

Vitamin D supplementation: what is right?

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Summary

The vitamin D system comprises a group of metabolites, of which calcitriol or 1,25(OH)₂D is the most active form, although its substrate calcidiol or 25(OH)D is also able to activate the vitamin D receptor.

In order to have a correct vitamin D supplementation policy, it is mandatory to understand the regulation and functionality of the vitamin D system, the definition of “normality” and the objectives to achieve.

Although 25(OH)D activity is lower than 1,25(OH)₂D by a factor of 100, its serum concentration is 1000-times higher, so 25(OH)D is believed to substantially contribute to the overall vitamin D effect on target organs.

For several years we have been using a wrong threshold for 25(OH)D “sufficiency” mainly in people older than 50 years. Nowadays, however, several studies indicate that the most adequate or sufficient 25(OH)D levels in patients under risk of metabolic bone diseases should be 30-40 ng/mL. Thus, considering the factors involved in vitamin D metabolism, the population at risk of vitamin D deficiency is extraordinarily high and should be considered as a public health priority.

In most European countries, fortification of dairy products is forbidden and in the USA the FDA (Foods and Drugs Administration) limited fortification exclusively to milk and cereals. Although food fortification has demonstrated being useful in the normalization of vitamin D levels, the issue on the adequate dose is still pending.

To summarize, the best attitude regarding vitamin D supplementation is to admit that most patients under risk of metabolic bone disease would need 25(OH)D supplementation. A dose of 800-1600 UI/day (with an adequate calcium intake), administered either daily or periodically would allow to achieve adequate levels in most patients.

KEY WORDS: calcidiol, calcitriol, vitamin D status, food fortification, vitamin D supplementation.

Despite the fact that vitamin D is still called and known as a vitamin, it actually comprises a group of very closely interrelated hormonal compounds also related to the other main regulatory

hormone of the mineral metabolism (and, therefore, bone metabolism), the parathormone (PTH). Accordingly, in order to develop a rightful vitamin D supplementation policy, it is mandatory to understand the regulation and functionality of the system, the definition of “normality”, the objectives to achieve and whether these objectives are therapeutic or if their aim is to optimize the possible effects of other therapeutic agents.

Vitamin D hormonal system

The vitamin D hormonal system comprises different metabolites derived from the cholecalciferol precursor (vitamin D₃), which is either synthesized in the skin under the influence of UVB light and temperature, or has a dietary origin. Endogenous vitamin D belongs to the vitamin D₃ series, whilst some vitamin D supplements belong to the vitamin D₂ series (plant origin) (1). The first enzymatic reaction takes place in the liver, where these metabolites are hydroxylated, thus forming the 25-hydroxyvitamin D [25(OH)D]. 25(OH)D has a long half-life of about 3-4 weeks and is the best indicator of vitamin D status in the body (2, 3). 25(OH)D is the substrate for the 1- α -hydroxylase which catalyzes the synthesis of 1,25-dihydroxyvitamin D [1,25(OH)₂D] or calcitriol mainly in the kidney, although nowadays the existence of this enzyme in many other tissues is well known (4). Calcitriol, which is actually the most active form of vitamin D [100-times higher than 25(OH)D] has a very short half-life, about a few hours.

Calcitriol and other metabolites act in their target tissues through its receptor, vitamin D receptor (VDR), which is a member of the steroid receptor superfamily. The VDR is a calcitriol-activated transcription factor that interacts with several coregulators, thus altering the transcription rate of the target genes. However, some non-genomic actions have been described for the vitamin D, and there is still controversy about whether these actions are carried out through the VDR or through a specific membrane receptor (4).

The activity of 1- α -hydroxylase in the kidney is the main mechanism of the calcitriol synthesis regulation. This enzyme is synthesized along the whole human nephron (5) and the reaction is normally not substrate-dependent, i.e. it does not depend on the plasma levels of 25(OH)D, although it is stimulated by the parathyroid hormone (PTH) and inhibited by phosphate.

Traditionally, the main action of vitamin D has been described thus: “to increase serum calcium and phosphate levels for a correct bone mineralization in order to avoid rickets in children and osteomalacia in adults”. Nevertheless, once these severe conditions have been solved, epidemiologic studies have highlighted the link between vitamin D deficiency and other prevalent diseases such as osteoporosis, common cancers and autoimmune diseases, leading, in the last five years, to the necessity of re-defining the normal levels of vitamin D in the normal population as well as in patients affected by these diseases.

Vitamin D actions depend on: the serum levels of vitamin D metabolites, the VDR density (upregulated by vitamin D), and the qualitative aspects of the VDR, as observed in several studies related to bone mineral density (6-12), intestinal calcium absorption (13-15) and bone response to different therapeutic agents according to VDR gene polymorphisms (16-18).

