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Vitamin D: update

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Paseo de la Castellana, 135 (7ª planta)
28046 Madrid (Spain)

Telf: +34-917906834
Fax: +34-917906869

e-mail: seiomm@seiomm.org

http://www.seiomm.org

Editing
Ibáñez & Plaza Asociados, S.L.
EDITORIAL TÉCNICA Y COMUNICACIÓN

Avda. Reina Victoria, 47 (6º D)
28003 Madrid (Spain)

Telf. +34-915 538 297
e-mail: correo@ibanezyplaza.com
http://www.ibanezyplaza.com

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Concha García García

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Andrew Stephens

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SUMMARY

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E-mail:
revistadeosteoporosisymetabolismomineral@ibanezyplaza.com

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Torres del Pliego E, Nogués Solán X
Servicio Medicina Interna - Unidad de Investigación en Fisiopatología Ósea y Articular (URFOA) - Instituto Hospital del Mar de Investigaciones Médicas (IMIM) - Red de Envejecimiento y Fragilidad (RETICEF) - Universidad Autónoma de Barcelona (UAB)

How to use vitamin D, and what supplementary dose would be the optimum to achieve the best balance between efficacy and security?

Correspondence: Xavier Nogués - Passeig Marítim, 25-29 - 08003 Barcelona (Spain)
e-mail: xnogues@hospitaldelmar.cat

Vitamin D is a steroid synthesised in the skin by exposure to sunlight and/or through ingestion of foods which contain it, and it plays a fundamental role in the mineralisation of the bone system at all ages. Vitamin D is not only a nutrient but is also considered to be a true hormone with various functions, a principal one of which is to maintain blood calcium at a physiologically acceptable level for it to carry out its metabolic functions, the transduction of signals and neuromuscular activity[1].

The process of synthesis and metabolisation of vitamin D has been well known since the 1920s. In summary, the process is initiated by the transformation of 7-dihydrocholsterol into provitamin D and subsequently to vitamin D, initially inert, which then requires two hydroxylations to become biologically active (Figure 1). The first hydroxylation, whether it is of vitamin D_2 (ergocalciferol) or vitamin D_3 (colecalciferol), takes place in the liver, where it becomes bonded to the binder protein of vitamin D, which turns into 25 (OH) vitamin D, its main circulating form, and whose blood levels are those used to evaluate its state of deficit, normality or intoxication. The second hydroxylation happens mainly and essentially in the kidney – although there are other tissues in which it is also produced, such as the breast, colon, prostate, etc. – where it converts into the biologically active form, 1,25 $(OH)_2$ vitamin D, or calcitriol, whose essential functions are to increase the absorption of calcium and phosphorus in the intestine, inhibit the formation of osteoclasts for bone reabsorption and to reduce the production of the parathyroid hormone (PTH)[2]. But in addition, the 1,25 $(OH)_2$ vitamin D produced locally in tissues not related to calcium metabolism may have the aim of regulating a wide variety of biological functions, including cell growth, apoptosis, angiogenesis, the differentiation and regulation of the immune system, which would be called the non-classical actions of vitamin D. Thus, given that this vitamin participates in no end of physiological functions, an association between a deficit of vitamin D and many acute and chronic diseases, including alterations in the metabolism of calcium, some cancers, type 2 diabetes, cardiovascular disease and infectious diseases[3] has been confirmed.

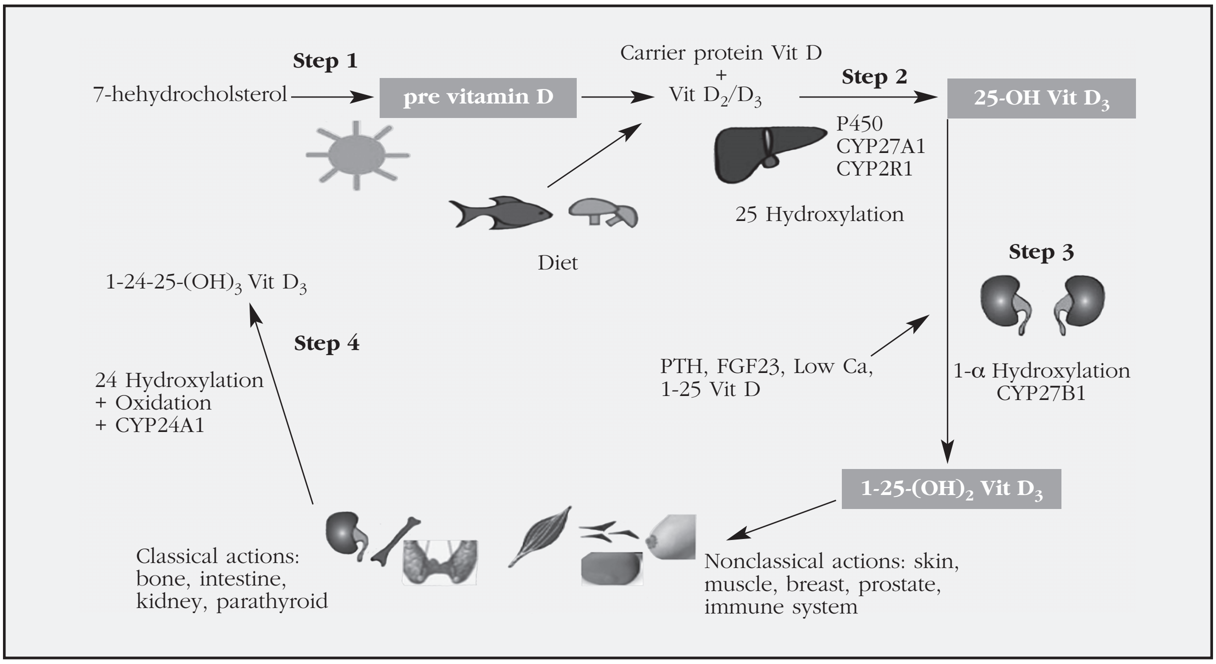
Optimum levels of vitamin D

Considering the many and important functions of vitamin D both in the skeleton and outside it, it seems logical to assume that the levels of this vitamin need to be optimum for it to be able to fulfil its functions[4]. However, there is still much controversy as to what are the optimum levels of 25(OH) vitamin D for the maintenance of bone health and to reduce the risk of its deficit.

Understanding what are the optimum levels of 25(OH) vitamin D is the starting point for knowing what would be the supplementary intake of vitamin D necessary to reach these levels, given that it is widely known that there is a general deficiency in vitamin D in the population[5,6].

