	-12.5

stimulating tubular calcium reabsorption, renal hydroxylation of calcifediol to calcitriol, RANKL expression on osteoblasts and ultimately creating an imbalance in bone homoeostasis leading to dissolution of the mineralised bone matrix.[4]

There is no agreement on minimum 25(OH) D serum levels sufficient to prevent osteoporosis. According to the foregoing, levels > 30 ng/mL are optimal, as stated by the *International Osteoporosis Foundation* (IOF) and the *Endocrine Society* and the *National Osteoporosis Foundation* (NOF). Yet, the *World Health Organization* (WHO), the *European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis* (ESCEO) and the *National Osteoporosis Society* (NOS) have deemed 25(OH)D levels at ≥ 20 ng/mL, the threshold transposed in Note 96, to be sufficient. Recommendations and guidelines based on findings from the literature mirror this controversy whilst also being open to criticism for their methodology. For example, a recent systematic review[7] assessed the method of developing 47 Bone Health Guidelines published between 2009 and 2019 (which set out recommendations for serum 25(OH)D levels for the prevention of osteoporosis and fractures, ranging from 10 to 30~100 ng/mL) on the basis of 25 criteria adopted by WHO for the proper development of guidelines, whilst on average each guideline met only 10 out of the 25 methodological criteria.

A further disconcerting factor is the lack of standardisation of methods for measuring serum 25(OH)D levels, especially in studies prior to 2009 (the year when the first certified measurement procedures were im-

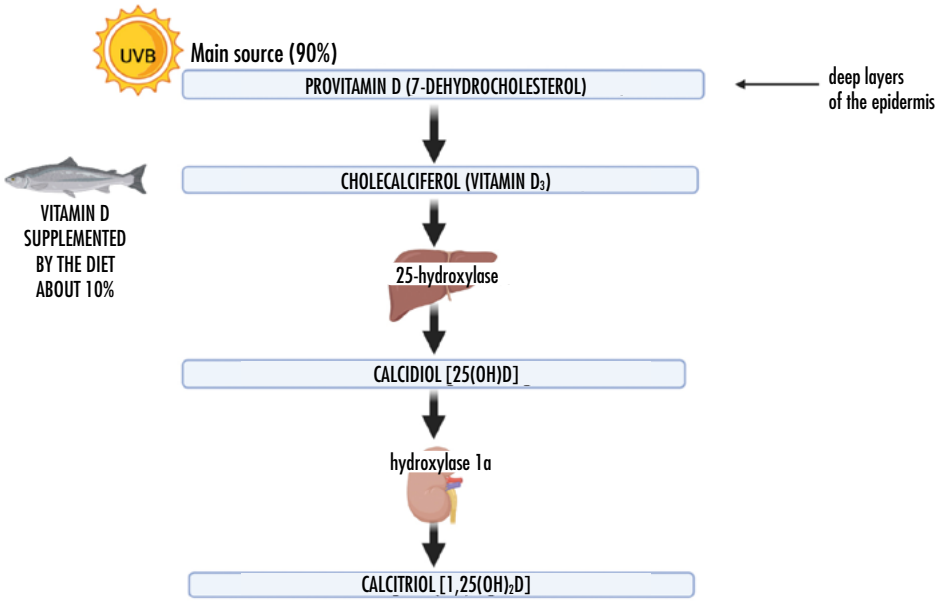

FIGURE 1.
Vitamin D metabolism. The main source (90%) is represented by the conversion of provitamin D in the deep layers of the epidermis, by exposure to solar UVB rays, into cholecalciferol, which will undergo a two-step hydroxylation (first hepatic, then renal) giving rise to the active metabolite, calcitriol.