Importance of 25(OH)D

In the past, it was assumed that the 25(OH)D concentration was largely irrelevant because of the biologically active metabolite, 1,25(OH)₂D or calcitriol, which is synthesized in the kidney and it is more potent by a factor of more than 100. On the other hand, 25(OH)D is able to activate the VDR, although with lower affinity. Since the 25(OH)D concentration is higher than the 1,25(OH)₂D concentration – by a factor of more than 1000 –, many investigators believe that 25(OH)D contributes substantially to the overall vitamin D effect on target organs. Besides this fact, it also bears consideration that many tissues, for instance osteoclasts and vascular smooth muscle cells, express 1- α -hydroxylase activity. Although such locally produced 1,25(OH)₂D does not make a major contribution to circulating 1,25(OH)₂D (as reflected by the low 1,25(OH)₂D concentrations in anephric individuals), the local 1,25(OH)₂D concentrations in such tissues may be another matter and may actually make a significant contribution to hypothetical local paracrine actions (e.g. in bone) (4). Under normal circumstances, the activity of the renal 1- α -hydroxylase is strictly regulated by product inhibition, and the synthesis of 1,25(OH)₂D is not substrate-dependent. In contrast, in some pathological states including chronic kidney disease, renal 1- α -hydroxylase does become substrate-dependent. This implies that if the concentration of 25(OH)D₃ is raised, the production of 1,25(OH)₂D₃ increases (19).

Thus, the real importance of the 25(OH)D levels in patients whose renal function is worsened with age is conditioned by four different aspects (20):

1. Since 1- α -hydroxylase becomes substrate-dependent, 25(OH)D levels influence calcitriol levels.
2. Both 25(OH)D and calcitriol can bind VDR. Calcitriol affinity is higher by a factor of 2400, but 25(OH)D concentration is 1000-times higher.
3. Some vitamin D actions, like intestinal calcium absorption, are mostly VDR independent (1:8 Potency Ratio).
4. 25(OH)D levels can play an important role as a paracrine local factor due to the existence of the extra-renal 1- α -hydroxylase activity.

There has been an erroneous concept regarding which concentrations of 25(OH)D are optimal. The distribution of values follows a Gaussian curve and the mean value depends on age. The age-dependent decline in 25(OH)D₃ is not desirable, however because, for the reasons given above, it is associated with a diminished intestinal calcium absorption, an increased resorption of skeletal mineral and increased PTH concentrations.

Observations in general population indicate that PTH concentrations are lower, the intestinal calcium absorption rate is higher and less mineral is released from the skeleton when 25(OH)D concentrations are in the range of 20 ng/mL (50 nmol/L) or higher. Moreover, intestinal absorption curve reaches plateau when 25(OH)D levels are around 30-40 ng/mL (21). When it comes to diagnosing a vitamin D deficiency and pinpointing the exact level at which it occurs, there is no definitive consensus. Traditionally, vitamin D values below 5-7 ng/mL induce osteomalacia; values lower than 10-12 ng/mL lead to secondary hyperparathyroidism and osteoporosis; and levels above 18-20 ng/mL could be considered normal (22). These values, which may be adjusted to reflect what happens to young people, have proven to be insufficient for an adequate calcium and bone metabolism homeostasis in elderly people. These observations have recently led to an "upward" revision of what is supposed to be the optimal serum concentration of 25(OH)D.

Several factors determine vitamin D levels: those affecting the skin synthesis of vitamin D through ultraviolet radiation and nutrition, and those which can modify the vitamin D metabolism (2). Moreover, vitamin D measurement methods have a great

variability intra- and inter-laboratories, masking the effect of the aforementioned factors, and thus making the comparison between different populations difficult (23, 24).

It has been recently proposed that: 1) levels > 40 ng/mL (> 100 nmol/L) are desirable; 2) hypovitaminosis D occurs when the concentration is between 20 and 40 ng/mL (50-100 nmol/L); 3) there is a vitamin D insufficiency when the concentration is between 10-20 ng/mL (25-50 nmol/L) and 4), there is vitamin D deficiency when values are lower than 10 ng/mL (< 25 nmol/L) (25).

The prevalence of vitamin D deficiency depends on the cut-off point used, as well as the type of population studied. Therefore, a vitamin D deficiency was found in almost all chronic geriatric patients (26) and in 57% of the American acute symptomatic patients (27). This prevalence was 36% of men and 47% of women in European elderly population. Surprisingly, the most southerly countries showed the lowest levels (28), and in women with post-menopausal osteoporosis, the deficiency prevalence was 0% in Singapore, 3.5% in the USA and slightly above 10% in France and Spain (29). Furthermore, a 95% of centenarian patients had undetectable (< 5 ng/mL) levels of 25(OH)D (30).