In general, the common understanding of the experts and most of the scientific societies concer-

Figure 1. Schema of the different steps in the synthesis and metabolisation of vitamin D. Step 1: Conversion of 7-hehydrocholsterol to colecalciferol brought about by ultraviolet rays from the sun. Step 2: First hydroxylation of the C atom situated in position 25 in the liver. CYP2R1 is probably the most important enzyme in this first hydroxylation. Step 3: Second hydroxylation in the kidney thanks to the enzyme 1α hydroxylase controlled by CYP27B1. This step is regulated by various factors such as FGF23, PTH and $1,25(OH)_2$ vitamin D itself. Step 4: Deactivation of vitamin D by means of 24 hydroxylase (CYP24A1) which makes it metabolically inactive [$1,24,25(OH)_3$ vitamin D, or calcitroic acid]



ned with this matter is to consider a deficiency of vitamin D to be at values lower than 20 ng/ml, insufficiency at between 21-29 ng/ml and sufficiency at values >30 ng/ml, with the a range of 40-16 ng/ml being preferred, and vitamin D intoxication in general, at values higher than 150 ng/ml (Table 1)[7-9]. By general agreement, values below 20 ng/ml are insufficient. However, the argument centres on whether it is necessary to reach 30 ng/ml to achieve vitamin D's effects in and outside the bone[9]. There are histomorphometric data which indicate that at levels below 30 ng/ml the osteoid volume would be higher, and biopsy data for which there would be a diagnosis of osteomalacia in 25% in individuals with these levels of vitamin D[10].

In the bone, levels of between 24 ng/ml and 32 ng/ml appear to be sufficient to reduce the risk of fracture and even of falls[11].

How to achieve these optimum levels of vitamin D?

The primary and most important source is exposure to sunlight, from which is obtained 90% of vitamin D, whose production depends on the particular angle of the sun. Thus, for example, it has been observed that exposure to the sun of the whole body with minimum erythema (reddening of the skin 24 hours after exposure to the sun) results in the achievement of levels of vitamin D comparable to taking 10,000 to 25,000 UI of vitamin D orally[12]. However, exposure to sunlight in winter at certain latitudes does not produce any vitamin D_3[13]. Hence, in certain places such as Boston, it is recommended that white men and women should expose their face and arms or arms and legs to sunlight approximately three times a week for 25% of the duration which would produce slight sunburn in spring, summer and autumn[12,13]. Other factors which influence reduction in the production of vitamin D by exposure to sunlight are sun protection creams, greater skin pigmentation and older age (essentially older than 65 years)[14,15].

Dietary sources contribute to the achievement of optimum levels of vitamin D. The number of foods which naturally contain a significant quantity of vitamin D is limited, which meant that in Britain in the 1930s some of these, for example, milk, fizzy drinks, bread and even beer, were enriched with vitamin D. However, apparent cases of vitamin D intoxication occurred in children in the 1950s, which resulted in much tighter European regulation, which only permitted the enrichment of margarine, something which continues to the present day. On the other hand, in the United States, since 2003 juices have been enriched, which seems to have had a similar degree of effectiveness as oral supplements[3]. The recommended daily intake of vitamin D is currently the subject of argument. The US Institute of Medicine (IOM), the endocrinology societies and the Task Force are not in agreement as to the necessary daily amount, although they agree that there is a deficiency in the population. The coherent explanation of this matter would be that the IOM and the

Task Force have made recommendations for the general healthy population, while the medical societies have tried to make recommendations for patients and special cases[16,17]. This situation has created confusion among staff who are not experts in the field, and editorial arguments between the experts themselves[18].

The IOM recommends 600 UI/day for the population between 1 and 70 years of age and 800 UI/day for the population of 71 years or older, and with a maximum level of daily intake of 4,000 UI to maintain levels of 25(OH) vitamin D above 20 ng/ml, which would be necessary for the general health of the population[19]. On the other hand, the US Society for Endocrinology would recommend levels higher than 30 ng/ml, which means a daily intake of 1,500-2,000[20].

Table 1. Levels of 25(OH) vitamin D and clinical significance

25(OH) vitamin D (ng/ml)	25(OH) vitamin D (nmol/l)	Diagnostic
<20	<50	Deficiency of vitamin D
20-30	50-75	Insufficiency of vitamin D
>30	>75	Sufficient levels of vitamin D

Along the same lines, the IOF (International Osteoporosis Foundation) also recommends levels higher than 30 ng/ml (75 nmol/L) of 25(OH) vitamin D, requiring, to reach this threshold, supplements of between 800 and 1,000 UI/day (20-25 µg/day). Furthermore, it was established that there is a correlation between the quantity of vitamin D supplements and blood level of 25(OH) vitamin D reached, which would be approximately 2.5 nmol/L (range 1.75-2.75 nmol/L) for each 100 UI (2.5 µg) of additional vitamin D[21]. You would think, therefore, that supplementation in the upper range of the recommendations of IOF (1,000 IU/day) would increase the likelihood of patients achieving levels of 30 ng/ml, compared with a lower dose supplementation. Like the Endocrine Society, the IOF also considers that supplementation with vitamin D could reach 2,000 UI/day in certain patients, among others, obese or osteoporotic people, those with limited exposure to sun (for example institutionalised people), those with problems of absorption, etc[21].

In relation to the above, in terms of bone in general, doses higher than 800 UI would be sufficient to reduce hip and non-vertebral fractures in patients over 65 years of age[22].

Excess or intoxication by vitamin D

The administration of excessive doses of vitamin D does not carry greater benefits, but does have a higher risk of intoxication. The risk of intoxication is determined by the levels of 25(OH) vitamin D and the presence of hypercalcemia. It is certain that intoxication would probably require a dose much higher than 4,000 UI/day. Thus, an excessive intake of vitamin D (normally >10,000 UI/day) over many months may provoke vitamin D intoxication, which is detected by notably raised levels of 25(OH) vitamin D, hypercalcemia and hyperphosphatemia. However, regimens with high doses (of 5,500 to 11,000 UI daily for more than 20 weeks)) in patients with low baseline deficits without hypercalcemia occurring have been described[23].

In obese patients it has been seen that the necessity for vitamin D supplements are greater, which is why some authors have suggested the following formula:

Necessary dose of vitamin D in UI = [weight x desired change in 25(OH) x 2.5] – 10[24].

However, there are various studies which suggest that there is a non-linear relationship between 25(OH) vitamin D and mortality[25], with an increase at both low and high blood levels of 25(OH) vitamin D. Thus, Melamed et al.[26] found an increase in the risk of all causes of mortality in women with doses of 25(OH) vitamin D <20 ng/ml, but also if >50 ng/ml. A U curve phenomenon appears evident in relation to levels of mortality and vitamin D. Michaëlsson et al.[27] observed 50% higher total mortality in 1,194 males with an average age of 71 years with low levels of 25(OH) vitamin D (around 18.5ng/ml), but also with higher levels (around 39 ng/ml). A recent meta-analysis has shown similar data, with benefits in terms of optimum values of mortality at between 31 and 35 ng/ml[28].

