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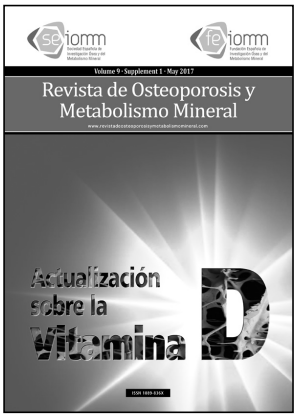

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SUMMARY

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-The publication reflects the views and findings of the authors signatories.
-The active and listed medicines must comply with the instructions the technical data approved in Spain.

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Vitamin D in the 21st century. Beyond osteoporosis

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Introduction

Interest in vitamin D has increased dramatically in recent years. As shown in figure 1, the number of journal articles published and indexed in the PubMed database has multiplied almost by 4 from 2000 to 2016.

Vitamin D, which maintains its name by habit or history related to its discovery, is actually a complex hormonal system[1], its structure being very similar to that of steroid hormones.

Hormone D, as it should actually be termed[2], began to be studied and related to bone mineral metabolism. It is well known that its deficiency produces a skeletal disease in children referred to as rickets and osteomalacia in adults[3]. Subsequently and already in the 20th century, it was verified that practically all the cells of the organism have receptors for this hormone. Thus our knowledge was expanding into other pathophysiological and clinical aspects, including osteoporosis[3-5] as in other bone diseases. The relationship of vitamin D to these processes has been termed "extra-bone effects of vitamin D"[3,6-9].

Nowadays we have a better understanding of vitamin D's relation with muscle and falls[1], with diabetes mellitus, both type 1 and 2[10], with arterial hypertension and ischemic heart disease[11], immune system and autoimmune diseases[12], respiratory infections[13], Bronchial asthma[14] or cancer[3,7,8,15], to name some of the relationships on which an increasing number of articles have been published.

Vitamin D has a complex, delicate and well-known regulatory system, according to whether its cutaneous synthesis or its ingestion produces vitamin D3 or cholecalciferol, which is transported to the liver where it is hydroxylated in 25-hydroxyvitamin D or calcifediol, this being the metabolite that best measures the organic reserve of vitamin D. Subsequently, in the kidney, a new hydroxylation takes place that leads to the formation of the active metabolite of the hormone that is 1.25 dihydroxicolecalciferol or calcitriol[1,16-19].

These differences should be taken into account, as there is no established bioequivalence between the different metabolites, nor are vitamin D3 or cholecalciferol, 25-hydroxyvitamin D or calcifediol[20] nor the final metabolite, 1,25 hydroxyalcalciferol, which by their potency and therapeutic limitations, its pharmacological presentation would require an inspection stamp for its prescription.

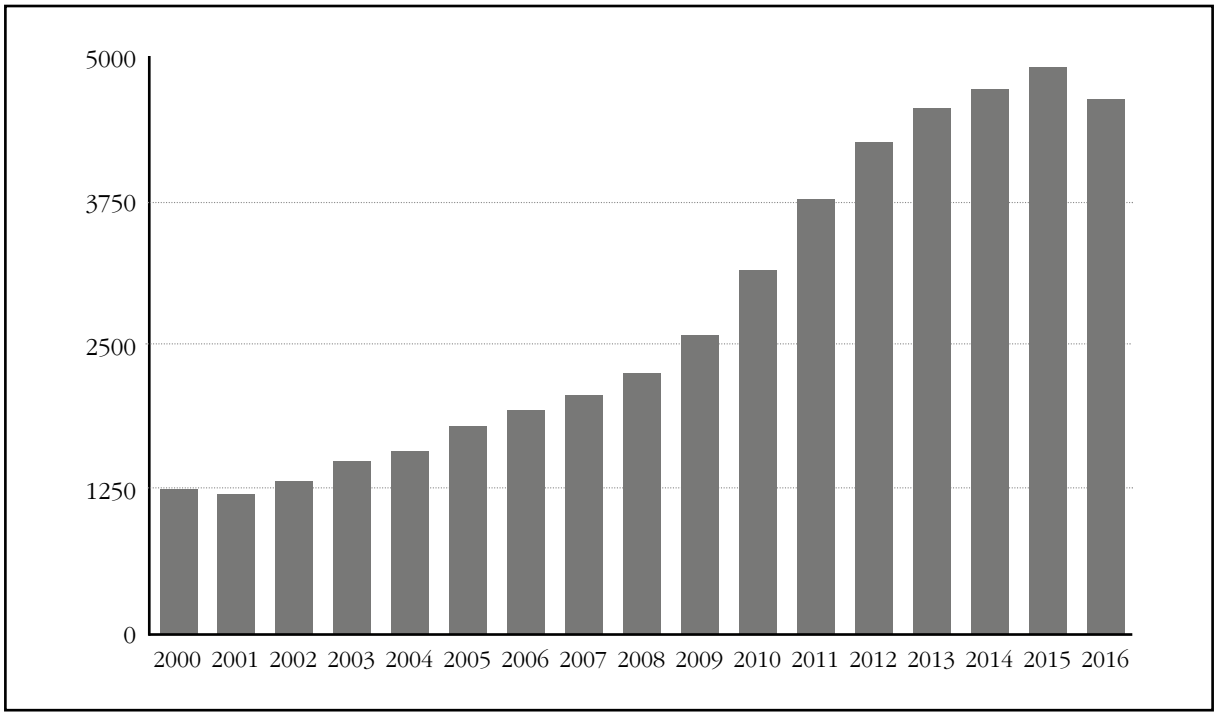
In this paper, we intend to make an update on some of the aspects that have seemed most interesting about vitamin D, such as the prevalence of vitamin D deficiency in our country, something that from a theoretical point of view would be difficult to accept in our "sunny Spain", to other less well-known aspects like vitamin D deficiency in children, as well as a different view of vitamin D in women.

We complete the paper with an update on vitamin D and its use in the prevention and treatment of osteoporosis and fractures due to fragility, and other aspects such as endocrine and rheumatic diseases.

The collaborators are all authors of recognized prestige and great experience in the field of bone mineral metabolism. We can only hope that readers find the paper useful for better treatment of patients, which is medicine's raison d'être.

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

Figure 1. Publications in PubMed including only the term "vitamin D" from January 1, 2000 to December 31, 2016



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

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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

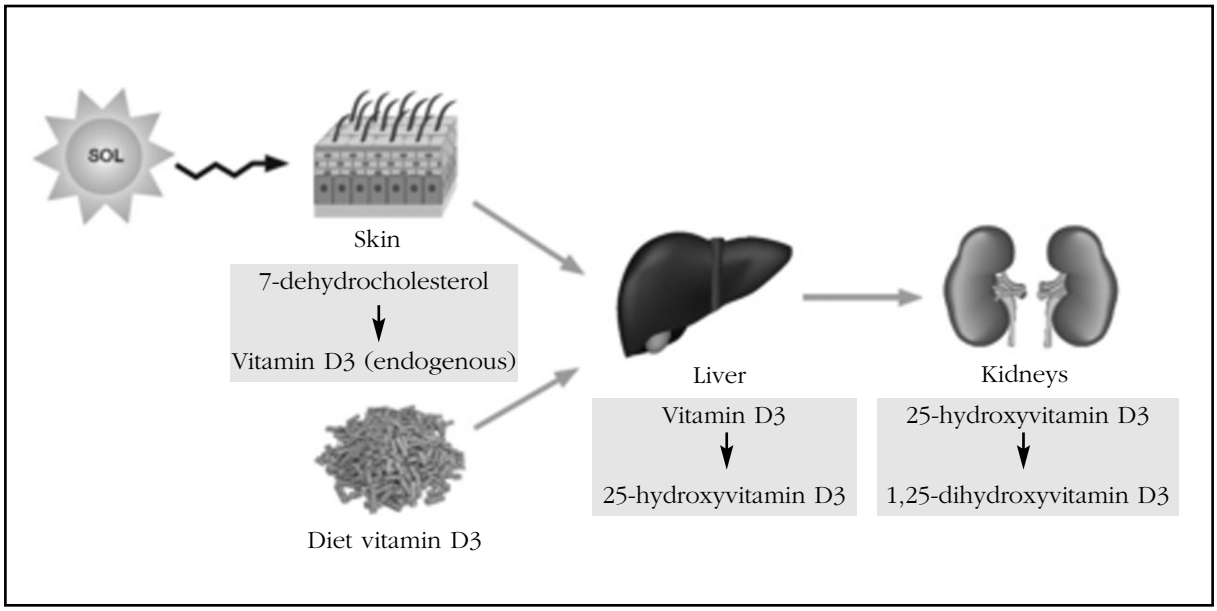


Table 1. Vitamin D metabolites

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?

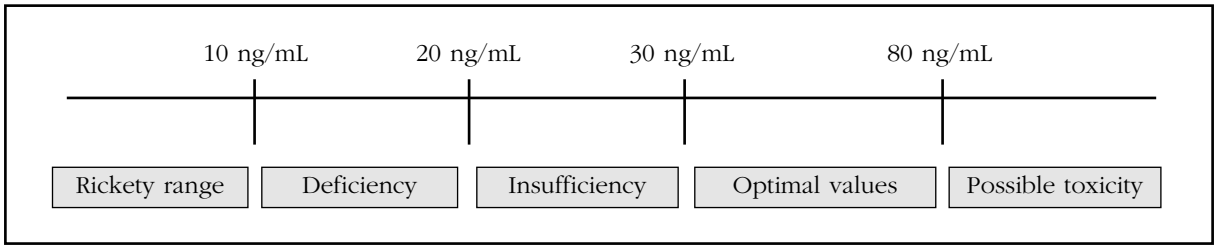
In Spain, the same dose of calcidiol as vitamin D3 (cholecalciferol) is prescribed in the treatment of osteoporosis, although there is not enough evidence available to prove its equipotency. In a recent study by Quesada et al., carried out with 40 postmenopausal patients with osteopenia and vitamin D 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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Prevalence of hypovitaminosis D in our environment

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Introduction

After the 19th century rickets epidemic, caused by vitamin D deficiency due to inadequate sun exposure, insufficient vitamin D (deficiency or insufficiency) is once again recognized as a universal pandemic with serious consequences for human health[1]. Prolonged vitamin D deficiency causes rickets in children and osteomalacia in adults, while vitamin D insufficiency is a major contributor to osteopenia and osteoporosis, loss of bone mass and muscle weakness, falls and fractures[1-4]. In addition, vitamin D deficiency has been associated with an increased risk of certain chronic and degenerative diseases such as cancers, autoimmune processes, infectious diseases, hypertension and cardiovascular disease, among others[1-5].

Vitamin D has a dual origin, on the one hand, by the synthesis of skin under the influence of solar energy by ultraviolet B (UVB) radiation (wavelength, 290-315 nm); on the other, by oral intake, through limited natural sources of vitamin D and fortified foods.

The concept of "vitamin D" means the combination of vitamin D2 and vitamin D. Vitamin D2 was believed to be less effective than vitamin D3 in maintaining 25-hydroxyvitamin D [25-HCC] or calcidiol levels because of its more rapid metabolism[2]. Recently, it has been shown that both are equipotent for maintaining serum 25-HCC levels.

Vitamin D is metabolized in the liver to 25-hydroxyvitamin D, the major metabolite of the endocrine system of vitamin D, which has a long half-life (between 10 and 19 days), and is commonly accepted as a clinical indicator of vitamin D status in the body[6] as it reflects levels of intake and cutaneous synthesis.

The status of 25-HCC is critical for human health, because HCC is the substrate to form 1-25 dihydroxyvitamin D3 [1,25 DHCC or calcitriol] in the kidney, where it is hydrolyzed by 1-alpha hydroxylase, which is strictly regulated by parathyroid hormone, and serum levels of calcium and phosphorus and plays a fundamental endocrine role in calcium homeostasis and bone. 1,25 DHCC regulates gene transcription through the high affinity nuclear receptor for vitamin D in classic organs: intestine, bone, kidney and parathyroid glands.

In addition, 25 HCC is the substrate to form 1,25-DHCC in other organs and tissues such as muscle, heart, brain, breast, colon, pancreas, prostate, skin, and immune system. 1.25-DHCC regulates about 3% of the human genome, controls cell growth and maturation, inhibits renin production, stimulates insulin secretion, and modulates the function of activated T and B lymphocytes and macrophages, as well as many other cellular functions in an autocrine-paracrine manner[7].

Using the serum values of 25-HCC as a measure of vitamin D status, these will depend on a number of factors, such as the season of the year, the number of hours of sunlight and the duration of sun exposure, the use of sunscreens, the pigmentation of the skin and even the latitude of the locality. In fact, vitamin D synthesis is extremely limited during the winter months above the 35th North parallel and decreases considerably with aging. Dietary sources of vitamin D are lower and include fortified milk, fatty fish and fish oils, products available only in some regions of the world[6].