In our self-ambulating non-selected population the prevalence of 25(OH)D values < 18 ng/mL was 50% in the summer and 72% in the winter, in those between 55-65. These percentages increased to 58% and 80% in the summer and the winter respectively when people older than 65 were selected (19). On the other hand, no cases of hyperparathyroidism were observed in those people whose levels of 25(OH)D were 30 ng/mL (75 nmoles/L) or higher; only a 7% of the population presented levels of 25(OH)D above this value during the whole year.

Which 25-D-hydroxyvitamin serum values should be the goal to achieve in adult populations?

The previous considerations indicate that the most adequate or sufficient 25(OH)D levels in our population under risk of metabolic bone diseases should be 30-40 ng/mL. These levels are considered clinically adequate and safe for the management of patients under risk of developing metabolic bone diseases and/or secondary hyperparathyroidism (31) and they are located where intestinal calcium absorption is optimized, PTH levels are maintained within the normal range, and a higher bone mineral density and lower risk for peripheral fractures with respect to a vitamin D deficient population were observed (Figure 1).

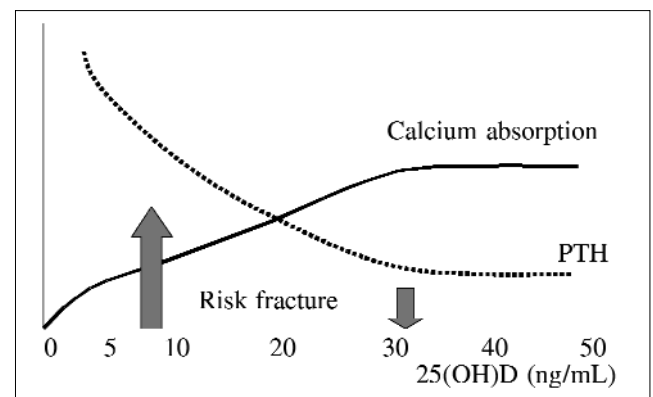


Figure 1 - The picture shows a schematic representation in which can be seen how while 25(OH)D levels increase, calcium absorption also increases, and PTH levels and the risk of fractures decrease. 30 ng/mL of 25(OH)D are necessary to achieve the maximum calcium absorption, the lowest PTH levels and a low risk of osteoporotic fractures.

In osteoporotic patients, considering different criteria (PTH levels, calcium absorption, bone mass, falls and reduced risk for non-vertebral fractures) and based on the results from controlled clinical trials, an experts' committee proposes a minimum level of 25(OH)D between 20-32 ng/mL, and a desirable objective between 28-32 ng/mL (32). In order to achieve these levels, a dairy dose of vitamin D₃ of 800-1600 UI, with an adequate calcium intake, was necessary.

Who should receive vitamin D supplementation?

The factors influencing 25(OH)D concentrations can be grouped into three broad categories (2):

- (i) First, factors which affect the cutaneous synthesis of vitamin D under the influence of UVB radiation. These factors comprise age, melanin concentration in the skin and conditions modulating the intensity of sun exposure, such as season of the year, latitude, altitude and type of clothing.
- (ii) Second, nutritional factors (although, under normal circumstances, the dietary supply of vitamin D makes only a minor contribution to the overall vitamin D status). Dietary sources of vitamin D include raw and cooked fish and dairy products, as well as polyvitamin preparations containing vitamin D or (in the USA) food items enriched with vitamin D, such as milk products and vegetable fats (2).
- (iii) Third, the 25(OH)D concentration is modulated by factors which affect the metabolism of vitamin D. Examples include substances which diminish intestinal absorption or interrupt the intestinal resorption of vitamin D metabolites (enteric recirculation) as well as drugs which alter the activity of the hepatic CYP enzymes and accelerate the catabolism of 25(OH)D into inactive vitamin D metabolites in the liver.

Considering the factors involved in vitamin D metabolism and the epidemiologic data mentioned above, the population at risk of vitamin D deficiency is extraordinarily high and could even be considered a Public Health problem. Vitamin D supplementation, however, is still not recommended under the age of 65 (33) in some prestigious guidelines for clinical practice on Osteoporosis.

It is important to highlight the relevance of the repletion of 25(OH)D deposits, even in chronic kidney disease patients, in which a partial or total deficit of 1- α -hydroxylase activity exists. In fact, the correlation between PTH and 25(OH)D levels is maintained in patients in haemodialysis as well as in those who have received a kidney transplant (19, 20, 34-37).