Contrary to what one might assume, there is no unanimous position on the maximum level of vitamin D to avoid an alleged risk. Therefore, controlled randomised studies are required, with the administration of different doses of vitamin D to establish with certainty what are the optimum doses and what doses may become harmful[18,28].

Conclusion

In clinical practice, taking decisions about treatment is always difficult, and even more so when there is disagreement about when and how. At present, the evidence and the consensuses, the guides of the scientific societies and the opinions of the experts show the importance of vitamin D as a hormone which has an influence on numerous metabolic processes, among which, bone metabolism is the most important. All are in agreement that there is a deficit in the general population and, above all, in the population affected by osteoporosis. However, views on the optimum levels of vitamin D may be torn between 20 and 39 ng/ml, although it seems that there is enough consensus in establishing a minimum level of 30 ng/ml. Nor is there unanimity regarding the maximum level which should be reached and if this could be quite dangerous, not in producing serious metabolic alterations such as hypercalcemia, but due to possible increases in cardiovascular mortality.

In terms of supplements, there is agreement on their necessity but the doses are also the subject of argument. It seems clear that for the majority of individuals, between 800 and 1,000 UI a day would be necessary and that a supplement in the range higher than this interval (1,000 UI/day) would increase the probability that the patients would achieve blood levels of 25(OH) vitamin D higher than 30 ng/ml, although it is also possible that some special groups require even higher doses (up to 2,000 UI/day) to reach these levels.

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Navarro Valverde C[1], Quesada Gómez JM[2]
1 Servicio de Cardiología - Hospital Universitario Virgen de Valme - Sevilla
2 Unidad de Gestión Clínica de Endocrinología y Nutrición - Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC) - Hospital Universitario Reina Sofía - RETICEF

Vitamin D deficiency in Spain. Reality or myth?

Correspondence: José Manuel Quesada Gómez - Unidad de Gestión Clínica de Endocrinología y Nutrición - Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC) - Hospital Universitario Reina Sofía - RETICEF - Avda. Menéndez Pidal, s/n - 14004 Córdoba (Spain)
e-mail: jmquesada@uco.es

Vitamin D_3 (colecalciferol) is formed from its precursor 7-dehydrocholesterol in the skin by ultraviolet irradiation. In the liver the vitamin D_3 is hydroxylated to form 25-hydroxyvitamin D_3, which is metabolised to its active metabolite 1,25-dihydroxyvitamin D_3 preferentially in the kidney. Vitamin D_3 may also be provided in the diet, which is a significant source of supply only in the case of insufficient exposure to sunlight. Blue fish naturally contains large quantities of vitamin D_3, while other foods contain significant quantities of vitamin D only after being fortified. For fortification, in many countries vitamin D_2 is used (ergocalciferol) obtained from vegetable sources[1].

The presence of the enzyme CYP27B1, which drives the synthesis of dihydroxyvitamin D from its principal substrate, 25-hydroxyvitamin D, and the vitamin D receptor (VDR), distributed almost universally in the cells and tissues of the organism, confers on vitamin D (although it would be increasingly more correct to say the endocrine system of vitamin D) a broad role in health. This is not only in the regulation of calcium and bone metabolism but also in relation to the cardiovascular system, innate or acquired immunomodulation, the regulation of cell growth, etc., such that around 3% of the human genome is regulated by the hormone 1,25$(OH)_2$ vitamin D_3[1-3].

It is therefore not surprising that basic scientific and clinical interest in vitamin D[4], as well as interest in the non-specialist press and in the general population[5], has increased almost exponentially in the last decade.

25-hydroxyvitamin D, marker for the status of vitamin D in the body

For some years there has been universal consensus that the measurement of the levels of the metabolite 25-hydroxyvitamin D in the blood is the marker for the status of vitamin D in the body, including the endogenous synthesis due to exposure to sunlight, dietary consumption in foods, supplemented or not, and pharmacological treatments[1,2]. However the measurement of concentrations of 25-hydroxyvitamin D in the blood has been, and continues to be, highly problematic, in spite if current improvements in precision and accuracy[6].

Paradoxically, two fundamental questions - what are the levels of vitamin D necessary for the optimum health of bone and of the organism in general? - and as a consequence – what dose should be used to achieve these levels? – still remain unresolved to this day. The diversity of opinions on this matter has generated strong arguments between researchers[7,8] and scientific societies. In fact the different scientific societies have proposed as cut off points for normality for vitamin D two blood levels of 25-hydroxyvitmin D: above 20 ng/ml by the Institute of Medicine[9], and above 30 ng/ml for the International Osteoporosis Foundation (IOF)[10], the latter supported by the recommendation of the Endocrinology Society of the US[11] and in Spain by the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM)[12].

However, the studies used to determine these points measured levels of 25-hydroxvitamin D using CREB-binding protein (CBP) and/or radioimmunoassay (RIA), and had at that time wide variability in precision and accuracy which reached up to 50%, which constituted a significant limitation and which suggests to us that the prevalence of deficit or insufficiency in vitamin D is test-dependent.

The commercial tests available, even though highly simplified, have problems with accuracy when they are compared with the "gold standard", liquid chromatography, in tandem with mass spectrometry[6,13-15], so much so that the platforms for the routine analysis of 25OHD may differ by up to 20% above or below the values obtained using the gold standard[6]. However, while they could be substantially improved, the methods available in our normal contact with patients, or in research, are sufficiently suitable, and ought to be used more in our clinical practice for diagnosis (and the subsequent follow up treatments with vitamin D). Nevertheless, we should be cautious in the interpretation of our own results or of those of epidemiological or of randomised clinical trials, when in the tests used to quantify levels of 25OHD the calibration does not conform with international standards, such as DEQAS (www.dequas.org) or the NIST standard[16].

We would agree that an absolute minimum objective would be to achieve blood levels of 25-hydroxyvitamin D above 20 ng/ml (to convert to nmol/L multiply by 2.5). This means achieving an average in the whole population of nearly 30 ng/ml[17], and preferably higher than 30 ng/ml to ensure an optimum status for bone health[18], which probably ought to be even higher if we are proposing to meet other health objectives[2,3,8,19]. Thus, if our patients achieve levels of 25-hydroxyvitamin D above 30 ng/ml we will be harmonising with existing recommendations, with the methodological limitations of the studies that generated them and we will detail the limitations of our own method of measurement.

