Reyes Domínguez AI[1], Gómez de Tejada Romero MJ[1,2], Sosa Henríquez M[1,3]

1 Universidad de Las Palmas de Gran Canaria - Instituto Universitario de Investigaciones Biomédicas y Sanitarias - Grupo de Investigación en Osteoporosis y Metabolismo Mineral - Las Palmas de Gran Canaria (España)

2 Universidad de Sevilla - Departamento de Medicina - Sevilla (España)

3 Hospital Universitario Insular - Unidad Metabólica Ósea - Las Palmas de Gran Canaria (España)

Vitamin D. Physiology. Its use in the treatment of osteoporosis

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Correspondence: Manuel Sosa Henríquez - Universidad de Las Palmas de Gran Canaria - Grupo de Investigación en Osteoporosis y Metabolismo Mineral - C/Espronceda, 2 - 35005 Las Palmas de Gran Canaria (Spain)
e-mail: manuel.sosa@ulpgc.es

Introduction. Physiology of vitamin D

Vitamin D is actually not a vitamin in the strict sense of the word. It is not an essential dietary component, and it is entirely possible, in most places, to obtain it through exposure to the sun, as it is synthesized in the skin by the influence of solar ultraviolet rays[1] (Figure 1).

In order to be functional, hydroxylation is needed in the liver, where it is converted into 25-hydroxy-vitamin D3 or 25-hydroxycholecalciferol (25-HCC). Subsequently another hydroxylation occurs in the renal tubule, becoming 1,25 dihydroxy-vitamin D3 (1,25-DHCC) or calcitriol, the true hormone D, with physiological actions in individuals of all ages[2,3] (Table 1). The most well-known physiological function of this hormone is to regulate of calcium and phosphorus metabolism, in order to keep the concentrations of these ions stable in blood, and adequate mineralization of the skeleton[2].

The endocrine system of vitamin D is critical, not only to maintain bone health, but to keep the whole organism healthy. The effects of vitamin D on other cells and body tissues and its influence on all types of diseases have been called extra-dose actions of vitamin D4, and will be discussed in more detail in other sections of this paper.

Determination of vitamin D status

25-HCC is the only vitamin D metabolite used to determine if patients have vitamin D deficiency, sufficient levels or if they are intoxicated[5,6]. This metabolite is the main way to circulate vitamin D and has a half-life of approximately 2-3 weeks. 25-HCC is a sum of vitamin D both that produced from sun exposure and that which is ingested[5,6].

Although 1,25-DHCC is the biologically active form of vitamin D and, therefore, it could be thought to be the ideal metabolite to ascertain the state of vitamin D, it actually is not. There are several reasons for this. First, the circulating half-life of 1,25-DHCC is only 4-6 hours. Furthermore, circulating levels of 1,25-DHCC are a thousand times lower than those of 1,25-HCC. As the patient becomes vitamin D-deficient, there is a decrease in intestinal calcium absorption, which temporarily reduces ionized calcium. This signal is recognized by the calcium sensor in the parathyroid glands to increase the production and secretion of parathyroid hormone (PTH), which, in addition to increasing the tubular reabsorption of calcium in the kidney, increases the mobilization of calcium in the skeleton and also increases renal output by 1.25-DHCC[6,7]. So, when a patient begins to have insufficient or deficient levels of vitamin D, the compensatory increase in PTH causes serum values of 1,25-DHCC to be normal or even elevated. Therefore, its determination is not useful as a measure of the status of vitamin D, although it has been used effectively in the diagnosis of several acquired and inherited disorders in calcium metabolism involving the alteration in renal or extra production 1,25-DHCC[7-9].

We currently have several laboratory techniques to measure 1,25-DHCC. The gold standard is still high-pressure liquid chromatography (HPLC), but it is a complex technique and not available in all laboratories. So instead the use of simpler automated methods such as immune-chemiluminescence have been more widely accepted[8,9].