Daily vitamin D requirements

According to the United Nations Food and Agriculture Organization (FAO) recommendations[6], the minimum requirements for vitamin D would be 200 IU/day (5 µg) in childhood and adults up to 50 years of age, 400 IU (10 µg) in people aged 51 to 65 years and 600 IU/day (15 µg) in those over 65 years. In Spain, the recommen-

ded intake in people aged 65 and over is practically the same, of 10-15 µg/day. According to new evidence suggesting that previous recommendations are conservative, the US Department of Health now counts as a minimum requirement for vitamin D 400 IU/day (10 µg), which should be increased to 1000 IU/day (25 µg) People older than 70 years or those with dark skin and limited sun exposure (institutionalized)[7]. The Institute of Medicine (IOM) and the Endocrinology Society's recommended doses are listed in Table 1.

On the other hand, the measurement of 25-HCC has been a subject of controversy and there is concern about the reliability and consistency of laboratory results of serum 25-HCC[8]. Historically, 25-HCC measurements were carried out at research centers using high pressure liquid chromatography (HPLC) or competitive protein-binding methods (CPB). Radioimmunoassay (RIA) and other standard methods such as the Enzyme Linked Immunosorbent Assay (ELISA) were developed in the 1990s. The recent clinical availability of liquid chromatography using spectroscopy (LCMSMS) and HPLC[9] technologies have improved the performance of the 25-HCC assay. This has led to greater agreement between measurements obtained in different clinical laboratories.

Despite the variability of the assays and even though there is no universally established consensus on the appropriate level of 25 HCC, there is a growing trend that a serum concentration of 25 HCC above 30 ng/mL constitutes an optimal state of vitamin D to ensure bone health[1,5,10].

Therefore, the minimally desirable serum concentration of 25-HCC should exceed 20 ng/mL in all individuals, because this implies a population level of about 30 ng/mL[11]. Serum vitamin D deficiency of 25 HCC <10 ng/mL and moderate deficiency (or insufficiency) of 10-20 ng/mL and suboptimal serum levels of 25 HCC between 20-30 ng/mL would be considered as severe vitamin D deficiency. A sufficient or adequate condition would have serum levels of 25 HCC greater than 30 ng/mL[12].

Based on this definition, more than half the population worldwide has vitamin D deficiency or insufficiency. These data have been described in both healthy and postmenopausal young women, especially African-American and middle-aged women, as well as in older adults[1,10]. Vitamin D insufficiency is especially prevalent among osteoporotic patients, particularly in postmenopausal patients and individuals with fragility fractures[1].

Vitamin D levels vary greatly between different countries in North America, Europe, the Middle East and Asia, with seasonal variations in countries that are below the 37º latitude[1,2,13,14]. This is caused by different sun exposure, intake of vitamin D by diet and the use of supplements of this hormone.

The state of vitamin D. Situation in Spain and its neighboring countries

In the European SENECA study[15], a high percentage of low levels of calcidiol were observed during the winter months in people aged 80 to 86 years. Percentage of deficiency, contrary to expectations, was higher in Mediterranean area countries than in northern Europe, probably due to the fact southern European food is not enriched. In the studied Spanish population (27 men and 29 women from Betanzos), 52% of males and 86% of females had serum calcidiol levels below 12 ng/mL (30 nmol/L). As risk factors for insufficiency or deficiency are described: age, low sun exposure (institutionalization, use of clothing or other means of sun protection) as well as thinness and other data or parameters of low nutrition. These factors, as well as a high prevalence of vitamin D insufficiency have been observed in our country in women with high risk of fracture.

In addition, an outpatient study conducted in France and Spain on osteoporotic women over 67 years of age showed a high prevalence of vitamin D insufficiency. Thus, 50% of French women and 65% of Spanish women receiving treatment for osteoporosis had 25 HCC serum levels lower than 30 ng/mL[16]. In the same line, the French SUVIMAX study (latitude 51º to 43º), carried out in a younger population of 765 men and 804 women between the ages of 35 and 65 years, showed that the serum levels of 25 HCC were 17±8 ng/mL, with a solar exposure of 1.06 hours in the north (29% vitamin D deficiency) compared with 37.5±15.2 ng/mL (0% vitamin D deficiency), with 2 hours of sun in the southwest. In this study, serum levels of 25 HCC correlated positively with sun exposure and negatively with latitude, as seems logical. But even in a healthy young urban population in the Mediterranean coastal region, 7% of subjects had vitamin D deficiency (<12 ng/mL). The mean intake of vitamin D was low: 3.4±7.6 µg/day, much lower than the recommended 10 µg/day[17]. Similar results have been reported in medical students of the University of Las Palmas de Gran Canaria, in the sunny Canary Islands[18]. Vitamin D status and the prevalence of vitamin D insufficiency in Spain in children, in adults –living in the community or in nursing homes– and in treated or untreated osteoporotic women are shown in Table 2[14,19-29].

The low prevalence of vitamin D in our country is a result of inadequate exposure to the sun since, logically, in the presence of high temperatures people try to avoid sun exposure and seek out places where the temperature is more comfortable. In addition, many people, rightfully so, are very concerned about the effect of direct sun exposure and the risk of skin cancer. In southern Europe, due to low nutritional intake and having more pigmented skin, probably with less efficient vitamin D production, there is poor vitamin D status during the winter and early spring, especially in the elderly.

The results of a recent cross-sectional observational study in Spain from north to south show that 63% of postmenopausal women receiving therapy for osteoporosis and 76% who do not receive treatment had levels of 25HCC less than 30 ng/ML[29] similar to other reports in other parts of the world[16,17,30]. The high prevalence of vitamin D insufficiency in this study was found in all ages and geographical areas of Spain.

Table 1. Intakes recommended by the IOM committees and the Society of Endocrinology guide

	Groups (years)	Recommendations Institute of Medicine (IOM)				Committee recommendations for patients at risk for vitamin D deficiency		
		IA	EAR	RDA	MTL	Daily requirement	MTL	
	Neonates							
	0 to 6 months	400 IU (10 µg)			1,000 IU (25 µg)	400-1,000 IU	2,000 IU	
	6 to 12 months	400 IU (10 µg)			1,500 IU (38 µg)	400-1,000 IU	2,000 IU	
	Children							
	1-3 years		400 IU (10 µg)	600 IU (15 µg)	2,500 IU (63 µg)	600-1,000 IU	4,000 IU	
	4-8 years		400 IU (10 µg)	600 IU (15 µg)	3,000 IU (75 µg)	600-1,000 IU	4,000 IU	
	Mens							
	9-13 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	600-1,000 IU	4,000 IU	
	14-18 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	600-1,000 IU	4,000 IU	
	19-30 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	
	31-50 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	
	51-70 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	
600 y 800 IU	>70 years		400 IU (10 µg)	800 IU (20 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	600 y 2,000 IU
	Women							
	9-13 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	600-1,000 IU	4,000 IU	
	14-18 ayears		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	600-1,000 IU	4,000 IU	
	19-30 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	
	31-50 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	
	51-70 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	
	>70 years		400 IU (10 µg)	800 IU (20 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	
	Pregnancy							
	14-18 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	600-1,000 IU	4,000 IU	
	19-30 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	
	31-50 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	
	Lactation							
	14-18 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	600-1,000 IU	4,000 IU	
	19-30 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	
	31-50 years		400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)	1,500-2,000 IU	10,000 IU	

The recommended dietary allowance (RDA) (sometimes referred to as the recommended daily allowance) is defined as the average daily dietary intake sufficient to meet the nutritional requirements of almost all healthy individuals (approximately 98%). The Endocrine Society recommends that the vitamin D used be D3 (Cholecalciferol).

IA: adequate intake; EAR: estimated average requirement; RDA: recommended dietary allowance; MTL: maximum tolerable level.
Requirement for mothers: 4,000-6,000 IU/d (intake in mothers of infants if the child is not receiving 400 IU/d).
Ross AC et al. J Clin Endocrinol Metab. 2011; 96:53-8. Hollick MF, et al J Clin Endocrinol Metab. 2011;96:1911-30.

Table 2. Prevalence of vitamin D deficiency in Spain

Ref.	Population studied	Place	Station	Age (years)	Number	25OHD3 mean±SD ng/mL	Prevalence under 25OHD seric	Definition of low 25OHD ng/mL seric	Techniques
19	Both genders Home Senior residence	Córdoba 37º6'	Spring	27-49 67-82 70-85	32 32 21	22.1±11 14±6 15±10	32% 68% 100%	15	CBP
20	Both genders Home	Córdoba 37º6'	Spring	20-59 60-79 >8	81 31 17	38.0±13 18±14 9±4.6			CBP
21	Women postmenopausal	Granada 37º10'	Winter - Spring	61±7	161	19±8	39%	15	RIA
22	Women postmenopausal	Madrid 40º26'	Winter - Spring	47-66	171	13±7	87% 64% 35%	20 15 10	RIA
23	Elderly both sexes Senior residence	Sabadell 41º35'		61-96	100	10.2±5.3	87%	25	RIA
24	Elderly both sexes Home	Sabadell 41º35'	Winter - Spring	72±5	239	17±7.5	80% 17%	25 10	RIA
25	Elderly both sexes External consultation	Barcelona 41º23'	Winter - Spring	75±6	127		34.6%	10	RIA
26	Elderly domicile Mens Women	Oviedo 43º22'	All year Spring Winter	68±9 68±9 <65 65-74 >65	134 134	17±8 17±9	 72% 80% 72%	 18	RIA
27	Older children living at home	Cantabria 43º27'	Invierno Verano	8±2	43	15±5 29±10*	31% 80%	12 20	RIA P<0.001
28	Elderly of both sexes living in senior residence	Valladolid 41º38'	All year	75±85 83 ±7	197 146	15±8 17±7	31 79 32 91	10 20 10 20	RIA
29	Postmenopausal osteoporotic women Untreated Treated	Spain 43º28'	Late spring	71±5 71±5	190 146	22±10 27±11	11% 44% 76% 5% 29% 63%	10 20 30 10 20 30	HPLC

Chronic insufficiency of vitamin D in adults may cause secondary hyperparathyroidism, increased bone turnover, loss of bone mass, increased muscle weakness and cataracts, as well as increased risk of frailty fracture. Some observational studies have linked vitamin D insufficiency with an increased risk of other non-vertebral and hip fractures[31]. All therapeutic guidelines for the treatment of osteoporosis recommend a supplement of calcium and vitamin D[32]. However, the results of several recent cross-sectional observational studies carried out in Spain[32,33] showed a very high prevalence in postmenopausal women receiving osteoporosis therapy who had levels of 25 HCC lower than 30 ng/mL, potentially reducing the effectiveness of therapy, especially in patients with a low calcium intake.

On the other hand, based on current evidence, vitamin D deficiency may have health consequences at an extra skeletal level. Increasingly, prospective or retrospective epidemiological studies indicate that vitamin D insufficiency is associated with an increased risk of colon, prostate and breast cancer, with a higher mortality of these cancers and an increase in autoimmune diseases, such as diabetes mellitus type I, multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease[31].

In addition, vitamin D deficiency also increases the risk of metabolic syndrome, arterial hypertension, cardiovascular diseases[34], peripheral arterial disease, risk of myocardial infarction34 and cardiovascular mortality[35]. On the other hand, vitamin D supplementation seems to be associated with decreases in total mortality rates[36].

According to these data, it is important to emphasize the need to improve both patient and physician understanding of the optimization of vitamin D status, regardless of the hypothetical availability of sunshine hours in Mediterranean countries. The medical community has a responsibility to increase individual health surveillance efforts and thus ensure adequate intake of vitamin D in patients, in addition to informing the general population of the need to have adequate levels of vitamin D hormone.

However, the public health message is complex. Many people do not know the safe dose of sun exposure, which can vary depending on the pigmentation of the skin. At present, the scientific community, paradoxically, places greater emphasis on the risk of over-exposure to ultraviolet (UV) radiation than on the need for under-exposure. We know that certain populations, including infants, children, pregnant women, postmenopausal women, elderly people and especially women who cover most of their skin when outdoors, are at risk of vitamin D deficiency. Health policy will have to decide whether food enrichment or supplement intake is the best way to achieve adequate levels of vitamin D in populations with certain at-risk groups[37].

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

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Vitamin D deficiency in childhood

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Introduction

The importance of vitamin D in bone development during childhood has been known since the beginning of the last century. As early as 1554, Thedosius published an observation of rickets taken from an individual, but its relationship to vitamin D was not established until 1917, when McCollum et al. isolated an anti-rickets factor in cod liver oil and suggested the term vitamin D[1].

Since then, the disease has been extensively studied. In addition to the nutritional cause, genetic causes and resistance to vitamin D have been discovered, as well as its relation with hypophosphatemia.

However, in the course of the study of adult osteoporosis, low levels of vitamin D have also been found to endanger the bone, without necessarily reaching levels that produce osteomalacia (the equivalent of rickets in adults). Although this aspect will be discussed more fully elsewhere in this paper, it has been established that vitamin D values below 30 ng/ml may be detrimental to bone metabolism in adults. However, can these limits be applied to the growing individual? In other words, is vitamin D deficiency the same in children as in adults? Throughout this paper, we will discuss various issues regarding hypovitaminosis D in children and adolescents.