State of vitamin D insufficiency globally

Currently, levels of vitamin D insufficiency, or even true deficiency determined by 25-hydroxyvitamin D, constitutes an "epidemic" across the globe, affecting more than half its population[3,20], reported in children, young people, adults, postmenopausal women and older people, and above all in those with osteoporotic fractures where the prevalence of low levels of 25-hydroxyvitmain D reaches 100%[20].

A recent excellent review of works available across the world found that 88% of samples evaluated had blood levels of 25-hydroxyvitoman D below 30 ng/ml, 37% had levels below 20 ng/ml and up to 7% had levels below 10 ng/ml[21].

State of vitamin D insufficiency in Spain

This state of calciferol insufficiency is replicated in Spain, with results which we show in table 1[22-38].

The interlaboratory variation in the different methodologies used makes a rigorous comparison difficult, but the table illustrates clearly that, in spite of a theoretical climatological ease of vitamin D synthesis in Spain, the levels are similar to, or even lower than those reported for central Europe or Scandinavia, as has been described in earlier works[39]. This apparent "paradox" which Spain shares with other countries of the Mediterranean basin[39,40] has been attempted to be explained speculatively by the scarcity of vitamin D in the diet which cannot be compensated for by synthesis in the skin. Most of Spain is above the 35ºN parallel where the possibility of synthesising vitamin D in winter and spring is low, and because most Spanish people have darker skin which makes the synthesis of vitamin D more difficult[39].

We observed that in Spain, as in the rest of the world, insufficiency, or even true deficiency in vitamin D is already found in children or young people, and persists in adults, postmenopausal women (osteoporotic or not), and in older people who live in their own homes, and that it is even higher if they live in residential homes, with a seasonal variation which barley reaches normal levels after summer-autumn[22-39].

Although this high prevalence of low levels of vitamin D occurs due to inadequate exposure to sunlight, in older Spanish people lower levels have been described in the summer months due to the high temperatures which occur in the cities of southern Spain such as Murcia or Cordoba at this time of year, which are commonly between 30 and 40° C. The older people avoid being in the sun and prefer to remain indoors where the temperature is more comfortable. Furthermore, older people are highly averse to the risk of skin cancer due to the direct exposure to sunlight, but in autumn or during the winter months they benefit from more favourable temperatures (20-25°C) which allows them to be in the sun with light clothing and, therefore, synthesise vitamin D[22,23,32].

The high prevalence of vitamin D insufficiency is independent of geographic zone and the cut off point established by different authors, in postmenopausal Spanish women and in Spanish older people (table 1).

These results have together been confirmed by a transverse study carried out in units for the study and treatment of osteoporosis in the whole of Spain at the end of spring. The 25-hydroxyvitamin D was quantified after separation by HPLC[38], and from which there was evidence that more than three quarters (76%) of osteoporotic postmenopausal women who had not even started treatment had levels of 25-hydroxyvitamin D below 30 ng/ml, and that 44% had levels below 40 ng/ml.

The available data confirmed that there is insufficiency, and even deficiency in the Spanish population in all ages studied and in both sexes, similar to that across the world, including in very sunny regions[39,41], and to that in other countries of the Mediterranean basin[40] with similar possibilities of exposure to sun. The prevalence of deficiency is even higher in patients with risk factors for having low blood levels of vitamin D, obese people and those in poverty[42].

Table 1. High prevalence in Spain of insufficiency/deficiency in vitamin D in postmenopausal women and older people. Evidenced by different authors and with different methods

Author Year (Ref.)	Study population (home)	City	Season	Age (years)	n	25OHD average±SD (ng/ml)	Prevalence low serum 25OHD	Low serum definition 25OHD ng/ml	Comments
Quesada 1989 (22)	Both sexes (Home)	Córdoba 37º6'	Spring	27-49 67-82 70-85	32 32 21	22.1±11 14±6 15±10	32% 68% 100%	15	CBP
Quesada 1992 (23)	Both sexes (Home)	Córdoba 37º6'	Spring	20-59 60-79 >80	81 31 17	38.0±13 18±14 9±4.6			CBP
Mata- Granados 2008 (24)	Blood donors Men Women	Córdoba 37º6'	Spring	18-65 18-64	116 9	18±10-5 15±9.2	14% 51% 65%	10 20 30	HPLC
Mezquita- Raya (25)	Women PM	Granada 37º10'	January- Spring	61±7	161	19±8	39%	15	RIA
Aguado 2000 (26)	Women postmeno- pausal	Madrid 40º26'	Winter- Spring	47-66	171	13±7	87% 64% 35%	20 15 10	RIA
Lips (27)	Women osteoporotic PM	All Spain 43-37º	Winter- Summer	64±7	132	24±14	41.7% 10.6%	20 10	RIA [Study MORE]
Larrosa 2001 (28)	Both sexes Elders (Residence)	Sabadell 41º35'		61-96	100	10.2±5.3	87%	25	RIA
Vaqueiro 2006 (29)	Both sexes Older people (Home)	Sabadell 41º35'	Winter- Spring	72±5	239	17±7.5	80% 17%	25 10	RIA
González 1999 (30)	Both sexes Older people Outpatients	Barcelona 41º23'	Winter- Spring	75±6	127		34.6%	10	RIA
Gómez- Alonso (31)	Both sexes Older people (Home) Men Women	Oviedo 43º22'	All year Winter	68±9 68±9 <65 65-74 >65	134 134	17±8 17±9	 72% 80% 72%	18	RIA
Pérez- Llamas (32)	Both sexes Older people (Residence)	Murcia 37º59'	All year Autumn Winter Spring- Summer	77±8	86	20±13 25±15 16±9	58.2%	20	RIA
Docio (33)	Children (Home)	Cantabria 43º27'	Winter- Summer	8±2	43	15±5 29±10	31% 80%	12 20	RIA

Table 1. (cont.)

Author Year (Ref.)	Study population (home)	City	Season	Age (years)	n	25OHD average±SD (ng/ml)	Prevalence low serum 25OHD	Low serum definition 25OHD ng/ml	Comments
Almirall (34)	Both sexes 53% older women 64 years	Sabadell 41º35'	Winter	72±5	237	17±7.6	80%	20	RIA
Gómez (35)	Men and women	Hospitalet de Llobregat	All year		253	23±21			
Muray (36)	Men 58 and women	Lérida	Autumn		391				
Pérez Castrillón (37)	Older people (Home)	Valladolid 41º38'	All year						RIA
				75±85	197	15±8	31% 79%	10 20	
	(Residence)			83±7	146	17±7	32% 91%	10 20	
Quesada (38)	Osteoporotic women PM	All Spain 43-28º	Final Spring						HPLC
	Not Treated			71±5	190	22±10	11% 44% 76%	10 20 30	
	Treated			71±5	146	27±11	5% 29% 63%	10 20 30	

25OHD: 25-hydroxyvitamin D; PM: postmenopausal; SD: standard deviation.