Figure 1. Physiological regulation of vitamin D

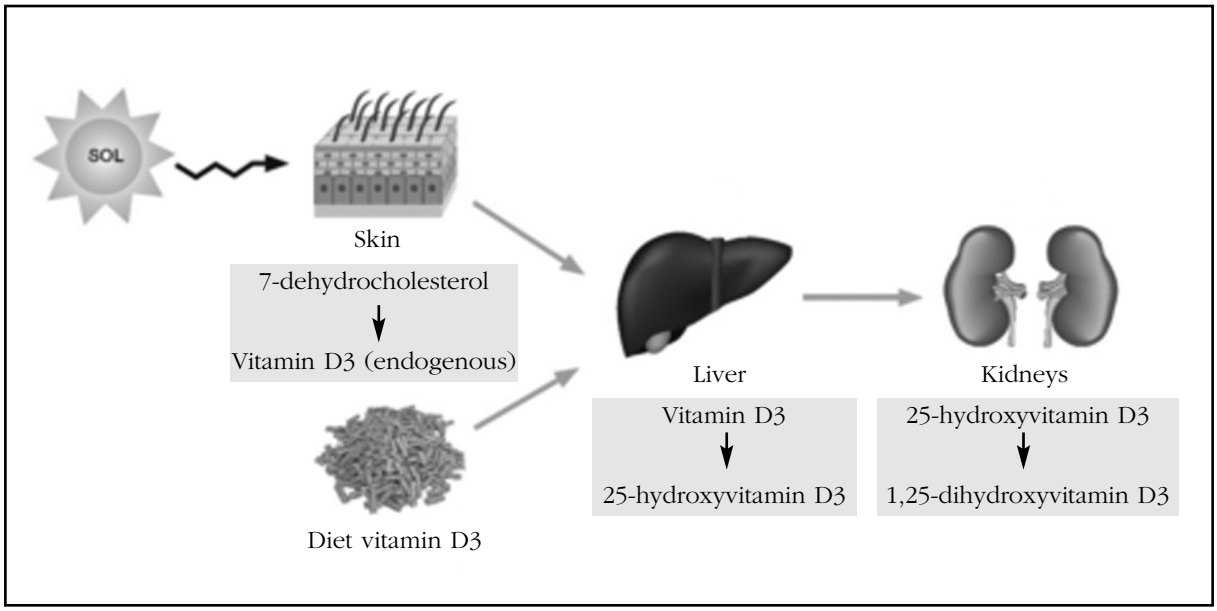


Table 1. Vitamin D metabolites

First name	Abbreviations used	Function
Cholecalciferol or vitamin D3	CC, (D3)	Substratum
Calcifediol, calcidiol	25HCC, 25(OH)D3	Measures the reserve
Calcitriol	1,25DHCC, 1,25(OH)2D3	Active metabolite

What are optimal levels of vitamin D?

A fundamental problem in the determination of 25-HCC is the precision and reproducibility of the methods available for its measurement. Despite the variability among the available methods for measuring vitamin D and although there is no universally accepted consensus on adequate calcifediol levels, it is increasingly agreed that concentrations of 25-HCC greater than 30 ng/mL (to pass to Nmol/L multiplied by 2.5) is an optimal vitamin D status that ensures bone health, although higher levels of calcifediol are probably required to ensure other health goals. The minimum desirable serum concentration of calcifediol should be in all individuals above 20 ng / mL, which would mean an average of around 30 ng /mL in the whole population[3,7].

Table 2 shows the values of 25-HCC that have been considered optimal for the prevention of various events, although there is no consensus on this.

Patients are considered to have severe vitamin D deficiency with serum calcifediol levels below 10 ng/mL and moderate deficiency or insufficiency when they are between 10 and 20 ng/mL, with optimum values above 30 ng/mL. Calcifediol serum levels are not clearly defined, but may be derived from populations highly exposed to the sun, where it is very difficult to exceed a serum concentration of calcifediol of 65-70 ng/mL. Therefore, serum levels of calcifediol between 30 and 70 ng/mL of 25-HCC seem the most physiological and are advisable. In a review of thirty studies no toxicity has been demonstrated in patients with calcifediol levels below 100 ng/mL[3,7] (Figure 2).

Are all metabolites of vitamin D equivalent?

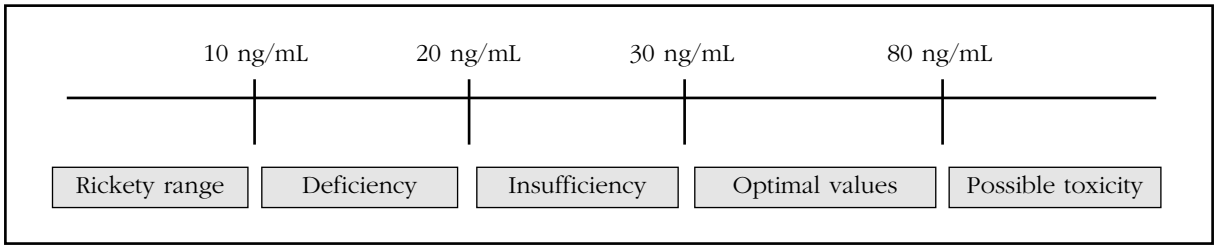
In Spain, the same dose of calcidiol as vitamin D3 (cholecalciferol) is prescribed in the treatment of osteoporosis, although there is not enough evidence available to prove its equipotency. In a recent study by Quesada et al., carried out with 40 postmenopausal patients with osteopenia and vitamin D deficiency, it was established that vitamin D3 and its metabolite 25-HCC are not equipotent, based on the increase of 25-HCC by calcitriol and cholecalciferol. These are molecules with different pharmacological mechanisms that must be prescribed with different doses to obtain the same result[10].