Since the cited studies offer values of 25-hydroxy vitamin D in different units (either ng/ml, or nmol/ l), to give uniformity to the review all results are shown in ng/Ml, after converting them according to the equivalence 1 ng/ml=2.5 nmol/l.

Rickets and vitamin D deficiency

In rickets, bone deformities occur with increased risk of fractures, decreased growth, muscle weakness, delayed motor development, as well as hypocalcemia and its consequences (tetany, epilepsy, dilated cardiomyopathy). It is not the only cause, but vitamin D deficiency is one of the most frequent, along with low intake of calcium in the diet.

The prevalence of rickets currently remains high in Africa, Asia and the Middle East, mainly due to nutritional causes, but is increasing in countries where there is no nutritional deficit, such as the United States, Australia, New Zealand, the Netherlands Denmark or the United Kingdom[2-4].

Today, it is generally accepted that with significant vitamin D deficiency (<10 n/ml of 25-hydroxy vitamin D serum) the mineralization alteration characteristic of rickets or osteomalacia, defined as severe vitamin D deficiency, are observed. A study by Ramavat et al. 80% of newborns with rickets studied reported levels of 25-hydroxy vitamin D below 20 ng/ml[5]. It is possible that the disease will occur with levels>10 ng/ml if this is similar to a significant deficit in calcium intake[6,7].

However, inadequate levels, though not so low as to produce these diseases, may also be detrimental to bone health. As in adults, low levels of vitamin D may lead to secondary hyperparathyroidism that releases calcium from the bone to maintain calcemia, with consequent effect on bone mass, as shown by several studies[8,9]. Outila et al. also found an association between vitamin D levels, parathormone (PTH) and bone mineral density (BMD) in adolescent girls[10], as did Cheng et al.[11]. However, other authors did not find this association in adolescent girls between 16 and 20 years of age[12,13]. Stein et al., in a study of girls aged 4 to 8 years obtained adequate vitamin D levels, but did not find a positive correlation with BMD, although it did with BMD[14]. A recent study with a total of 4,532 children of both sexes aged 0 to 7 years found a correlation between their levels of 25-hydroxy vitamin D and

BMD measured by quantitative ultrasound (QUS) (OR=0.984; 95% CI: 0.977-0.991, p<0.001)[15]. Another cross-sectional study published in the same year and conducted in Sweden on 120 children aged 8-9 years of both sexes found that 50% of them had levels of 25-hydroxy vitamin D <20 ng/ml, and only 5% had levels above 30 ng/ml. However, 82% had a BMD measured by dual radiological absorptiometry (DXA) with a Z-score >0.0, so that no correlation was found between both parameters, vitamin D and BMD. The authors concluded that the vitamin D deficiency did not affect these children's bone health, although they recognize that the long-term effects should be studied[16]. The disparity of results may reflect the lack of uniformity in the populations studied (age, sex) and methods and locations of BMD measurement. However, there is insufficient evidence that, in the absence of rickets, the mere existence of low levels of vitamin D affects BMD, and unless the risk of fracture increases,[7,17] continued research in this area is required to obtain clearer conclusions and, above all, to see if there can be a later effect in adulthood.

Do we define vitamin D deficiency in children as we do in adults?

According to the recommendations published in 2011 by the Institute of Medicine, serum values >30 ng/ml of 25-hydroxy vitamin D are considered ideal for maintaining calcium homeostasis, and levels between 21 and 29 ng/Ml are insufficient, those below 20 ng/ml being deficient[18]. These limits are assumed and accepted by much of the scientific community[19]. However, these definitions are not without controversy today, even for adults. There are no data from children's populations that can support the levels that are sufficient, insufficient or deficient in children, so data are extrapolated from adult studies[3]. In 2008, the American Academy of Pediatrics recommended that, among children, serum concentrations of 25-hydroxy vitamin D should be maintained above 20 ng/mL, considering lower numbers as deficient. Although it did not establish the limit between sufficiency and insufficiency, recognizing that this figure is determined on the basis of recommendations made for adults, and that, as at present, there was no consensus on children[20].

In a consensus paper by Muns et al., published in 2016, the recommendations on classification of vitamin D status were sufficient for values >20 ng/ml, insufficiency for values between 16-20 mg/ml and deficiency to values <16 mg/ml[7]. These recommendations were based on studies that showed an increase in the incidence of nutritional rickets with values <16 ng/ml[21-26].

Binkley et al. conclude that the basis for these different criteria may be attributed to the lack of standardization of vitamin D measurements, a problem that must be overcome beforehand, and it seems reasonable that the studies focus first on establishing the vitamin D values are associated with rickets or osteomalacia and are identified as severe vitamin D deficiency[27].

However, the description of cases of rickets with numbers >30 ng/ml on the one hand, and the fact that most children with <30 ng/ml are asymptomatic, causes researchers to doubt the establishment of this limit as true for diagnosing rickets. As we wrote at the outset, some authors point out that vitamin D deficiency should be considered as important as calcium deficiency in intake, which may justify the previous contradiction[7].

Prevalence of vitamin D deficiency in childhood and adolescence

Aside from cases of rickets not produced by vitamin D deficiency, nutritional deficiencies and those of genetic cause, rickets would reflect the prevalence of vitamin D deficiency. However, we have already pointed out that not always rickets and vitamin D deficiency levels go together, even though there is no other cause than vitamin D deficiency. Furthermore, a large number of studies in healthy children have shown low levels of 25-hydroxy vitamin D in a high percentage throughout the world and from previous times to date, similar to studies carried out in adults.

It is expected that populations living in areas with limited sunlight or suffering food deficiencies present a high prevalence of vitamin D deficiency. However, the situation goes further. In the large sample (n=6,275) of children and adolescents aged 1 to 21 studied in the US National Health Surveillance Program NHANES (National Health and Nutrition Examination Survey 2001-2004), 9% values <15 ng/ml, and in 61% they were between 15-29 ng/ml[28].

In our country, a prevalence of vitamin D deficiency (values <20 ng/ml) was detected in winter in a study of 423 healthy children and adolescents with no nutritional deficiency between 3 and 15 years of age and both sexes and spring of 19.3% and 15.5%, respectively, figures that decreased considerably in summer (3.6%). However, only 24.7% presented values >30 ng/ml in spring[29]. Another study carried out in Italy (country at a similar latitude to Spain) shows similar results. Vierucci et al. determined serum 25-hydroxy vitamin D in 652 children and adolescents of both sexes aged between 2 and 21 years of age in Tuscany (Northern Italy) and who did not suffer from diseases that could affect the metabolism of vitamin D. The percentage of subjects with values below 20 ng/ml was 45.9%. In addition, 9.5% had levels <10 ng/ml. It is also noteworthy that in summer the mean level of 25-hydroxy vitamin D was 27.1 ng/mL[30].

If we go to less favorable latitudes, the results are equally disheartening, as might be expected. We have previously commented on the study conducted in Sweden by Videult et al., who found 25-hydroxy vitamin D levels <20 ng/ml in 50% of the children studied, and only during the months of July to September media levels were higher than this figure, but even then it was <30 ng/ml (24.8 mg/ml)[16]. In a study of 376 Finnish children aged 6 to 8 years and both sexes, Soininen et al. repor-

ted mean levels of 25-hydroxy vitamin D of 27.4 ng/ml, below the sufficient level and 19.5% had values <20 ng/ml, with no significant differences between the sexes[31]. In Iceland, Bjarnadottir et al. considered 278 healthy children aged 7 years and both sexes and found that 65.2% had mean levels of 25-hydroxy vitamin D <20 ng/ml. Whereas mean levels in September were 23.95 ng/ml and in November 15.04 ng/ml, a difference that was very significant ($p<0.001$)[32]. As a final example, Munasinghe et al. measured 25-hydroxy vitamin D levels in 2,270 Canadian children and adolescents of both sexes (3-18 years). 5.6% had values <12 ng/ml, and only 23.5% showed values 30 mg/ml. Percentages increased and decreased, respectively, in winter (14.6% and 12.3%, respectively)[33].

A large study in China by Zhao et al. reported that 5,571 children aged 1 to 3 years and both sexes showed that 16.1% had levels of 25-hydroxy vitamin D <20 ng/ml, and 38.8% between 20 and 30 ng/ml[34].

In the northeastern US, Weng et al. carried out a study in 382 healthy children and adolescents of both sexes and between 3 and 21 years old, published in 2007. The mean levels of 25 (OH) vitamin D were 28 ng/ml, and the percentage of children with levels <30 ng/ml was 55%[35]. Also in the USA (Pittsburgh), a study of 237 children and adolescents aged 8-18 years of both sexes showed that the mean levels of 25 (OH) vitamin D were 19.4 ng/ml, and that 55.7% had figures <20 ng/ml[36].

On the other hand, studies in populations located in more sunny latitudes do not show better results. Bener et al. determined the levels of 25-hydroxy vitamin D in 458 healthy children and adolescents of Qatar (<16 years of age) of both sexes. Of these, 315 (approximately 68.8%) had values lower than 20 ng/ml, without showing differences with respect to sex (153 males/162 females). However, when grouped by age, the group of adolescents (between 11 and 16 years old) showed the highest prevalence of vitamin D deficiency (61.6%), followed by the group of 5 to 10 years (28.9%), being that of children under 5 years of age the lowest prevalence of deficiency (9.5%)[2]. Santos et al. carried out a study in the south of Brazil that included 234 healthy girls and adolescents between the ages of 7 and 18 years. In 36.3% of them 25-hydroxy vitamin D levels were below 20 ng/ml, and 54.3% had values considered insufficient (between 29 and 20 ng/ml). Only 9.4% matched or exceeded 30 ng/ml. In this study, however, they did not find significant differences in 25-hydroxy vitamin D values with regard to age[37].

In Mexico, 1,025 children aged 2 to 12 years and both sexes were found by Flores et al. to have a mean level of 37.84 ng/ml, 16% of which had values <20 ng/ml and 39% <30 ng/ml. Bearing in mind the age, children younger than 5 years showed values lower than those of 6 or more years, reaching values <20 ng/ml 20% of these smaller and <30 ng/ml 50% of them[38].

Rovner et al., in a review published in 2008 to assess vitamin D deficiency in US children, concluded that, although vitamin D deficiency was not very common, there was a frequent occurrence of insufficiency[39]. It should be taken into account that most studies analyzed marked the deficiency limit in serum 25-hydroxy vitamin D values well below 20 ng/ml (15, 12, 11 and even some, 5 ng/ml) currently considered to be deficient, which leads us to believe that the prevalence of deficiency, according to currently accepted criteria, would have been much higher. Recently published, Kraimi and Kremer discuss in another review the widespread presence of vitamin D deficiency worldwide, and especially in a sunny country like Israel, demonstrating that the infant population is also at high risk of vitamin D deficiency[40]. Analyzing studies carried out in Europe, Braegger et al. reported in a review that, even considering the limitations of the observed studies (small sizes, different designs, different definitions of deficiency), a considerable number of children and adolescents in Europe may be expected to have vitamin D deficiency[41].

Without losing sight of the limitation of lack of consensus on vitamin D deficiency and uniformity of 25 (OH) vitamin D determinations, there is widespread recognition that, as in the case of adults, the child population does not have adequate levels of vitamin D. Most researchers agree that poor sun exposure, caused on the one hand by decreased outdoor activity and on the other by measures of prevention of skin cancer, is identified as the main cause of this high prevalence of vitamin D deficiency, aggravated by racial and cultural considerations.

Special mention should be made of the neonatal population. Several authors indicate that newborns are at high risk of vitamin D deficiency, since their inability to produce it during gestation makes their levels dependent on those of the mother. But also after birth the risk can be maintained, since breast milk is not rich in vitamin D[42]. Therefore, vitamin D levels in mothers during gestation and lactation will be transcendent to maintain adequate levels in their children during these periods. However, studies in pregnant women have detected a high prevalence of vitamin D deficiency in these women. Elsori et al. note that studies in sunny countries such as Ethiopia, India, Kuwait and Qatar found that 80%, 66%, 75% and 48% respectively of pregnant women were vitamin D deficient due to several reasons, including low sun exposure (clothing, staying at home) and predominance of dark skin[42].

A recently published study conducted in Odense (Norway) analyzed 2,082 umbilical cord blood samples taken during delivery of serum 25 (OH) vitamin D. Of these, 16.7% showed values <10 ng/Ml, and in 41.0% the values were between 10 and 20 mg/ml. Considering the criterion of vitamin D deficiency in values <20 ng/ml, 57.7% of the samples showed deficient levels[43].

Even in a very recently published study, a relationship has been found between the mother's BMD and the presence of rickets in her children[44].

It is concluded that, as in adults, the infant population (from infants to adolescents) throughout the world shows a considerable prevalence of vitamin D deficiency, and it seems clear that the causes can be identified as the same in adulthood. We do not know if these low levels of vitamin D may be affecting developing bones, but it seems logical to think that it is not a favorable environment for bone health.