Therefore, vitamin D deficiency in Spain is not a myth (a person or a thing to which are attributed qualities or benefits they do not possess, or even a reality which they lack), but a reality with significant repercussions on bone health and probably on the health of the organism as a whole.

Impact on bone

Vitamin D deficiency stimulates the secretion of PTH, increases bone remodelling, results in loss of mineral density and quality of bone, increases the risk of falls, factors which interact to increase the risk of osteoporosis and osteoporotic fracture[43-45].

Surprisingly, conventional treatments do not normalise absolutely blood levels of vitamin D, with levels of 25-hydroxyvitamin D lower than 30 ng/ml and 20 ng/ml being found in 63% and 30% respectively of Spanish postmenopausal women in treatment for osteoporosis[38], data consistent with other results described previously for Spain[46], other countries in Europe[46] or the United States of America[46,47]. This may appear shocking at first sight because in all the therapeutic guides and recommendations of professional organisations for the treatment of osteoporosis it is widely known and recommended that an adequate supply of calcium and vitamin D is the basis, and should always be associated with, treatment with osteoactive drugs for osteoporosis[48].

The high prevalence of women with vitamin D insufficiency, despite being subject to treatment, could be an indication of a potential absence of compliance[49]. Another possibility may be that the genetic makeup of our patients conditions for lower levels of vitamin D[50]. Both possibilities could be evaluated by establishing an osteoactive treatment with antiresorptive or anabolic therapies.

The available evidence indicates that, in addition to an insufficient supply of calcium, inadequate blood levels of vitamin D potentially reduce the response to treatments for osteoporosis. In fact, two Spanish groups have reported that vitamin D insufficiency or deficiency (blood levels below 20 or 30 ng/ml) are an important contributory factor to an inadequate response to antiresorptive treatment[51,52].

In conclusion, even in sunny regions such as Spain, it is important to highlight the necessity of the knowledge of the doctor and the patient with respect to the optimisation of the consumption of calcium and vitamin D in patients with osteoporosis. This would increase the observance of treatment and, therefore the optimisation of bone health by improving the response of bone to medicines for osteoporosis.

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Gómez de Tejada Romero MJ
Departamento de Medicina - Universidad de Sevilla

Extraskeletal effects of vitamin D

Correspondence: Mª Jesús Gómez de Tejada Romero - Departamento de Medicina (Facultad de Medicina) - Universidad de Sevilla - Avda. Dr. Fedriani, s/n - 41009 Sevilla (Spain)
e-mail: mjgtr@us.es

Introduction

Since it was discovered by McCollum in 1922 how vitamin D was involved in bone mineralisation and was responsible for rickets[1], much new knowledge has come to light. From being a vitamin it has become considered to be a hormone[2], and with parathormone and calcitonin makes up the calciotropic hormone group. Its important role in the homeostasis of calcium and its direct action on bone tissue have made it the object of continual research in the study of mineral metabolism.

However, receptors for vitamin D (VDR) have been detected in almost all human tissues, and its capacity to regulate the expression of numerous genes has been discovered[3]. A randomised double blind clinical trial, recently published and carried out in 6 subjects over the winter to see the effects of vitamin D supplements over 2 months on gene expression found that at the start of the study there was a significant difference in the expression of 66 genes between subjects with vitamin D deficiency (<20 ng/mL) and those with initial levels >20 ng/ml. After 2 months with vitamin D supplements the expression of these 66 genes was similar in both groups. Furthermore, 17 genes regulated by vitamin D were identified as new candidates for the response to vitamin D, which have been shown to be important for the regulation of gene transcription, immune function, response to stress and DNA repair[4].

This suggests that vitamin D has a hormonal effect beyond the bone, and it is gradually being conceded that vitamin D has a significant role in general human physiology[5,6].

Numerous studies have been carried out over the years in order to provide evidence of these actions outside the bone, the most significant being those which take place in the muscle, in cancers, in glucose metabolism and the immune system, which are those which we analyse in this review.

Vitamin D and muscle activity

The intervention of vitamin D in muscle function has been known for many years and has been widely studied. It has long been observed that a deficiency in vitamin D leads to myopathy characterised by proximal muscular weakness and atrophy[7], and the presence of VDR in the muscle tissue of the skeleton has been evidenced in various studies[8-10], with a decrease in these receptors being observed with age[11].

Vitamin D regulates muscle development and contractility, and this occurs though genomic actions, stimulating the proliferation of muscle cells and their differentiation through transcription, mediated by nuclear-specific receptors, of genes which express an increase in the synthesis of cell DNA, followed by the induction of specific muscular proteins (proteins which bond to calcium and myosin). But it also exerts non-genomic actions, interacting with the receptor specific to the muscle cell membrane, which then brings about the stimulation of adenyl cyclase and the phospholipases C, D and A2, and the action of the intracellular signalling pathways, such as the MAPK (Mitogen-activated protein kinase) cascade, which finally acts on the DNA inducing cell division[12,13]. In a recently-published study the authors observed that mice recently born of vitamin D deficient mothers had smaller muscles cells than those whose mothers had sufficient levels[14].

However, it should be said that the existence of VDR in muscle cells is questioned by some authors. In a study carried out by Wang et al., the researchers were unable to detect VDR in mouse muscle cells and observed that the antibodies use to detect the VDRs are not specific to those receptors, which could explain the possibly false positive results in earlier studies. The authors concluded that the effect that vitamin D has on the muscle should be indirect[15]. However, some authors consider that these findings may be due to differences in experimental conditions and the possible existence of the close bonding of the VDR with the specific hormonal response element of the DNA when coupled with vitamin D[16]. In any case, a small presence of VDR in the muscle may be sufficient to allow the action of vitamin D in these cells. Another possibility is that there may be differences in the expression of the VDR in the muscle of different species and over the different stages of muscle differentiation[17]. Lastly, some researchers have suggested that, apart from VDR specifically, it is possible that other cytoplasmic receptors (such as the steroids, given their molecular similarity) may be responsible for the rapid actions of the vitamin D metabolites in the muscle[18].

On this basis, it is easy to understand that vitamin D takes a significant role in muscle activity[19]. As we indicated at the start, various studies have already for some time been demonstrating that a deficit in vitamin D is associated with diffuse myalgia, muscle weakness[20,21] and sarcopenia, all caused by muscular atrophy, principally of type II muscle fibres, and affecting above all the proximal musculature[22,23]. To understand the relationship between levels of vitamin D and risk of falls and muscle weakness, Stewart et al. carried out a study in 242 healthy postmenopausal women. In order to achieve this they looked for a correlation between some indicators of good physical health, such as the android fat mass, the lean body mass, balance and the strength of grip, the strength of the torso and the strength of the lower limbs. They found that the levels of vitamin D were correlated with all these factors except strength of torso and lower limbs, concluding that levels of vitamin D may contribute to these indices of physical health in healthy postmenopausal women[24].