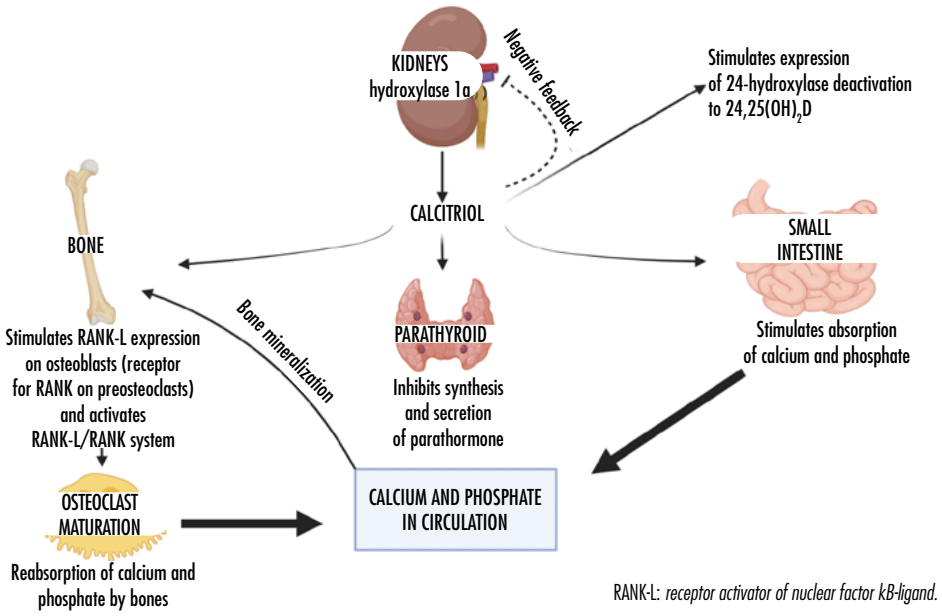

FIGURE 2.
Effects of calcitriol [1,25(OH)2D] on phosphocalcic metabolism.

plemented by the US National Institute of Standards and Technology, NIST), which were considered in several meta-analyses and inevitably coloured their results. The results of 25(OH)D dosage assays done with non-standardised methods showed significant variations when done retrospectively after standardisation.[8]

VITAMIN D AND OSTEOPOROSIS PREVENTION

If on the one hand, a great deal of evidence suggests that correction of hypovitaminosis D reduces the risk of osteoporosis, fragility fractures and falls, especially in the elderly (where hypovitaminosis D is more frequent due to reduced exposure to the sun, lowered capacity for synthesis by the skin and decreased dietary intake), all the more so in the case of medical treatment for osteoporosis,[3] where results of some RCTs (randomised controlled trials) and related meta-analyses do not reveal these benefits, recommending their use only in rare conditions of rickets and osteomalacia.[9] A number of critical issues make these latter conclusions poorly generalizable, starting with the recruitment of the sample, which 7 times out of 10 is characterised by individuals with normal serum 25(OH)D levels at baseline.[10] Since vitamin D is a nutrient, the subjects who would benefit most from supplementation are those most deficient in the nutrient itself, who paradoxically are "scarcely considered" in the trials. This is even more compelling if these subjects are healthy and at low risk of osteoporosis and falls, since they are not likely see an improvement in a risk that is already contained. Moreover, in some cases, sub-analyses referring to groups with vitamin D deficiency and osteoporosis risk showed positive effects after supplementation. A meta-analysis based on RCTs characterised by a population aged >65 years including administration of adequate vitamin D doses at close intervals (at least 800 IU/day, as suggested by the latest recommendations for the elderly population[11] and not in boluses, which might be counterproductive or ineffective [12]), in combination with calcium, showed a significant 15% reduction in total fractures (relative risk, RR = 0.85; 95% confidence interval, CI 0.73-0.98) and 30% fewer femur fractures (RR = 0.70; 95% CI 0.56-0.87) than placebo.[13] Furthermore, the failure to dose 25(OH)D at the endpoint in several studies, considering the variability in dosage and frequency of administration used in the various trials, leaves the doubt that some of the deficient patients did not in any event reach a sufficient vitamin D level at the end of the study, which lessens the reliability of the results. Then again, several RCTs lasted no longer than 12 months, not guaranteeing an adequate observation period to assess long-term effects such as fractures or significant changes in BMD.[3] And we should not forget the already discussed issue of the methods used to measure 25(OH)D levels with no standardisation.[8]

CONCLUSIONS

Based on the foregoing considerations, for the prevention of osteoporosis and its complications, maintenance of 25(OH)D levels above 20 ng/mL (a range of 30-40 ng/mL is desirable, to provide maximum benefits, particularly important for the elderly and those at risk), together with adequate calcium intake, if deficient are required.[14] Those who are vitamin D deficient or whose vitamin D intake is insufficient and those who are at risk of deficiency, benefit most from supplementation. Instead, those with adequate levels of vitamin D already enjoy the benefits of this natural condition. Maintenance dosing of the levels achieved should be provided for the elderly, those at risk of deficiency or who are undergoing treatment for osteoporosis. Needed are RCTs with standardised measurements of 25(OH)D, involving subjects with vitamin D deficiency and at risk of osteoporosis, with assessment of whether normal serum levels are actually achieved after supplementation. Finally, based on Note 96 monitoring, the uncertainty that perhaps reduced consumption in age groups that are at risk may lead to insufficient supplementation seems to emerge. It should be borne in mind that the costs incurred by supplementation are amply covered by the savings linked to avoiding the complications of osteoporosis. Clearly, prevention remains the winning formula, also from the standpoint of costs.

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