Hypovitaminosis D and other diseases

As in adults, vitamin D deficiency has been associated with various diseases in children and adolescents[3]. Let us consider here the most relevant.

Obesity and metabolic syndrome

The most studied relationship in this respect is between vitamin D deficiency and obesity, as well as the metabolic syndrome[40].

In a 2008 study of 127 obese children aged 10 to 16 years to find a relationship between obesity and calciotropic hormones, 74% of the children had serum values of 25-hydroxy vitamin D <30 ng/ml, and 32.3%, <20 mg/ml. But these children also presented a higher body mass index (BMI), greater fat mass, higher intact PTH levels and a lower quantitative insulin sensitivity index (QUICKI) than the group of children with levels >30 ng/ml (p=0.01). There was a negative correlation of fat mass with levels of 25-hydroxy vitamin D (r=-0.40, p<0.0001) and positive with intact PTH (r=0.46, p<0001) without racial or ethnic influences. In addition, 25-hydroxy vitamin D correlated positively with QUICKI (r=0.24, p<0.01), but negatively with glycosylated hemoglobin, HbA1c (r=0.23, p<0.01)[45]. Currently, Flores et al., in a study of 2,695 children aged 1 to 11, found that obese or overweight school-age children (<5 years) were at increased risk of vitamin D deficiency compared to children of normal weight (OR=2.23, 95% CI: 1.36-3.66, p<0.05)[46]. In our country, Durá-Travé et al. have recently published a study of 546 children of both genders and ages between 3 and 15 years old, in which they observed a high prevalence of hypovitaminosis D (values of 25-hydroxy vitamin D <20 ng/ml) among children with severe obesity (81.1%) and obese (68.2%), whereas it was lower in the group of overweight (55%) and normal weight (58.1%) (p=0.001). In addition, children with obesity (simple or severe) had more prevalence of hyperparathyroidism than overweight or normal weight children (p=0.001). There was a negative correlation between vitamin D and BMI (r=0.198), and positive correlation between PTH and BMI (Z-score) (r=0.268)[47].

This relationship between vitamin D deficiency and obesity has been found in many studies on the prevalence of hypovitaminosis D in children and adolescents[28,32,33,36]. However, when the population studied had non-obesity criteria the researchers found no correlation between weight and serum levels of 25-hydroxy vitamin D[16,29,30,35,37], and even some found that the BMI correlated positively with the values of 25-hydroxy vitamin D[2,38].

Vitamin D deficiency associated with obesity is caused by its deposition in adipose tissue, leading to a decrease in its bioavailability48, but it has also been observed that obese children with vitamin D deficiency have lower insulin sensitivity44,49, and increased risk of metabolic syndrome, and therefore, increased cardiovascular risk49,50-52.

Autoimmune diseases

Furthermore, autoimmune diseases have been associated with vitamin D deficiency levels. Because of the immunomodulatory role attributed to vitamin D, diseases such as juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), and Hashimoto's thyroiditis (HT) and diabetes mellitus type 1 (DM-1) have been studied for possible relations.

Comak et al. studied 47 children with JIA with a mean age of 9.3±3.9 years and both sexes, and found an inverse relationship between 25 (OH) vitamin D levels and disease activity (p=0.01, r=0.37). Mean JADAS-27 (disease activity calculator) score was significantly higher in patients with levels of 25 (OH) vitamin D <15 ng/ml than those with levels >15 ng/ml (p=0.003)[53]. Stagi et al. compared the vitamin D levels of 152 patients with JIA (16.2±7.4 years) to a control group of similar age and sex ratio. Patients with JIA had values of 25-hydroxy vitamin D significantly lower than those in the control group (p <0.001). Among patients, those with the highest activity of their disease had lower numbers than those without active disease (p<0.005)[54].

Dağdeviren-Çakir et al. did not find a link to JIA activity, but found that vitamin D levels were lower in sick (n=64) than in healthy subjects (n=100): 18.9±11 ng/ml and 18.6±9.2 ng/ml during periods of disease activity and remission respectively, vs 26.7±10.5 ng/ml in healthy children[55]. Similar results were obtained by Garf et al. When they studied 70 children with SLE in front of 40 healthy children[56], as well as Perracchi et al.[57]. Stagi et al. also found lower levels of vitamin D in children, adolescents and young people with SLE compared with healthy subjects[58]. In a study of 221 children with SLE who participated in the APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythematosus) clinical trial, the authors found that vitamin D deficiency is common among pediatric patients with this disease, and was independently associated to high levels of C-reactive protein, marker for inflammation[59].

On the other hand, other studies, such as the one carried out by Pelajo et al. in 156 patients with a mean age of 10.6±4.5 years[60], and de Sousa et al. performed in 50 patients of 13.4±4 years[61], did not show this association. A recently published study obtained the same results[62].

In a meta-analysis published by Nisar et al. in 2013, there was no clear evidence of a relationship between vitamin D and JIA[63].

Finally, a study of 56 children and adolescents with Hashimoto's autoimmune thyroiditis (TH) versus 56 healthy subjects found that the mean level of 25-hydroxy vitamin D was significantly lower than that of the control group (6.48±3.28 vs

13.56±5.08 ng/ml, p<0.001), and that 25 (OH) vitamin D values correlated positively with those of free thyroxine. They conclude that, although low levels of 25 (OH) vitamin D were an independent risk factor for HT, they could not be considered as an independent factor for the progression of HT towards hypothyroidism after adjusting for other confounding factors, such as age, sex and BMI[64]. In another study, the authors determined the levels of 25-hydroxy vitamin D in 90 patients with HT of 12.32±2.87 years of middle age and 79 healthy children and adolescents of the same age (11.85±2, 28 years), observing that the prevalence of deficiency (<20 ng/ml) was higher among HT patients (71.1%) than in healthy children (51.9%) (p=0.025) and that the mean value of 25-hydroxy vitamin D in the patient group was significantly lower than in the control group (16.67±11.[65] vs 20.99±9.86 ng/ml, p=0.001)[65]. These findings were similar to those found by Sönmezgöz et al.[66].

Studies to observe the influence of maternal vitamin D deficiency during pregnancy on the risk of DM-1 in children show contradictory findings[67,68]. A recent study by Sørensen et al. carried out in 113 mothers of diabetic children compared to 220 mothers of healthy children, observed that during pregnancy, levels of the vitamin D transporter protein and 25-hydroxy vitamin D decreased in the 3rd trimester, and that their values tended (without becoming significant) to be lower in the mothers of children with DM-1 compared to controls[69].

However, a recent study found that the use of multivitamin supplements with vitamin D in pregnant women did not reduce the risk of DM 1 in their offspring[70], which calls into question the possible effect of vitamin D on infant DM-1.

Mental diseases

Vitamin D deficiency has also been associated in children with mental illness, such as depression[71]. Vitamin D is an environmental factor that plays a role in cerebral homeostasis and neurodevelopment, and at a higher level has been suggested to have an impact on the risk of autism. The prevalence of autism in the USA is higher in regions where doses of solar UV radiation are lower[72]. There has also been an increased risk of autism in preterm infants with vitamin D deficiency in mothers during pregnancy, which may act as a risk factor for preterm birth and cause abnormal brain development in the child and an increased risk of alterations in language development[73,74].

An interesting study conducted in Sweden by Fernell et al. recruited 58 pairs of siblings, one of whom had autism. From the blood samples taken during the neonatal period for metabolic screening and stored, vitamin D levels were determined. Children with autism had lower vitamin D levels than their siblings, even taking into account Different seasons of the year in which they were born75. This relationship between vitamin D deficiency and autism has been explained by several mechanisms[3,76].

Hypovitaminosis D in childhood: a real problem?

The importance of vitamin D in musculoskeletal development and in calcium homeostasis is beyond discussion. Rickets are still a health problem in many countries with nutritional deficiencies, but the scarce exposure to the sun that the population of countries without nutritional problems suffers causes the disease to spread to the whole world.

However, much remains to be determined. It is vitally important to define consistently the limits that mark hypovitaminosis D as a situation of deficiency (which would imply an impairment in health) and insufficiency (which would be a risk situation), as well as vitamin D limits considered as healthy, suitable and therefore desirable. More robust and more homogeneous designs are needed to help us achieve this goal.

Even so, it is not arguable that a considerable percentage of the infant population present low vitamin D values, and although its clinical effect is yet to be elucidated, it seems reasonable to conclude that, if maintained over time, they may not only affect bone health but also to promote the appearance of various chronic diseases in adulthood.

Since the main causes of these low levels of vitamin D are easily treatable (adequate sun exposure, high calcium and vitamin D), efforts should be directed at promoting outdoor activities on sunny days and fortifying foods with calcium and vitamin D (especially in countries with low insolation), while supplements should be considered in those individuals or populations at high risk (pregnant, lactating, very little or no sun exposure for geographical, ethnic or cultural reasons)[3,6,7,19,30,31,40,41]. In this sense, and as an example, there is international consensus among societies and pediatric institutions on supplementing all newborns and children under 1 year of age with 400 IU/day of vitamin D3 (cholecalciferol) as a preventive measure[6,7,19,41,77-79].

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Vitamin D and women

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Introduction

There is increasing interest to learn how vitamin D acts. Both its established or classic functions such as bone metabolism, as well as the emerging areas of study into the different stages of women's lives. In this review, we will pay special attention to the latter even as we recognize the limited amount of quality information currently available.

Childhood and adolescence

Child and adolescent nutrition is undoubtedly one of the major health concerns in developed countries. Regarding vitamin D, a high prevalence of deficiency has been reported among school-age children and adolescents. In some series, 40% of adolescents present values below 25 ng/ml, with low levels more frequent among girls. Thus, adequate nutrition or supplementation are recommended in case of deficiency or insufficiency[1].

Children and adolescents require adequate levels of vitamin D to achieve proper mineralization and bone growth. When vitamin D levels are low, there is a reduction in intestinal absorption of calcium and phosphate. Also bone resorption increases and this may lead to alterations in the integrity and strength of the bone as in the case of rickets, a problem that is increasingly prevalent in countries such as the United Kingdom[2].

In sunny areas, this need has also been shown, however, especially among dark-skinned and obese adolescents. In contrast, adolescents with higher serum vitamin D levels have more physical activity, better cardiovascular health and something of great importance at present, less depressive tendencies[3].

Serum levels of 25-OH-D are directly related to bone mineral density, with the highest bone gain when they are at 40 ng/ml or more[4].

In children, the recommended daily dose is estimated at 600 IU.

A meta-analysis of 6 clinical trials suggests that there is a lack of information to support the recommendation to supplement the diets of children and adolescents with normal serum vitamin D levels as no specific benefits have been documented. However, supplementation in children and adolescents with deficient serum levels produces significant increases in the level of 25-OH-D and this would have clinical implications such as improvement in bone mineral content, especially in the lumbar spine[5].

Universal screening in children and adolescents is not recommended, but it would be in groups at high risk of deficiency such as malabsorption, gastric bypass, liver disease, nephrotic syndrome or treatments with drugs that affect the metabolism of vitamin D .

Fertile time

During the fertile time of the woman, several situations of high prevalence in the field of gynecology have some type of relation with vitamin D serum levels.

Hormonal contraceptives

A different response to vitamin D supplements has been reported among hormonal contraceptive users, compared to non-users, with the former having higher baseline levels and achieving a better response at the end of the period, compared to non-user.

Previous studies have indicated that, at baseline, 25-OH-D levels are 20% higher in users of combined hormonal contraception compared to non-users of this method. This effect may be attributed to the increased synthesis of the vitamin D binding protein (DBP), and the modification in the hepatic metabolism of vitamin D. All this has a clinical implication which is that when determining 25-OH-D serum levels, it should be taken into account whether the woman is taking or has recently taken combined hormonal contraceptives as, in this case, they may be higher.

Reproduction

The relationship of vitamin D to reproductive capacity and to the success of assisted reproduction techniques and in particular with *in vitro* fertilization (IVF) has been studied.

Women with normal pregnancies have been shown to present higher vitamin D serum levels than those ending with early spontaneous abortion[7]. The investigation of correlations between

serum levels and levels in follicular fluid, or whether vitamin D would influence the ovule or the embryo, have concluded that the beneficial effect described is established through action on endometrial tissue[8].

Women who have raised 25-OH-D serum levels are four times more likely to be successful in the IVF technique compared to those with low levels[9].

Therefore, in reproductive studies and especially when assisted reproduction techniques are applied, it is considered appropriate to evaluate the serum levels of vitamin D and taking into account the high safety of the measurement, supplementary or treat the deficiency if necessary.

Polycystic ovarian syndrome

This affects 5-10% of reproductive age women. A significant association has been documented between this syndrome and vitamin D deficiency, indicating that in some series, 73% of women with polycystic ovary syndrome (PCOS) are <30 ng/mL[10].