Furthermore, migration movements that have led people from Southern countries to Northern countries, with darker skin and with dietetic and clothing habits that result in a lessened sun exposure, may imply a higher risk for such populations (38, 39).

Would food fortification be enough?

Sun exposure, in order to stimulate vitamin D synthesis in the skin, sets out difficulties due to the lower capacity of synthesis elderly people possess, the negative effects on senile skin injuries and even due to the fact that melanin induction blocks UV light transition. Therefore, the observation that in Mediterranean countries vitamin D levels are lower than those of Nordic countries would be determined by the natural protection a darker skin provides to solar irradiation. Thus, dietetic vitamin D sources play a predominant role.

Fortification of several foods was set out several years ago when rickets and osteomalacia were frequent. Milk, bread, hot

dogs, refreshments and even beer were enriched with vitamin D (40). However, the outbreak of vitamin D intoxication in Europe and the strict regulations by the FDA (Food and Drug Administration) limited fortification exclusively to milk and cereals (41). In most European countries, fortification of dairy products is forbidden and the prevalence of lactose intolerance, milk allergies and the risk of intoxication in people whose diet is based on milk is not suitable for preventing vitamin D insufficiency. In addition, the vitamin D contents of milk is highly variable (42). Although food fortification, even in non-dairy food, has demonstrated being useful in the normalization of vitamin D levels (40), the issue on the proper dosage is still pending. Furthermore, fortified products have an added, higher, non-justifiable cost than non-fortified food.

Which is the best metabolite and the adequate dosage for vitamin D supplementation?

As Dr. Heaney emphasized: "Vitamin D is inexpensive to manufacture and to administer. (Maybe that is part of the reason for the problem). By contrast, the cost of vitamin D deficiency, while yet to be fully reckoned, may well be massive" (43).

Vitamin D metabolites availability is limited to vitamin D₂ (ergocalciferol), vitamin D₃ (cholecalciferol) and 25-hydroxyvitamin D (25-hydroxycholecalciferol or calcidiol). Paradoxically, calcidiol, the most effective and fastest way to normalize vitamin D levels, is not manufactured in the USA any longer (43). The most common one is vitamin D₃, although the specific presentations (without calcium) are also limited. In Spain there's only one commercial cholecalciferol solution available (drops) and a commercial calcidiol trademark (drops, blisters) but there are no parenteral solutions, which are available in other countries and that allow for more sporadic charging dosages while solving malabsorption problems.

Cholecalciferol effectiveness is higher than that of vitamin D₂ (44), and most of the published studies have been performed using vitamin D₃ alone or combined with calcium supplements (32, 45). Furthermore, taking calcidiol weekly or every 3 weeks has proven to be efficient in achieving an adequate vitamin D repletion (46).

Regarding the recommended dosages, the official recommendations in USA and Canada are 400 UI and 600 UI daily for people younger and older than 70, respectively (47). In Europe, 400 UI are maintained for elderly people (48) as well as the FDA recommendations (49). These dosages have clearly proven to be insufficient, and clinical evidences increase these dosages to 800-1600 UI, daily (32).

It is important to highlight that in recent studies of American women under osteoporosis treatment or prevention, of which 60% of them were receiving vitamin D supplements, the prevalence of women with levels of 25(OH)D < 30 ng/mL was 63% in those having less than 400 UI and 45% in those having 400 UI or more (50). The independent risk factors related to inadequate levels of vitamin D in this population were: age over 80, no Caucasian, BMI >30, medication that may interfere with the vitamin D metabolism, no sport practice, vitamin D supplementation under 400 UI, low cultural level, and no explanation by the physician about the importance of vitamin D.

Up to date, no vitamin D toxicity due to an excess of sun exposure has been described, only toxicity by hypervitaminosis D has been associated to daily dietary doses over 10,000 UI (250 μ g) (51). No toxicity was either observed when 4,000 UI (100 μ g) or 50,000 UI (1,250 μ g) were daily or weekly administered, respectively (52, 53). Moreover, in a double blind, randomized and controlled with placebo assay (n=2686), 100,000 UI (2,500 μ g) of Cholecalciferol every four months were safe

and efficient in decreasing the incidence of osteoporotic fractures (54).

To summarize, the most correct attitude regarding vitamin D supplementation, is to admit that most of the patients under risk of metabolic bone disease will be in need of such supplementation. 25(OH)D and PTH level quantifications will provide us with valuable information about their mineral homeostasis. An adequate dose, 800-1600 UI/day, administered either daily or periodically, would allow achieving levels of sufficiency in most patients. In cases of malabsorption or in cases of medical treatments which activate vitamin D degradation (phenitoin), larger doses or even parenteral administration may be necessary.

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