Calcidiol is more rapid, potent and polar, a characteristic that influences the intestinal absorption and its transport in the blood by the protein DBP (vitamin D binding protein). It is a metabolite with a shorter half-life and, logically, leads to a greater and faster concentration increase of 25-HCC.

Table 2. Serum values of 25-HCC suggested to achieve a clinical or analytical objective

Objetive	Serum values of 25HCC recommended (in ng/mL)	Author	Bibliographic reference
Optimum absorption of calcium	32	Heaney	20
Reduction of fracture risk globally	30	Trivedi	21
Avoid secondary hyperparathyroidism	24	Kuchuk	22
Optimal bone mineral density	36-40	Bischoff-Ferrari	23
Fall reduction	24	Bischoff-Ferrari	24
Hip fracture reduction	40	Bischoff-Ferrari	25
Range of rickets/osteomalacia	8	Heaney	20

Figure 2. Classification of patients according to serum levels of 25HCC



The administration of 25-HCC implies a 2 to 5 fold increase in the activity of vitamin D3 administration in the induction of intestinal absorption and the mobilization of calcium from the bone and could lead to over-dosage and a high risk of hypervitaminosis D and Calcidiol-induced hypercalcaemia, as recently published in Clinical Medicine by García Doladé et al.[11].

Vitamin D3 needs to acquire the optimal serum values of 25-HCC

It is well known that the serum increase of 25-HCC following a dose of vitamin D3 is inversely proportional to the baseline value of vitamin D. In other words, the lower the vitamin D levels, established by the 25-HCC blood test, the higher will be the observed increase[12,13]. Thus, for every 40 IU of vitamin D3 administered orally daily, an average increase of 0.48 ng/mL of 25 HCC was calculated when the previous vitamin D values are low, but this increase, with the same 40 IU of vitamin D3, is as low as 0.28 ng/mL when 25 HCC levels were previously above 28 ng/mL.

In young and middle-aged adults, administration of 25 µg of vitamin D3 daily is sufficient to correct vitamin D deficiency and maintain levels of 25-HCC between 32 and 40 ng/mL[14]. Holick has suggested the administration of 50,000 IU of vitamin D3 every two weeks to achieve serum levels of 25-HCC between 30 and 40 ng/mL[13]. Patients with lower baseline levels of vitamin D may require higher doses. Interestingly, calcium intake does not appear to modify the effect of vitamin D3 administration on serum levels of 25-HCC[15].

In view of the recommendations made by the international clinical guidelines, a dose of vitamin D3 of 600-2000 IU is recommended, so that it could be administered daily or in its weekly or monthly equivalent[16-18].

Vitamin D in the treatment of osteoporosis

All baseline studies with drugs used for the treatment of postmenopausal osteoporosis have been performed by administering all calcium and vitamin D supplementation to the patients. The amounts of vitamin D varied, ranging from 350 IU in the FIT study with alendronate to 1,200 IU in others[22-34]. In some studies, a determination of the serum levels of 25-HCC was made and the dose indicated was adjusted accordingly. In others, the administration was uniform, with the same dose for all. A summary of these is shown in Table 3.

Vitamin D3 was always the only metabolite used. None of these studies have used calcifediol or calcitriol. Therefore, if we apply the criteria in Evidence-Based Medicine, any drug used for the treatment of osteoporosis should be prescribed together with a supplement of calcium and vitamin D3[19].

Conflict of interest: The authors declare they have no conflict of interest regarding this work.

Table 3. Approved drugs for the treatment of osteoporosis in Spain. Amount of vitamin D3 used in each study

Drug	Acronym	1st author	Vitamin D3	Bibliographic reference
Alendronate	FIT	Black	250	26
Risedronate	VERT	Harris	500	27
Risedronate	HIP	McClung	500	28
Ibandronate	BONE	Delmas	400	29
Zoledronate	HORIZON	Black	400-1200	30
Raloxifene	MORE	Ettinger	400-600	31
Bazedoxifene		Silverman	400-800	32
Calcitonin	PROOF	Chesnut	400	33
PTH 1-34. Teriparatide		Neer	400-1200	34
PTH 1-84		Greenspan	400	35
Strontium	TROPOS	Reginster	400-800	36
Strontium	SOTI	Meunier	400-800	37
Denosumab	FREEDOM	Cummiings	400-800	38

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