In a 30-year meta-analysis, the relationship between serum vitamin D levels and metabolic and endocrine abnormalities in women with PCOS is analyzed by determining the effects of vitamin D supplementation. The results indicate that vitamin D deficiency is common among women with PCOS and may be associated with endocrine and metabolic disorders of PCOS. Women with lower levels of vitamin D had more frequent alterations in carbohydrate metabolism, increased fasting glucose, and increased insulin resistance than women with normal values. However, vitamin D supplementation was not found to correct these alterations[11].

Pregnancy

There is currently a notable interest in the knowledge of the effect of vitamin D on various aspects related to fetal development and the end result of gestation.

During pregnancy, the maternal intestine increases the calcium absorption capacity, which allows, even in situations of calcium deficiency or vitamin D deficiency, fetal levels to be adequate to allow fetal skeletal development. However, when the maternal supply is discontinued after delivery, the newborn may develop hypocalcemia.

Vitamin D deficiency is considered to be three times more frequent in winter and spring than in summer and fall, and this is related to the time of pregnancy. A study in Germany in pregnant women indicated that 25-OH-D levels in winter were below 50 ng/ml in 98% of mothers and in 94% of cord blood tests. This indicates the need to improve serum levels in this population, especially in winter. Thus, the authors suggest that since many pregnant women plan pregnancy and take prenatal micronutrient supplements, they should provide 800 IU/day of vitamin D, especially in winter[12].

Racial differences in serum vitamin D levels have also been identified during gestation, and in a population study of women recruited at 27 weeks of pregnancy and living in London, levels <25 ng/ml were found among Asian women 47%, 64% in the Eastern countries, 58% in the black and 13% in the Caucasian[13].

Another relevant factor to consider in the pregnant woman is obesity, having described that in those women with BMI ≥30, 61% had vitamin D deficiency, compared to those with a BMI of 25 or less, where the deficiency appeared in 36%[14].

A relevant question is the clinical implication that for the health of the mother or the fetus would have the deficiency of vitamin D. Several actions have been postulated:

- *Preeclampsia*

Analysis of the studies carried out with this aim indicates conflicting results and some find a direct relationship between serum vitamin D levels and the presence of hypertension or preeclampsia, while others do not.

It has been reported that mothers with serum levels below 50 ng/ml have a five-fold increased risk of severe preeclampsia[15]. In one study, women who developed severe preeclampsia before 34 weeks had serum levels of vitamin D lower than the control group. Low levels in the first half of gestation were associated with increased risk of preeclampsia and double risk in neonates being deficient <37.5 ng/m[16]. It has also been noted that in cases of early onset of severe preeclampsia and small children for gestational age (PEG), vitamin D levels were significantly lower than those with severe preeclampsia early onset, but without PEG[17].

However, other studies have failed to demonstrate these associations, although two meta-analyzes have concluded that vitamin D insufficiency is associated with preeclampsia and low birth weight infants for gestational age[18,19].

Vitamin D deficiency has been associated with low birth weight[20]. An Australian study reports that children born to mothers with vitamin D deficiency had a mean weight lower than 200 g compared to children of mothers with normal serum levels[21].

Analysis of the association with the risk of developing diabetes during gestation shows controversial results since it has shown a positive association in several cohort studies[22,23], and in others it has not been demonstrated, although relevant confounding factors such as Pre-gestational weight or ethnicity[24].

A 31-year meta-analysis has shown that vitamin D insufficiency is associated with a higher risk of developing gestational diabetes[25].

Regarding the perinatal results, it has been reported that vitamin D deficiency is associated with four times greater risk of cesarean delivery than controls[26] and a higher presence of bacterial vaginosis in pregnant women[27].

Therefore, a debate in development at the moment is The desirability of performing universal screening and/or supplementation of all pregnant women in order to improve maternal and infant outcomes.

If there is greater agreement in the identification of the pregnant women of greater risk (obese, of dark skin, total clothes, limited mobility) and to propose strategies of supplementation, at least in them. On the other hand, supplementation has proven to be safe in pregnancy.

Table 1. Recommendations for vitamin D supplementation in pregnancy

General population	400 IU/day cholecalciferol
High-risk population	800 - 1000 IU/day cholecalciferol
Treatment	20,000 IU weekly of cholecalciferol for 4-6 weeks. Then standard supplementation

Some agencies recommend information and supplementation to pregnant women and infants with 400 IU/day, especially in women at higher risk, with three levels of recommendation being established, although the optimal dose of vitamin D in pregnancy is not fully established[28] (Table 1).

Treatment of women with vitamin D deficiency and vitamin D supplementation is safe during gestation and may represent short- and long-term benefits.

An issue that has been raised with regard to supplementation or treatment is whether the administered dose would be added to that ingested by the diet and this could lead to exceeding the safe limits. In this sense, the analysis of the average intake with a pregnant woman's diet is estimated at about 1.8 µg (72 IU) of vitamin D per day, which is far from a possible toxicity.

A Cochrane review of 2016 concluded that pregnant women receiving vitamin D supplements at a single or continuous dose have an increase in serum 25-OH-D at term and a possible reduction in the risk of preeclampsia, low birth weight And premature delivery. However, when vitamin D and calcium are combined, the risk of preterm birth increases. The clinical significance of increased serum 25-OH-D concentrations is still unclear. Due to the above, these results should be interpreted with caution. A relevant fact is that no study of those analyzed reported adverse effects[29].

At the moment, we are working in the Spanish Society of Gynecology and Obstetrics (SEGO) to establish recommendations appropriate to the characteristics of pregnant women in our environment

Post menopause

In post menopause, the estrogen production deficit is the main pathophysiological factor of osteoporosis where vitamin D plays a relevant role. Decreased intake, absorption, and vitamin D synthesis that occurs with aging are associated with reduced plasma calcium levels and a consequent secondary hyperparathyroidism which, together with decreased estrogen, lead to increased resorption and decreased mass bone fractures, factors that determine the risk of fractures. This section is developed in detail in another section of this same review.

Other considerations

Blood pressure

Minor blood pressure values have been identified in women with vitamin D supplements. Sun exposure is the major source of vitamin D formation and lower numbers of AT have been associated with sun exposure[30].

In an intervention study in 148 elderly women with vitamin D deficiency, supplementation with 800 IU of vitamin D and 1200 mg of calcium showed a 9% reduction in systolic BP compared to those supplemented with calcium alone[31].

Oncological processes

Based on epidemiological studies that have reported a different prevalence of cancer among countries with different latitudes and therefore exposure to ultraviolet radiation, the hypothesis has been raised of the preventive role that vitamin D could have in at least some types of cancer of high prevalence in women such as colon and breast. A 50% reduction in the risk of cancer has been reported when serum vitamin D levels exceed 32 ng/ml[32]. Specifically, this beneficial association has been reported in relation to breast cancer[33]. *In vitro* studies in breast cancer cell lines have revealed mechanisms of action of vitamin D by which it modifies the cell growth of the tumor lines, increasing the cellular apoptosis and diminishing the angio-genesis.

The relationship of serum vitamin D levels to tumor prognosis has recently been reported in women with breast cancer, with the lowest levels of vitamin D being found in women with advanced tumors and in premenopausal women with triple-negative tumors. Vitamin D levels are also related to tumor progression, recurrence and death from this cause[34].

Although there are no specific recommendations on these aspects, and the safety of supplementation, if necessary, it is reasonable to consider the need to reach recommended daily doses to achieve adequate serum vitamin D levels.

In general, daily doses of 600-800 IU/day are recommended to achieve serum levels of 25-OH-D> 30ng/ml. It can be administered in daily, weekly, monthly or annual guidelines.

Summary

The evidence provides information on the relevant role of vitamin D in various areas of women's health. Knowing that the prevalence of insufficient or clearly deficient levels is high at any stage of life, including pregnancy, it seems reasonable to be alert to the identification of those women who may benefit from supplementation or treatment to achieve adequate levels.

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Diabetes mellitus type 2

In the 1970s the link between vitamin D and diabetes (DM) began to be studied with research suggesting resistence to insulin and insulin secretion[1]. Several studies suggest that vitamin D stimulates insulin secretion and decreases insulin resistance[2-5] and correlates with impaired glucose tolerance, fasting hyperglycemia, and type 2 diabetes mellitus (DM2)[6].

In the case of DM2, numerous case-control and cohort studies have been published which analyze the relationship between vitamin D deficiency and the incidence of DM2 with conflicting results. In 2013, Song et al. carried out a meta-analysis to assess the strength and form of the association between the levels of 25-hydroxycholecalciferol (25HCC) and the incidence of DM2[7]. This meta-analysis includes a total of 21 prospective studies with a population of 76,220 subjects and an incidence of DM2 of 4,996 cases.

Comparing the highest to the lowest levels, the relative risk of developing DM2 was 0.62 (95% CI 0.54-0.70). The highest levels of 25HCC were related to a lower risk of diabetes, regardless of sex, follow-up time in the study, sample size, diagnostic criteria for diabetes or method of vitamin D analysis. This inverse relationship was maintained, although it was diminished when adjusted for adiposity and other metabolic parameters related to obesity. This decreased risk was most evident from levels of 25 HCC greater than 20 ng/ml. In the same meta-analysis, each 4 ng/ml increase in 25 HCC levels was associated with a 4% decrease in DM2 risk.

Subsequently, in January 2017, a systematic review was published that includes the studies of the meta-analysis of Song and other later studies[8]. The relative risk for DM2 was 0.77 (95% CI 0.72-0.82) when subjects with levels of 20-30 ng/ml of 25 HCC were compared to the lowest levels of vitamin D. Association between vitamin D and risk of DM2 presented a U-curve, with nadir at 65 ng/ml, a concentration that was associated with the lowest relative risk.

In agreement with these results, other meta-analyzes such as Parker et al.[9] or Forouhi et al.[10], find the same correlation. In the latter, the relative risk of DM2 comparing the highest and lowest quartiles of 25HCC was 0.59 (0.52-0.67), with a low heterogeneity [I (2)=2.7%, p=0.42] among the 11 included studies through 2012.

Nowadays, it is vital to know if this increased risk of diabetes can be reversed using vitamin D supplements. It is important to know the benefit in the general population as well as in subgroups of age, gender and ethnicity and evaluate the effect of different dose supplements. To date, there are no large-scale, long-term intervention trials that meet these criteria and thus provide definitive results.

The RECORD study is a randomized clinical trial where patients received 800 IU / day of vitamin D, 1,000 mg of calcium, both drugs or placebo. In this paper, we evaluated the incidence of diabetes among the different groups, but this was a secondary objective (the primary aim was the rate of fractures). A relative risk reduction of DM of 33% was found in the supplemented patients but it was not statistically significant[11]. In WHI (Women's Health Initiative Calcium/Vitamin D Trial) study 33,951 women were randomized to 400 IU of vitamin D or placebo for 7 years, monitoring the onset of diabetes. There were no statistically significant benefits[12]. The possible explanation for the lack of beneficial effects in this large trial is the low dose of vitamin D administered (which is also suggested by the lack of effect on fractures and difficulties in adherence).

Other studies include a limited number of patients and have not been shown to reduce the incidence of DM2. Mitri et al. carried out a meta-analysis with 11 randomized clinical trials and another with 8 observational studies. The research carried out with observational studies concluded that individuals with a vitamin D intake greater than 500 IU/day had a 13% reduction in the risk of DM2 compared with an intake of less than 200 IU/day. In the meta-analysis of randomized clini-

cal trials, they found that vitamin D supplementation does not show any beneficial effect on blood glucose measurements among people with normal glucose tolerance but does have a benefit in people with glucose or insulin intolerance basal resistance[13].

In conclusion, there is enough scientific evidence that associates an increased risk of diabetes in people with vitamin D deficiency and there is sufficient biological plausibility. However, the effect of vitamin D supplementation on diabetes prevention has so far not been proven.

Diabetes mellitus type 1

There is evidence to suggest a link between vitamin D and autoimmune diseases. We know that there are vitamin D receptors in both the beta cell and the immune system. Studies in animal models have shown that severe vitamin D deficiency increases the risk of developing DM1[14].

In vivo, a study in 8 healthy adults conducted by the Holick group, showed that vitamin D supplements regulate the expression of 291 genes in leukocytes that interfere with more than 160 pathways linked to cancer, cardiovascular disease and autoimmune diseases. This study demonstrates that vitamin D is an important immunomodulator of both the innate and adaptive response[15]. Multiple observational studies have linked vitamin D levels and autoimmune diseases such as diabetes mellitus type 1[16-22] but so far clinical trials for prevention of DM1 using vitamin D or 1,25-DHCC are inconsistent.

A meta-analysis published in 2008 of 5 observational studies found a significantly lower risk of DM1 in children who had been supplemented with vitamin D compared to those who did not take supplements (odds ratio 0.71, 95% CI 0.60-0.84)[23]. However, studies published involving patients with recent onset DM 1 or LADA (latent autoimmune diabetes of the adult) have shown no improvement in C-peptide levels or in the preservation of the beta-cell[24,25].

As with type 2 diabetes mellitus, there is a paucity of well-designed randomized controlled trials that answer the question of whether vitamin D supplementation plays a therapeutic role in the prevention or treatment of type 1 diabetes mellitus.