In addition, and in agreement with what has been said earlier, various studies have shown that vitamin D supplements improve considerably muscle strength, especially in the elderly population with hypovitaminosis. Bunout et al. evaluated the effects of resistance training and the provision of vitamin D supplements on the physical condition of 96 healthy older people with low levels of vitamin D, concluding that its addition improved the speed of movement and stability, while the training improved muscle strength[25]. In a randomised placebo-controlled study, carried out in outpatients over 65 years of age with a history of falls and hypovitaminosis, and whose aim was to see the effect on physical and muscle function of a vitamin D supplement (ergocalciferol) administered in a single intramuscular dose of 600,000 UI, the authors found as a result that, at 6 months, the subjects who had received the vitamin D supplement achieved significant benefits in physical function, reaction time and balance, although not in muscle strength[26]. In a study by Bischoff-Ferrari et al. the authors demonstrated that vitamin D with calcium improves the postural and dynamic balance of institutionalised older people[27]. Moreira-Pfrimer et al. studied muscle strength in 46 institutionalised subjects of ≥65 years of age, to whom had been administered randomly over 6 months, either daily calcium plus placebo, or daily calcium plus vitamin D. By the end of the study, and in the absence of physical exercise, the strength of the hip flexors increased in the group who received vitamin D by 16.4% (p=0.0001), and the strength of the extensors in the knee by 24.6% (p=0.0007)[28].

However, there are studies which conclude that in healthy older people vitamin D supplements do not prevent the decrease in muscle strength due to age-related regression[29,30]. In a review carried out by Annweiler et al., the results regarding the association between vitamin D and physical function were arguable[31], although a more recent meta-analysis concluded that vitamin D supplements at daily doses of 800 to 1,000 UI were shown to have beneficial effects on muscle strength and balance in older people[32].

Muscle weakness associated with hypovitaminosis D, if a certain limit is surpassed, may affect functional capacity and mobility, which puts especially older people at greater risk of falls, and therefore of fracture[26,30]. A study carried out in institutionalised older women showed that those who took calcium and vitamin D for 3 months had a reduction in the risk of falls of 49% compared with those who only took calcium, and their musculo-skeletal function improved significantly (p=0.0094)[33]. Similar results were obtained by Pfeifer et al. in a study carried out in older people of both sexes[34]. With regard to the effect on falls of vitamin D, in a placebo-controlled randomised study of multiple doses, it was shown that the administration of 800 UI/day of vitamin D for more than 5 months reduced the adjusted-incidence rate of falls by 72%[35]. Various meta-data analyses published in recent years indicate that vitamin D supplements reduce the risk of falls in older people[36]. One of these, carried out by Bischoff-Ferrari et al. with 8 randomised placebo-controlled trials (n=2,426), showed that vitamin D supplements at doses of 700 to 1,000 UI/day, or blood levels of vitamin D ≥24 ng/ml, reduces the risk of falls by 19% and 23% respectively. No benefits were observed with lower doses of supplements or levels of blood vitamin D than those indicated[37]. This observation is corroborated in a Cochrane review carried out in 2009 by Gillespie et al. who observed that vitamin D supplements did not reduce the risk of falls (RR=0.96, 95% CI: 0.92-1.10), but indicated that they may do so in people with low blood levels of vitamin D[38]. In another review it was concluded that these supplements reduce the rate of falls (rate ratio RaR=0.72; 95% CI: 0.55-0.95) but not the risk of falls (risk ratio RR=0.98; 95% CI: 0.89-1.09)[39]. In a systematic review accompanied by a meta-analysis carried out by Kalyani et al., the authors obtained the result that vitamin D supplements effectively reduce the risk of falls in older women[40].

In conclusion, there is evidence that the muscle responds to vitamin D, which ought to be an incentive for carrying out studies into its therapeutic potential in muscular pathologies. Furthermore, the evidence is sufficient to recommend that doctors take into account the observation of levels of vitamin D in patients with muscular disorders.

Vitamin D and cancer

The first publication on the association between exposure to sun and the reduction in mortality due to cancer in the US was produced in 1941 by Apperly[41]. Much later, in 1980, the Garland brothers proposed the hypothesis that vitamin D is a protector against cancer of the colon[42]. Since then, there have been many epidemiological studies aimed at evidencing this relationship, as well as with other types of cancer, mostly showing positive results. A recent systematic review carried out by Grant found a strong inverse relationship between sun exposure-vitamin D and the appearance of 15 different types of cancer: vesical, breast, uterine, colon, endometrial, oesophageal, gastric, lung, ovarian, pancreatic, rectal, renal, vulvar and Hodgkin and non-Hodgkin lymphoma[43]. Lappe et al., in a placebo-controlled double blind randomised trial carried out in 1,179 postmenopausal women to whom were assigned treatment with calcium only, or calcium and vitamin D or placebo found that improvements in the nutritional state of calcium and vitamin D reduced the risk of suffering any type of cancer[44].

In another more recent systematic review, van der Rhee et al.[45] found that almost all the epidemiological studies reviewed suggested that chronic (not intermittent) exposure to sun is associated with a reduced risk of colorectal, breast, and prostate cancer and non-Hodgkin lymphoma. In the case of colorectal cancer - and to a lesser degree in breast cancer – the levels of vitamin D are inversely associated with the risk of cancer, but not so in prostate cancer or in non-Hodgkin lymphoma. Other retrospective and prospective case-controlled studies, however, have found this inverse relationship in four types of cancer, colon, prostate, breast and non-Hodgkin lymphoma[46-52], although a recently published study found no association in the case of prostate cancer[53]. Vitamin D and its analogues inhibit the proliferation, the angiogenesis, the migration and the invasion of the malignant line cells of cancer of the colon, prostate and breast, and induce their differentiation and apoptosis[54,55]. Furthermore, the synthesis of prostaglandins and the Wnt/beta catenin signalling pathway are also influenced by vitamin D, which suppresses COX-2 expression and increases that of 15-PGDH, thus reducing levels of inflammatory prostaglandins. Thus are prostaglandin metabolism and signalling regulated, hence diminishing the promotion of the carcinogenesis promoted by them. This effect on the synthesis of prostaglandins also gives rise to a suppression of tumoral angiogenesis, by means of the regulation of the crucial factors which control it[56,57]. Vitamin D also regulates the signalling of the androgen and estrogen receptors, thus inhibiting the growth of some tumours dependent on these hormones, such as those of the breast and the prostate, reducing also in the latter the expression of aromatase, which contributes to the inhibition of its growth[58,59].