Autoimmune thyroid disease

With less scientific evidence, some observational studies have linked vitamin D deficiency with autoimmune thyroid disease, both Graves-Basedow's disease and Hashimoto's thyroiditis. A meta-analysis based on these studies has shown that vitamin D levels were lower in people with autoimmune thyroid disease than in healthy controls[26]. As for intervention studies, the results again do not show a clear effect, in some cases there has been a reduction in antibody levels in patients supplemented with 1000 IU / day of vitamin D3, but without changes in thyroid function with respect to controls[27]. We are still far from obtaining definitive studies that evaluate the role of vitamin D supplementation in people with autoimmune thyroid disease.

Primary hyperparathyroidism

Vitamin D deficiency is common in patients with primary hyperparathyroidism (PPH) and there is evidence that the clinical presentation of PPH is more severe in patients with low vitamin D[28] levels. This vitamin D deficiency has been associated with higher levels of PTH that fall after administering supplements without risk of worsening hypercalcemia or hypercalciuria[29,30]. It has also been associated with higher levels of calcium and alkaline phosphatase, lower levels of plasma phosphate, lower bone density in the hip and distal third of the radius, more severe bone disease and therefore an increased risk of hungry bone syndrome after parathyroidectomy[31]. It is therefore important in these patients to correct this deficit to maintain sufficiency.

Obesity

There is an inverse association of serum OH levels and body mass index (BMI), which associates obesity with vitamin D deficiency[32]. In Spain, this negative correlation has also been demonstrated in children younger than 15 years, where the prevalence of hypovitaminosis D was significantly higher in the severe obesity groups (81.1%) and obesity (68.2%) than in overweight children (55%) or normal weight (58.1%)[33].

Doubts arise as to how this association is established, whether it is obesity that produces a vitamin D deficit, whether it is the deficit that influences the development of obesity or both. Considering that vitamin D is lipo-soluble, it is possible that the adipose tissue will take vitamin D and decrease its bioavailability[32,34]. Vitamin D deficiency, on the other hand, may lead to adipose tissue dysfunction, with a negative correlation between the levels of 25HCC and leptin levels, as well as those of insulin[35]. The biological substrate is the existence of vitamin D and 1α hydrolase receptors in human adipose tissue. In addition, preadipocytes and differentiated adipocytes respond to calcitriol or active D hormone and this vitamin D has been shown to increase adipogenesis and regulate the growth and remodeling of adipose tissue[36].

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Vitamin D in rheumatic diseases

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Introduction

In the field of rheumatic diseases there is growing evidence that vitamin D plays a relevant role in the pathophysiological mechanisms of autoimmunity. To this must be added that vitamin D deficiency in patients with rheumatic diseases is high. In contrast, there are few clinical trials demonstrating that vitamin D supplementation may contribute to the severity of the activity or the risk of systemic autoimmune diseases.

It seems that with the current schemes of vitamin D3 supplements, autoimmunity is not affected in the expected way[1,2], postulating that for the regulation of immunological homeostasis it is necessary to administer doses of vitamin D much higher than those used in standard clinical practice[3,4]. There is no general consensus on what dose of vitamin D3 should be used, nor as to what levels of 25(OH) vitamin D (25HCC) –the metabolite that best reflects the vitamin D status of the organism– would be optimal to modulate favorably immunity or pain pathways.

As mentioned, most quality studies demonstrate a higher prevalence of 25HCC insufficiency in autoimmune rheumatic diseases[5]. The causes of this insufficiency could be –in addition to the classic factors for the failure of 25HCC in the general population– others that are characteristic of rheumatologic autoimmune processes such as the use of corticosteroids, photosensitivity, cutaneous fibrosis and intestinal malabsorption, among others have not yet been fully elucidated[6,7].

Vitamin D3 could be one of the key factors that would act as an immunomodulator in the control of self-tolerance[8].

In Nordic regions, which are less exposed to ultraviolet radiation and consequently with lower levels of 25HCC, a higher prevalence of autoimmune diseases such as multiple sclerosis and inflammatory bowel disease has been described[9,10]. However, in southern countries, where there is a high exposure to sunlight and one could expect sufficient levels of 25HCC, the high prevalence of vitamin D deficiency persists[11,12], despite the current supplementation guidelines which apply to many patients. Consequently, the existence of a possible malabsorption associated with the autoimmune disorder could be postulated[13,14]. Finally, in relation to greater or lesser sun exposure, the seasonal factor in the development of some autoimmune diseases is a well-known fact[15].

Our objective is to review the main evidence on the role of vitamin D in autoimmune rheumatic diseases, osteoarthritis, and fibromyalgia.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is one of the most prevalent systemic autoimmune diseases. It is a chronic process and clinically courses with multiorgan involvement and periods of exacerbation and remission.

Age and sex matched studies revealed a higher prevalence of 25HCC insufficiency in patients with SLE in relation to the controls. Kamen et al.[16], in the Carolina Lupus Inception cohort, compared 240 healthy controls versus 124 SLE patients, determining a higher prevalence of 25HCC insufficiency in these patients. It reached up to 67%, a figure consistent with that published in other cohorts of patients with this same disease[17] even in studies conducted in southern latitudes[17,18].

To date, the factors that have been associated with low levels of 25HCC in patients with SLE are: daily use of sun protection, elevated body mass index[17], use of glucocorticoids, seasonal change, serum creatinine[19], nephritis[20], altered protein/creatinine[21], low bone mineral density, fragility fractures[22], shorter telomere length in African American patients[23], lack of sun exposure and no treatment with hydroxychloroquine[24], a drug known to raise 25HCC levels at the expense of reduced levels of the active metabolite 1.25-DHCC.

Recently, the presence of low levels of 25HCC has been associated with a higher prevalence of

classic cardiovascular risk factors such as hypertension and hyperlipidemia[25], as well as with sleep disorders[26] and fatigue[27].

Many studies[27-34], though not all[16,17,27,35-39], have shown an association between 25HCC deficiency and increased SLE activity. It is important to emphasize that 4 of the 7 studies that did not find an association between 25HCC insufficiency and an increased SLE activity were performed in Spanish population groups[17,36,37,39], so that certain sociodemographic, geographic and ethnic factors could influence this type of association.

On the other hand, low levels of 25HCC have been associated with fatigue and sleep disorders[26,27]. Fatigue is a symptom and therefore a subjective variable, difficult to quantify, but present in up to 90% of patients with SLE, with the consequent impact on their quality of life[40]. Fatigue has also been associated with low levels of 25HCC in Iranian nurses[41], and these same findings have also been observed in other Spanish series of patients with SLE[27,39]. It is not known if the 25HCC insufficiency influences the level of fatigue in patients with SLE or vice versa. In 2016, Lima et al. carried out a placebo-controlled clinical trial in a young lupus population in which patients receiving vitamin D3 supplements improved the KSFS (Kids severity fatigue scale) scores when compared to the placebo group[42].

Glucocorticoids are known to activate the destruction of 25HCC and 1.25DHCC in inactive calcitriol acid. In 2010, Toloza et al. identified seasonal change, cumulative glucocorticoid dose and serum creatinine as factors associated with reduced levels of 25 HCC[19]. Recently, a significant correlation between failure of 25HCC and use of oral corticosteroids in women with SLE has been described in our country[39]. In fact, there was a positive correlation between the use of oral corticosteroids and the failure of 25HCC in patients who did not receive pharmacological vitamin D3 supplements, a fact that was not observed in the supplementation group[39]. At the European Rheumatology Congress (EULAR 2016), Lomarat W et al.[43] presented a randomized, placebo-controlled trial where it was found that high-dose supplementation of ergocalciferol could serve as a safe adjuvant therapy generating a saving effect of corticosteroids in SLE patients (supplemented patients had used less oral prednisolone).

Therefore, patients with SLE are a high-risk group for vitamin D3 insufficiency. Thus, it is imperative to study, monitor, prevent and treat alterations of bone metabolism in them. In addition, pending the full results of the study by Lomarat W et al.[29], it appears that vitamin D3 supplementation may reduce the use of corticosteroids. Given the benefit/risk profile, the possibility of supplementation with vitamin D3 as an adjuvant treatment in SLE should be considered.

Systemic sclerosis

Systemic sclerosis (SSc) is a connective tissue disease characterized by vascular obliteration, immune dysfunction, excessive deposition of the extracellular matrix and fibrosis of the connective tissue of the skin, lungs, gastrointestinal tract, heart and kidneys.

The prevalence of 25HCC insufficiency in SSc is high. According to Vacca et al., the figure was around 84% and the deficiency was 32%. 28% of patients had levels lower than 10 ng/mL[44]. These levels of insufficiency were associated with higher levels of disease activity and a higher negative correlation with ESR values, pulmonary fibrosis, and the value of the estimated pulmonary artery systolic pressure measured by echocardiography[44], a poor prognostic factor. Arson et al. found lower 25-HCC levels in patients than in controls. They did not find statistically significant differences when comparing the SSc subgroup limited with diffuse SSc and between genders.

Additionally, Vacca A et al. found that supplementation with standard doses of vitamin D3 did not fully protect against the deficiency. There were also no differences in levels according to the types of SSc, limited or diffuse[44].

In a multicenter study with 327 patients and 141 healthy controls, Arnson et al. found a negative correlation between 25HCC insufficiency and disease severity, skin thickness and age[45].

Caramaschi P et al. reported that patients with 25HCC deficiency had a significantly longer duration of illness from the first non-Raynaud symptom and that it was associated with a lower DLCO, an increased systolic pressure estimated in the pulmonary artery compared to the group in the range of failure[46]. They found no correlation with sex, age, antibody profile, cutaneous involvement assessed by the Rodnan score or presence or absence of digital ischemic ulcers[46].

Humbert P et al. found that increased fibrosis of cutaneous tissue was correlated with low levels of 25HCC[47].

Oral calcitriol supplementation in SSc showed positive cutaneous results in small open studies two decades ago[48,49]. Conversely, in a prospective, randomized, double-blind study, the effect of oral supplementation with calcitriol was no more effective than with placebo[50].

Recently the expression of the vitamin D receptor (VDR) in fibroblasts of SSc patients and in murine SSc models was analyzed, appearing diminished. It was observed that VDR is a negative regulator of the TGF-β/Smad pathway such that poor signaling through poor cell expression and low levels of its specific ligand could contribute to hyperactivation of GFR leading to the aberrant activation of the fibroblasts[51].

Cutaneous fibrosis plays a key role in the low levels of 25HCC both by inhibition of cutaneous synthesis and by malabsorption at the intestinal level. However, whether vitamin D3 deficiency in humans could perpetuate the mechanisms of fibrosis via the GFR-β/Smad pathway is insufficient in humans because of the impossibility of vitamin D3 deficiency for the down-regulation of this pathway and whether, in this case, high dose supplementation may have the expected effects.

Therefore, it seems that patients with SSc are at a high risk of vitamin D3 insufficiency. In an orphan disease of a therapy that modifies its clinical course, by the benefit/risk profile and cost/effectiveness, it would be prudent to recommend maintaining levels of sufficiency of 25HCC. It is unclear what supplement dosages would be adequate to achieve this goal, as well as the delimitation of optimal levels to be reached in blood to obtain the greatest clinical benefit. Higher quality clinical trials should be conducted to decide which doses are appropriate.

Sjögren's syndrome

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by a chronic inflammation of the exocrine glands mainly salivary and lacrimal glands. Xerostomia and keratoconjunctivitis sicca are the key clinical elements.

A recent study reported that 25HCC levels were significantly lower in patients with primary Sjögren's syndrome than in the general population. This difference was significant in women but not in men[52].

Baldini et al. assessed the prevalence of the 25HCC deficiency, concluding that it is associated with an early stage of the disease, not being related to the activity of the process or to glandular or extra-glandular clinical manifestations[53].

Agmon-Levin et al. replicated the study with a greater number of cases and controls, and demonstrated that 25 HCC levels were comparable between patients with primary SSc and healthy controls. Importantly, their research also revealed that low levels of 25HCC correlated with the presence of peripheral neuropathy and lymphoma[54], an association that has been studied by other authors. Thus, for example, 125DHCC has been reported to have an antiproliferative effect resulting in tumor regression in low grade non-Hodgkin follicular lymphomas of malignancy[55].

Lee SJ et al. investigated the association between disease activity and serum levels of 25HCC. Included in this study were 69 patients with primary SS and 22 controls. These investigators concluded that serum levels of 25HCC were significantly lower in patients with SS syndrome compared to controls matched for age and sex. When assessing the activity with EULAR Sjögren's syndrome disease activity index (ESSDAI) found a negative association with 25HCC levels[56].

With the data available to date, patients with primary SS are those with an increased risk of vitamin D3 deficiency. Therefore, alterations of bone metabolism in these patients should be studied, monitored, prevented and treated without being possible to venture with the available evidence what role supplementation might play in disease activity.

Mixed connective tissue disease

Mixed connective tissue disease (MCTD) is an uncommon connective tissue disease in which the clinical signs of systemic lupus erythematosus, scleroderma, polymyositis and/or rheumatoid arthritis are combined.