Association studies have certain limitations in terms of the establishment of a causal relationship between vitamin D status and a reduced risk of cancer. For example, low levels of vitamin D are also linked to confusion factors related to a greater risk of cancer, such as obesity, (as we see later, vitamin D is "retained" in adipose tissue) and a lack of physical activity (correlated with less time in the open air and exposure to sun)[50]. However, a double blind, randomised placebo-controlled trial of 4 years duration, carried out in more than a thousand postmenopausal women, whose principal secondary objective was the incidence of cancer, showed that the administration of calcium supplements (1,400-1,500 mg/day) and vitamin D (1,100 UI/day) reduced the relative risk of cancer by approximately 60% ($p<0.01$). The repetition of an analysis of cancer-free survival after the first 12 months revealed that the relative risk for the group with calcium and vitamin D was reduced by approximately 77% (95% CI: 0.09-0.60; $p<0.005$). Multiple regression models also show that treatment and blood concentrations of vitamin D are significant independent predictors of the risk of cancer[44].

Evidently, studies which relate vitamin D deficiency to the risk of cancer do not show that this is a causal relationship. More clinical trials are necessary aimed specifically at looking at the effects of vitamin D supplements in the development of neoplasms, and whether the maintenance of sufficient levels of vitamin D may be an effective preventative measure.

Vitamin D and metabolic diseases: diabetes and obesity

The hypothesis that vitamin D may be relevant to the risk of diabetes is consistent, given the numerous studies which have shown an inverse association between vitamin D deficiency and the disease, especially type 2.

A meta-analysis carried out in order to observe the association between the status of vitamin D or its supplement and the incidence of type 2 diabetes showed that those subjects with levels of the hormone >25 ng/ml, compared with those who had levels <14 ng/ml, had a 43% lower risk of developing type 2 diabetes, and that a daily supplement of vitamin D higher than 500 UI, compared with one <200 UI/day, reduced the risk by 13%[60]. Another study carried out by George et al., concluded however that there was not sufficient evidence of the beneficial effects to recommend vitamin D supplements as a measure to improve glycemia or resistance to insulin in patients with diabetes[61]. Song et al. have published another more recent study in which they conclude that there is a reduction of 38% in the risk of suffering diabetes type 2 when comparing people with higher levels of vitamin D with those with lower levels (RR=0.62; 95% CI, 0.54-0.70)[62]. The Nurses' Health Study conducted a follow up study of more than 83,000 women and it was observed that a daily intake of calcium >1,200 mg plus a vitamin D supplement >800 UI was associated with a lower risk (33%) of suffering diabetes type 2 (RR=0.67; 95% CI: 0.49-0.90) compared with an intake of calcium <600 mg plus 400 UI of vitamin D[63]. A prospective study which followed up more than 2,000 participants showed that the risk of progression from pre-diabetes to diabetes was 62% lower when those with levels of vitamin D in the highest quartile were compared with those who had levels in the lowest quartile[64]. This could be explained by the findings which indicate that vitamin D exerts various anti-diabetic effects[65]. The VDR is expressed in the pancreatic beta cells, and vitamin D stimulates the secretion of insulin[66,67]. Various studies have shown that vitamin D supplements result in an improved sensitivity to insulin[68-70], mediated, for example, by an increase in the production of insulin receptors[66], and modulates inflammation, which it is thought, also plays a role in diabetes type 2[67,71].

On the other hand, it has also been demonstrated that obese subjects have lower levels of vitamin D than those who are not obese[72-77]. These lower levels have been explained by, among other factors, the storage of vitamin D in body fat[78,79]. Furthermore, these obese subjects respond less well to vitamin D supplements, their increase in vitamin D being less than in those who are not obese with the same dose of supplements, their needs therefore being greater[72,76,77]. In connection with what has been said earlier, some studies have shown that the correction of a vitamin D deficit in obese subjects improves sensitivity to insulin[69], although some authors have not found a reduction in the resistance to insulin with vitamin D supplements in these subjects[74,80]. Indeed, in a recent randomised, double blind placebo-controlled study carried out by Salehpour et al. in 77 women who were overweight and obese, the authors found that the group of women who took vitamin D for 12 weeks showed a decrease in body fat mass significantly greater than the placebo group (-2.7±2.1 kg vs 0.47±2.1 kg; p<0.001), with a significant inverse correlation between the two parameters (r= -0.319, p=0.005), although the weight and the circumference of the wrist did not show any significant changes in either of the two groups[81]. These correlation data between vitamin D and body fat mass have already been reported by other authors[82,83].

These common findings fit within the framework of the metabolic syndrome. In a study carried out in 4,727 healthy young people who were followed up over a period of 20 years, it was observed that the prevalence of the majority of the components of metabolic syndrome (abdominal obesity, hyperglycemia and low blood concentrations of HDL-cholesterol) were reducing significantly over the quintiles for the intake of vitamin D (p=0.05).

There was a significant inverse association between the intake through the diet or by supplements of vitamin D and the risk of developing metabolic syndrome at 20 years[84]. Another follow up study over 5 years with 11,547 adults carried out in Australia observed that low levels of vitamin D were inversely correlated with a greater risk of metabolic syndrome, greater wrist circumference, higher levels of blood glucose and triglycerides, and greater resistance to insulin[85]. It has been observed in obese subjects that vitamin D supplements reduce levels of GH and IGF, which means that the adverse affects of the GH-IGF-insulin axis in the metabolism of glucose and the metabolic syndrome may be in part related to the deficit status of vitamin D[74].

All these studies demonstrate the involvement of vitamin D in the metabolism, although there are still many unknowns regarding its involvement in diabetes mellitus type 2 and obesity, and more generally, in metabolic syndrome, as well as in its etiopathogeny, and its potential therapeutic effect.

Vitamin D and diabetes mellitus type 1

There have also been studies carried out which look at the influence of vitamin D on diabetes type 1[86]. With a different etiopathogeny to type 2, diabetes type 1 may have a connection with vitamin D through its action on the immune system[87], which we analyse in the following section. Littorin et al. observed that young adults recently diagnosed with diabetes type 1 had lower levels of vitamin D than those subjects without the disease, who acted as a control[88]. Sorensen et al. followed up 29,072 pregnant women and their offspring, and observed that the children of the women who had lower levels of vitamin D during pregnancy had double the risk of suffering diabetes type 1 than those of mothers with higher levels[89]. A study carried out in a cohort of new-born babies who were followed up over a year found that those who took vitamin D supplements, both regularly and irregularly, had a lower relative risk of suffering diabetes type 1 than those who did not do so (RR=0.12; 95% CI, 0.03-0.51 and RR=0.16; 95% CI, 0.04-0.74, respectively)[90]. Li et al studied 35 patients with latent autoimmune diabetes who were randomly assigned either to a group treated with insulin only or to a group treated with insulin and vitamin D for a year. At the end of this study the levels of C peptide diminished in the group treated with insulin only (p=0.006), while in the group treated with vitamin D also remained stable. 70% of the patients treated with vitamin D maintained or increased their levels of C peptide, while 22% of those treated with insulin alone did so, the difference being significant (p=0.01)[91].