As in the rest of autoimmune entities, the prevalence of vitamin D insufficiency is higher than in the general population. Zold E et al. reported that 25HCC levels were significantly lower in patients with MCTD than in healthy controls. Dermatological manifestations (photosensitivity, erythema and discoid rash) and pleuritis were associated with levels of 25HCC insufficiency[57].

The same group postulated that those patients who ended up differentiating themselves from a specific connective disease had lower levels of 25HCC (in the range of deficiency) than those who remained as MCTDs, so that the failure of 25HCC could be a modifiable factor to prevent the progression of an MCTD to definite connective tissue disease[57].

Hajas et al. determined that patients with MCTD had levels lower than 25HCC than the control group. These low levels of 25HCC correlated inversely and significantly with intima-media thickness of the carotid artery, high levels of fibrinogen, total cholesterol, endothelin, and ApoA1. They also reported that 25HCC levels were inversely correlated with IL-6, IL-23 and IL-10 serum cytokines and that these patients were at increased risk for cardiovascular disease[58].

With the data available today, we can state that there is insufficient vitamin D3 in MCTD. There are no clinical trials that have investigated the role of supplementation over the clinical course and disease activity, so it would be prudent to conduct quality clinical trials to discern their role in this pathology. As practical clinical advice, we believe it judicious to keep patients at sufficient 25HCC levels.

Spondyloarthropathies

Spondyloarthropathies are chronic inflammatory arthritis, autoimmune rachis, spinal, and especially sacroiliac joints, which are characterized by sharing the same symptoms and therapeutic responses. In some cases, they are associated with HLA B27. These include: ankylosing spondylitis, psoriatic arthropathy, arthritis associated with inflammatory bowel diseases, reactive arthritis and undifferentiated spondyloarthropathies.

Cross-sectional studies show that 25HCC insufficiency is more frequent in patients with spondyloarthropathies compared to the general population[59-61]. Recently published data from the DESIR cohort was 11.7%, compared to 5% in the control population[62]. In addition, they suggest an inverse correlation between 25HCC levels, activity, radiological progression, and increase of acute phase reactants. They describe a higher percentage of patients with severe 25HCC deficiency in early axial spondyloarthritis, associating the 25HCC deficiency with an increased activity and severity of the disease as well as the presence of metabolic syndrome[61,62].

Erten et al. describe an increased 25HCC deficiency in male patients with ankylosing spondylitis as well as an inverse correlation with acute phase reactants[61].

In spondyloarthropathies, two opposing effects on bone metabolism have been described: on the one hand, an increase in osteoporosis and the prevalence of vertebral fracture related to trabecular bone resorption induced by the RANK-ligand positive regulation pathway[63,64]. On the other hand, an increase of bone formation in the entheses through morphogenic bone proteins[65], TFG-β[66] and positive regulation of the Wnt pathway[67-71].

In vitro studies demonstrate that vitamin D3 interferes with the molecular pathways of inflammation and ossification at the level of entheses, mainly at the level of IL-23 and increasing sclerostin (Wnt inhibitor). Saad et al. reported that serum levels of sclerostin (Wnt inhibitor) increased significantly after one year of treatment with anti-TNF, also improving bone mineral density of the lumbar spine[70].

In their study, Appel H et al. determined that serum levels of sclerostin were significantly lower in patients with ankylosing spondylitis (AS) than in healthy controls. Thus, low levels of sclerostin were associated with the formation of syndesmophytes, emphasizing the role of sclerostin in the suppression of bone formation at this level in spondyloarthropathies[67].

In addition, vitamin D3 insufficiency may also be related to intestinal inflammation and malabsorption in spondyloarthropathies[61].

Therefore, insufficient 25HCC levels have been reported in spondyloarthropathies that appear to correlate with increased disease activity. Supplementation with vitamin D3 could represent a therapeutic adjuvant pathway in this pathology. But quality clinical trials with vitamin D3 supplementation that take into account all the variables that may influence are necessary to discern the complex relationships between 25HCC insufficiency and spondyloarthropathies.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune systemic inflammatory disease, characterized by persistent inflammation of the joints, which typically affects the small joints of the hands and feet, causing their progressive destruction and generating different degrees of deformity and functional disability. Autoimmunity plays a major role in its origin, its chronicity and the progression of the disease. The disease is associated with the presence of autoantibodies (rheumatoid factor and citrullinated cyclic antibodies). Sometimes, it also manifests with extra-articular manifestations.

As in the rest of the systemic autoimmune diseases, the 25HCC insufficiency in patients with rheumatoid arthritis is higher than in the general population. Kerr GS et al. estimated the prevalence of 25HCC insufficiency in 84% of their series, while the prevalence of 25HCC deficiency was estimated in 45% of their patients[72]. According to Gopinath et al., the prevalence of the 25 HCC deficiency was 68.1%[73].

The onset, severity and outbreaks of rheumatoid arthritis have been described as seasonally dependent[74]. For example, Mouterde et al. suggested that patients who experienced the first symptoms of rheumatoid arthritis in winter or spring had a more severe progression of joint damage at 6 months than patients who experienced the first symptoms in the summer[74].

Merlino LA et al. linked 25HCC insufficiency in Caucasian patients, with an increased risk of disease development and increased disease activity[75]. In their series with 76% of Caucasian patients, Kerr GS et al. found a significant link between deficiency and failure of 25HCC for the anti-CCP positivity in non-Caucasian patients[72]. The deficiency, but not 25HCC insufficiency, was associated with a greater number of painful joints and higher values of high C-reactive protein[72]. In contrast to European cohorts, Craig SM et al. did not find associations with the disease activity in African-American patients[76]. Significant clinical improvement was correlated with the immunomodulatory potential of 1.25-DHCC[77].

To date, there are only three clinical trials that assess the efficacy of vitamin D3 supplements and disease activity.

In the open-label trial by Salesi and Farajzadegan, comparing patients on triple immunosuppressive therapy and supplementation with 1.25DHCC versus triple therapy alone, patients showed greater pain relief without any effect on disease activity[78]. In another randomized double-blind trial with methotrexate at steady-dose and supplementation with 25HCC 50,000 IU weekly versus methotrexate at steady-dose and placebo, there were no improvements in efficacy results[79]. Nor did supplements have the expected effect in a double-blind controlled trial in which supplements were given with 25 HCC 50,000 IU 3 times per week for 4 weeks and then 50,000 IU twice monthly for 11 months, with no improvement in disease activity or in measurements of bone mineral density and increasing levels of TNF-alpha in the supplemented group[79]. In the same line, Dehghan et al. concluded that 25HCC insufficiency is not a risk factor for increased disease activity, nor does it have an impact on the number of outbreaks[80].

With these results, patients with rheumatoid arthritis could be considered a high risk group for vitamin D3 insufficiency, so it is necessary to study, monitor, prevent and treat alterations of bone metabolism in patients who already present an independent risk factor for osteoporosis. There is insufficient evidence to recommend treatment at high doses of vitamin D3 in search of a potential immunosuppressive effect.

Arthrosis

Osteoarthritis or arthrosis is a chronic non-inflammatory disease caused by progressive wear of cartilage and joints. The affected joints cause pain, lose mobility and become deformed. It is the most frequent rheumatic disease, especially among the elderly. Observational data have suggested an association between low levels of 25HCC, pain and

radiographic changes in osteoarthritis[81,82]. A cross-sectional analysis of data from the Hertfordshire cohort suggested that 25HCC may be associated more to pain than to radiographic change[83]. The prospective study of the Framingham cohort concluded that low serum levels of 25HCC may be associated with an increased risk of osteoarthritis of the knee[84]. A recent prospective observational study demonstrated that vitamin D3 deficiency independently predicts the onset or worsening of knee pain in the next 5 years, and of hip in the following 2.4 years. Based on this association, it has been suggested that correction of 25HCC deficiency may reduce the worsening of knee or hip pain in the elderly, but supplementing those without non-deficiency would probably be ineffective[85].

However, two randomized clinical trials of vitamin D3 supplementation have found no benefit in this approach[86,87], although another trial reported a small degree of symptomatic improvement[88].

In the largest and most recent of these randomized controlled trials[86], 413 patients with symptomatic knee osteoarthritis and low levels of 25HCC participated. Supplementation with cholecalciferol (50,000 IU administered orally monthly) showed no significant difference compared to placebo in both knee pain and volume of the tibial cartilage measured by magnetic resonance at two years[86]. On the other hand, McAlindon et al. had obtained similar results in a previous study recruiting 146 patients who randomized cholecalciferol supplementation to 2,000 IU/day (with dose escalation if 25HCC levels remained below 36 ng/ml) or placebo. After 2 years of supplementation, when comparing the two groups, there was no difference either in pain or in the volume of cartilage lost[87].

Sanghi D et al. recruited 106 randomized patients to receive 60,000 IU per month of 25HCC or placebo and found a small but statistically significant improvement in pain and function. However, the differences in this study were 1 mm in the visual analogue scale and 2 in the WOMAC questionnaire[88].

Therefore, although vitamin D levels appear to be lower in the arthritic population than in the general population, the possible role of vitamin D3 in treating osteoarthritis is not entirely clear. Future studies are required with larger sample sizes, longer follow-up and probably higher doses of supplementation. Based on current evidence, it cannot be concluded that there is benefit for the arthrosic population when treated with high doses of vitamin D3.

Fibromyalgia

Fibromyalgia is part of central sensitization syndromes. Its main symptom is chronic, generalized musculoskeletal pain with a wide variety of accompanying symptoms, mainly cognitive (difficulty concentrating, sleep disturbances, anxiety, depression), fatigue, irritable bowel, sleep disturbances and bruxism.

Current therapeutic approaches for patients with fibromyalgia have a multidimensional nature, which includes patient education, behavioral therapy, exercise, pain management and relief of chronic symptoms, rather than mechanisms based pharmacological therapies Pathophysiology of the disease[89].

Vitamin D is assumed to play a role in regulating the processing of chronic, widespread pain in fibromyalgia through complex central and peripheral interactions, so its deficiency could result in an amplification of pain signals. The presence of the vitamin D receptor (VDR) and the 1-alpha hydroxylase and the vitamin D binding protein (VDBP) in the hypothalamus is suggested as a mechanism.

Some, but not all, observational studies report that 25HCC insufficiency is more common in fibromyalgia patients than in the general population. However, this association may be due to the existence of concomitant confounding factors, such as physical inactivity, obesity or depression[89-91].

To date there is only one randomized placebo-controlled clinical trial in patients with fibromyalgia[92]. Wepner F et al. included 37 women and 3 men whose serum levels of 25HCC were less than 32 ng/ml. Patients were randomly assigned to receive 25HCC or placebo for 20 weeks. The supplemented group received 2,400 IU/day if they presented deficiency levels and 1,200 IU/day if they were in levels of insufficiency, with the objective of reaching serum levels of 25HCC between 32 and 48 ng/ml[92] . In post hoc sub-analysis, significant results were found regarding pain improvement and functionality in patients who normalized the levels of 25HCC[92].

However, we have two randomized, placebo-controlled clinical trials in patients with non-specific generalized chronic pain[93,94], and several uncontrolled trials with multiple bias[95-99], both in patients with non-specific generalized chronic pain[95,96,99] and with Diagnosis of fibromyalgia[97-99]. From their analysis, most of the potential benefits of treatment with vitamin D3 on the pain and severity of the disease seem to be concluded.

Warner et al. contradict this possibility in their research[94]. Although methodologically they had a placebo control group, as in the rest of the studies, there are biases to consider. Patients included had a mean age of 60 years. Patients with levels below 9 ng/ml were excluded and supplementation was performed with ergocalciferol. In addition, the study was performed in summer, which would justify an improvement in the placebo group[94]. On the other hand, in the most recent uncontrolled trials[99], which included patients with non-specific generalized chronic pain (50% met fibromyalgia criteria), patients with 50,000 IU/week of oral 25HCC were supplemented for 3 months, with no control group. The authors reported improvements in musculoskeletal symptoms, depression level, and quality of life[99].

In the results of the European Male Ageing Study cohort, male patients included with non-specific generalized chronic pain had lower levels of 25HCC than those without pain. It was conclu-

ded that the 25HCC deficiency increased the risk of suffering generalized non-specific chronic pain by 50%[100]. After a follow-up period, those patients who had levels below 15.6 ng/dl had a significantly increased risk of developing non-specific generalized chronic pain[91]. On the other hand, a cross-sectional study with 75 patients demonstrated a relationship between 25HCC deficiency and anxiety or depression[101]. Therefore, patients with fibromyalgia are a high-risk group for vitamin D3 deficiency, particularly those with smoking and/or drinking and obesity and/or depression[91], so it would be prudent to keep these patients at levels of 25HCC sufficiency to minimize the risk of osteoporosis and maximize muscle strength. Given the current evidence, it is not possible to say whether vitamin D3 supplements may improve pain and function in these patients, and therefore more randomized, double-blind, and minimal-bias clinical trials are needed to provide high-quality evidence on this hypothesis .

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Vitamin D and fragility fractures

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Introduction

The so-called fragility fracture is a low-energy fracture that results from a fall from a height equal to or less than its own, or which occurs in the absence of evident prior trauma. It appears when the bone structure, under specific loading conditions, undergoes biomechanical failure as it is unable to withstand the force received by having its resistance capacity degraded[1].

Among the factors that are related to the genesis of this bone deterioration vitamin D stands out in a relevant way. Indeed, the low levels of vitamin D induce a persistent increase of the level of PTH and with this a stimulus of the bone resorption, which determines A progressive decrease of the amount of bone formed and a thinning of all its structural elements, with the consequent decrease of the bone resistance. In addition, low vitamin D levels are associated with decreased tone and neuromuscular control, and therefore with the increased risk of falls that induce vitamin D deficiency.

In another section of this study, we have seen how vitamin D deficiency is a real health problem worldwide[2] given its high prevalence in all regions and in all population groups and not only in groups traditionally considered at risk[3,4]. Despite this, vitamin D deficiency is notoriously underdiagnosed possibly due to different factors[5], among which, undoubtedly, the failure to consider this disease an etiopathogenic agent stands out[6].

Its prevalence increases progressively in the elderly, in the institutionalized and in those who have suffered one or more fractures[7]. The rates of vitamin D deficiency in patients with hip fracture vary according to the series: 36% in Finland[8,9], 40-68% in the United Kingdom[10-12], 50-78% in the United States[13,14], 62-90% in Japan[15,16], 67-91% in Spain[17,18] and 96,7% in India[19], rates much higher than those found in "healthy" populations and lower than those found in institutionalized individuals[20]. These studies found that a large number of patients with hip fracture and inadequate vitamin D levels had previously suffered vertebral and non-vertebral fractures, excluding hip fractures[9,17-19]. Studies focusing on these fractures have demonstrated the existence of high rates of vitamin D deficiency in patients with peripheral fractures[11,21] and vertebral fractures[15,22,23]. This deficit has also been linked to the recurrence of vertebral fractures after kyphoplasty[24].

However, despite the clear link between low-energy fractures and vitamin D insufficiency, there is still controversy in the literature about the preventive effect of these, as not all studies support this hypothesis.

According to Chapuy et al.,[25] the administration of 1,200 mg/day of tricalcium phosphate associated with 800 IU/day of cholecalciferol to elderly women (mean age 84 years) for 18 months decreased the rate of hip fractures by 29% and non-vertebral fractures in 24%, an effect maintained at 3 years of treatment[26].

Subsequent meta-analyses[27,28] show that administering vitamin D alone is unlikely to prevent fragility fractures, although when administered with calcium supplements it does reduce the risk of hip fractures, especially in institutionalized patients.

Avenell[29] analyzed 53 trials (n=91,791) in which the efficacy of vitamin D administration, whether or not accompanied by calcium, was measured in the prevention of fractures in the community, nursing homes or hospitals. The results revealed that vitamin D was unlikely to be effective in preventing hip fracture, but there was a small reduction in hip fracture risk (9 trials, n=49,853, p=0.01) when given with calcium. The reduction was higher in high-risk, institutionalized populations (54 hip fractures per 1,000 per year or, similarly, nine hip fractures per 1,000 older adults per year) than in low-risk populations (8 hip fractures per 1,000 per year, which is equivalent to one hip fracture per 1,000 older adults per year). This association of vitamin D and calcium only showed evidence of moderate quality of absence of a statistically significant preventative effect on clinical vertebral fractures. However, it proved to be highly effecti-

ve in reducing the risk of any type of fracture (10 trials, n=49,976, RR 0.95, 95% CI 0.90 to 0.99), mainly of non-vertebral fractures.

This efficacy was corroborated by Bischoff-Ferrari et al.[28], after analyzing 12 randomized placebo-controlled trials for non-vertebral fractures (n=42,279 individuals) and 8 randomized clinical trials for hip fracture (n=40,886 individuals) in which they compare vitamin D with or without calcium and with calcium or placebo. They found that the prevention of non-vertebral and hip fractures with vitamin D supplements was dose dependent. In their study, higher doses of vitamin D (>400 IU) reduced non-vertebral fractures in individuals living in the community (-29%) and in institutionalized patients (-15%), and their effect was independent of Additional calcium supplements. The antifracture effect of vitamin D was more important in patients older than 70 years, as well as in those who had low levels of vitamin D at the start of the study, as long as adherence to treatment was adequate.

Now that we are aware that vitamin D is a fundamental element in the appearance of fragility fractures, we must ask: what role does it play in the repair of the same?

Fracture healing is recognized as a complex biological process regulated by genetic, cellular and molecular factors in which four superimposed stages are recognized: inflammation, soft callus formation, hard callus formation, and bone remodeling that behave as if two phases were treated, a catabolic and anabolic[30]. In this context, vitamin D has a plural role, with the cellular effects that it causes in each of the four phases of fracture healing, as outlined in Gorter[31] (Figure 1).

Clinical studies are scarce. We will consider them in a logical sequence.

1. Bioavailability of the vitamin D metabolites at the time of fracture and during the healing process of the same

Studies focusing on the determination of 25HCC, 125DHCC and 24,25[OH]2D3 are performed in small and heterogeneous series of fractured patients.

Based on 25HCC, the results analyzed[32-37] show that after a fracture their levels remained within the range of normality without significant differences with the control group throughout the healing process of the fracture, even up to 6 months after the injury[36]. In the study by Wölfl et al.[37], although there was no significant difference, 25HCC values were slightly lower in patients with low mineral density over the 8 weeks of the study. Only Meller et al.[38] found values significantly lower than 25HCC in 41 geriatric patients with hip fracture within 6 weeks of the fracture. These results contrasted with those found by the same author in an earlier study in which there was no significant difference in young patients with fractures. This led them to consider that it would be due to a deficiency of the hormonal system regulating the calcium metabolism in the geriatric patients.

Concentrations of 125DHCC undergo a significant initial reduction[32,33,35,39,40], up to 21% at 6 weeks after fracture[33], a reduction that gradually disappears during the subsequent year[39]. This reduction would reflect the consumption of this metabolite during healing at the fracture site, according to Tauber[35].

In contrast, Meller et al. found a significant increase of 125DHCC after the fracture that remained above the values of the control group in the 6 subsequent weeks, although it decreased gradually in that same period.

More random is the levels of 2425DHCC. At times, no significant difference was found in their values with respect to the control group[32,33], while at other times they were elevated[34] or significantly decreased[35], which contrasts with the animal model in which 2425DHCC levels are elevated[33].

2. The effect of vitamin D deficiency in cases of altered healing processes of the fracture

Low levels of vitamin D may influence the occurrence of refractures[41] and the rate of pseudo-arthrosis and the time of consolidation[42]. However, Boszczyk et al.[43], in a study with many deficiencies, did not consider vitamin D deficit as a risk factor for the lack of union of the fractures, did not find a difference in the prevalence of vitamin D deficiency in the group that consolidated the fracture and the one that did not.

In patients with problems of fracture consolidation, lower vitamin D levels have been observed than in healthy patients[35,42-46]. This vitamin deficiency would cause elevation of parathyroid hormone and alkaline phosphatase numbers and the decrease of existing calcium levels, a secondary hyperparathyroidism.

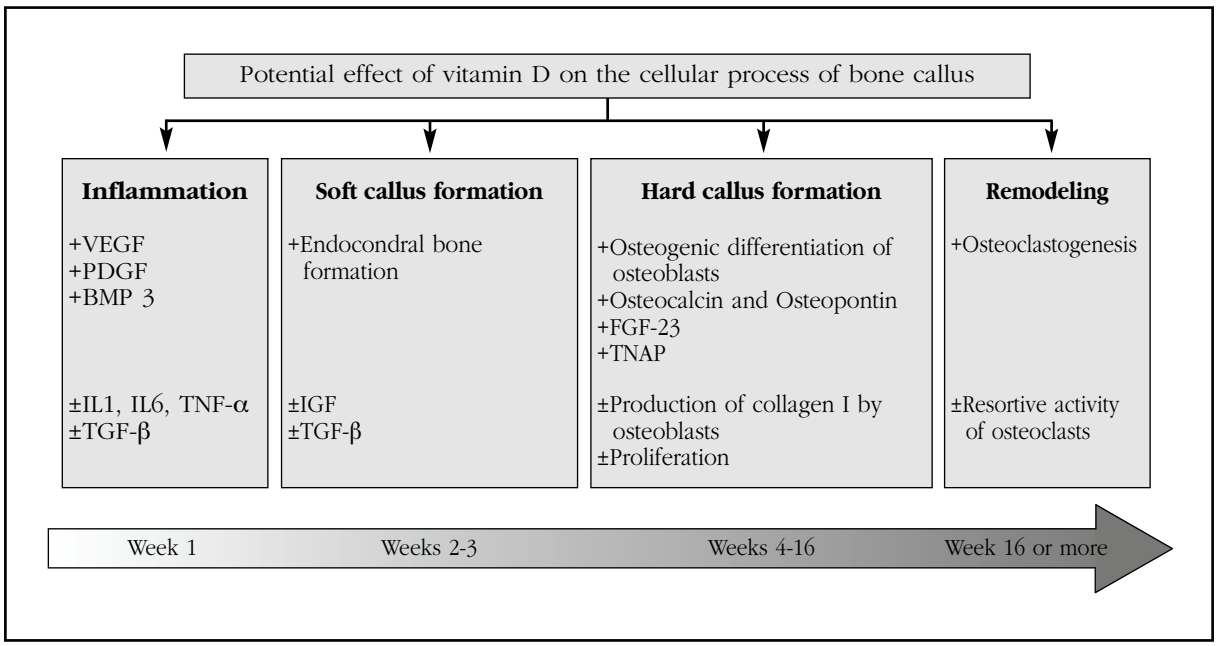
In the case of established pseudo-arthrosis, Haining et al.[47] found no significant difference in serum levels of 25HCC, 125DHCC and 2425DHCC, nor in those of bone markers. His hypothesis is that in patients with established pseudo-arthrosis the metabolic state of the bone normalized after fracture.

3. The effect of vitamin D supplements on fracture healing

Although abundant literature confirms the importance of obtaining and maintaining normal amounts of vitamin D in the serum to prevent falls and fractures, there is precarious evidence of the effectiveness of supplementation with vitamin D to improve the formation of bone callus[31,48,49].

We have only found two studies designed to quantify the healing process of fractures by administering vitamin D3 in terms of callus formation. Doetsch et al.[50] carried out a double-blind randomized study of 30 women with a humeral fracture who received vitamin D and calcium or placebo over 12 weeks. All underwent a radiographic and densitometric study focusing on the fracture focus at the time of fracture, at 2, 6 and 12 weeks. At 6 weeks, the improvement, expressed in g/cm^2, of the treated group was already significant.

Figure 1. Cellular effects of vitamin D during the four stages of fracture healing. + positive effect, - negative effect, ± uncertain effect (both + and -, or no effects described) in *in vitro* or *in vivo* studies. (Adapted from: Gorter EA, Hamdy NA, Appelman-Dijkstra NM, Schipper IB, The role of vitamin D in human fracture healing: a systematic review of the literature. Bone. 2014 Jul;64:288-97)[31]



Kolb et al.[51] conducted a prospective observational study in 94 women with a distal radius fracture who were given vitamin D and calcium. The main objective of the study was to detect the correlation between calcium metabolism and the formation of the fracture callus measured with pQCT. They found that patients who initially had normal levels of calcium and vitamin D had a greater area of callus of fracture. This finding was justified by a stimulating effect of calcium on osteoblasts and increased bone mineralization by normalizing 125DHCC levels above 30 ng/ml[52].

Other studies indirectly support the benefit of vitamin D administration to the formation of the fracture callus. Hoikka et al.[53] postulated that vitamin D could have an effect on fracture healing by finding elevated phosphatase numbers Alkaline solution after treatment for 4 months with 1α-OHD3 and calcium carbonate. It has even been proposed to apply local 2425DHCC in fragility fractures to accelerate its cure and prevent pseudoarthrosis[54].

In this same line, different types of therapeutic interventions with vitamin D and their metabolites have been proposed to improve the formation of the callus of fracture[55,56].

In conclusion:

- It is worth bearing in mind that deficiency in vitamin D levels condition the appearance and repair of low energy fractures.

- There are authors, such as van den Bergh et al.[57], who propose that all patients with osteoporotic frail fractures should be given vitamin D levels and vitamin D treatment should be initiated.

- The cost-benefit associated with the reduction of this type of fracture causes authors such as Sandmann[58] to propose that the public administration prioritize the supplementation of foods with vitamin D and calcium, as it offers significant potential for cost savings for health systems and social.

The reality is that it has improved the sensitivity of doctors on this health problem. Sprague[59] after consulting 397 orthopedic surgeons concluded that 65.8% of them routinely prescribed vitamin D to patients with fragility fractures and 25.7% to patients with other fractures.

Conflict of interest: The author declares that he has no conflict of interest.

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