A meta-analysis of observational studies concluded that vitamin D supplements at early ages may offer protection against the development of diabetes type 1[92]. However, other authors did not find this protective effect of vitamin D in subjects with recently occurring diabetes type 1[93,94] which means that more studies are required to help elucidate whether vitamin D may bring additional benefits to the treatment of these patients.

Vitamin D and the immune system

The participation of vitamin D in immunity has been studied for many years. VDRs are present in all the cells of the immune system[95], and a great number of genes related to the immune system are regulated by vitamin D[96].

Its involvement has been demonstrated both in natural and innate immunity (the beneficial effects of sunlight in patients with tuberculosis has been known for some time) and in acquired immunity. Vitamin D improves the antimicrobial effects of the macrophages and monocytes, as well as chemotaxis and the phagocytic capacity of these cells[97]. Cathelicidin and β2 defensin are antimicrobial peptides which act to destabilise the microbial membrane, and are produced by polimorphonuclears and macrophages. Vitamin D, through its VDR (along with the X retinoid receptors) directly activates the transcription of these peptides and their production[98-100]. In a study carried out in critical patients (with and without sepsis) the levels of vitamin D and cathelicidin were determined and compared with those of a group of healthy subject, and it was observed that the critical patients had lower values of both than the healthy subjects, and a positive and significant correlation between levels of vitamin D and cathelicidin was found[101]. There are also studies which show that vitamin D modulates the maturation of dendritic cells[102,103]. On the other hand, it has been reported that vitamin D inhibits the cytokines of the T cells such as IL-2 and 17, and the toll-like receptors of the monocytes responsible for the recognition of a wide range of microbial agents and for the stimulation of the inflammatory response to them[97]. Finally, it has been confirmed that high doses of vitamin D in healthy subjects leads to a reduction in IL-6 (pro-inflammatory cytokine) produced by the monocytes[104].

All this, combined with various studies which have found low levels of vitamin D in patients with different infectious respiratory diseases[105-108], and others which provide evidence of a more rapid recovery in patients with tuberculosis in those to whom vitamin D supplements are administered[109,110], supports the theory of the participation of vitamin D in natural immunity.

With respect to acquired immunity, vitamin D regulates the differentiation and proliferation of the T and B lymphocytes, especially when these have been activated, since it has been confirmed that in the state of cell activity the expression of genes activated by vitamin D though its nuclear receptors specific to these cells increases considerably, genes which are involved in the regulation of the proliferation and differentiation of these lymphocytes[111,112]. In the B lymphocytes this action has been seen to occur indirectly through the T lymphocyte co-operators or helpers, which induce the inhibition of the proliferation and differentiation of the B lymphocytes and the initiation of their apoptosis, as well as a lower production of immunoglobulins[113,114]. However, more recent studies have shown a direct effect of vitamin D on the B lymphocytes[97,111,115].

With respect to the activated T lymphocytes, vitamin D leads to a state of greater immune tolerance, suppressing the proliferation and differentiation of the T lymphocyte co-operators and modulating the production of its cytokines[113], inhibiting the pro-inflammatory cytokines (IL-2, interferon-γ, TNFα, IL-9, IL-22)[96,116-118], and promoting the production of anti-inflammatory cytokines (IL-3, IL-4, IL-5, IL-10)[119].

As a consequence, the relationship described by various authors between vitamin D deficiency and autoimmune diseases such as diabetes type 1 (as we have already mentioned), rheumatoid arthritis[120], systemic lupus erythematosus[121], multiple sclerosis[122], psoriasis[123], chronic inflammatory intestinal disease[124], etc, is not surprising. Although, as has already been said in relation to cancer, more studies should be carried out to discover the true involvement of vitamin D in the pathogeny of these diseases.

Conclusions

It is clear that vitamin D has an involvement in general health, and that it does not only benefit bone. Apart from the functions discussed above, numerous studies have looked at its relationship with other functions such as reproduction, the nervous system, cardiovascular disease, etc. We should not forget the close relationship which exists between vitamin D and calcium, a molecule which also has a wide involvement in cell function. To what extent vitamin D is involved in physiology outside the bone is yet to be determined. However, the ever more numerous studies which are carried out in this area are leading the way and inviting researchers to continue to deepen the understanding of the actions of this vitamin, which has become a calciotropic hormone, and which may perhaps become to be seen, as with the thyroid hormones, as a hormone which acts multisystemically.

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Jódar Gimeno E
Jefe de Servicio de Endocrinología y Nutrición Clínica - Hospital Universitario Quirón - Madrid
Profesor de Medicina - Universidad Europea de Madrid

Recommendations for the administration of vitamin D. National and international guides

Correspondence: Esteban Jódar Gimeno - c/Diego de Velázquez, 2 - 28223 Pozuelo de Alarcón - Madrid (Spain)
e-mail: esteban.jodar@quiron.es

Introduction

The D hormone system, in spite of having been known for more than a century, has been ignored until relatively recent years. Proof of this is its still erroneous naming as vitamin D. Since the end of the 1990s, and with the turn of the century, the interest and the potential beneficial effects of its supplementation and/or replacement has increased enormously, moving from a recommendation of a dose which empirically avoids infantile rickets to a recommendation of mega-dosage.

The better knowledge of its beneficial effects and its potential risks resulted in recommendations of limited intake by the Institute of Medicine in 2010 clearly lower than those recommended by other scientific societies. Since then, the controversy persists without a clear response, which we try to resume in this article.

Spanish declaration on vitamin D in the management of osteoporosis of March 9th 2006

The interest in the the effects of vitamin D and its deficit status in broad sections of the population, both osteoporotic and apparently healthy, started in our country with a generic declaration on the part of various scientific societies involved in the management of osteoporosis, brought to a consensus in 2006 and published in 2007[1]. In this document were proposed measures to understand its impact and correct its deficit.

Position document of the IOF (International Osteoporosis Foundation) on recommendations for vitamin D in older adults

In a document published in 2010, the IOF (International Osteoporosis Foundation) recommended levels higher than 30 ng/ml (75 nmol/L) of 25(OH) vitamin D, with supplements of between 800 and 1,000 UI/day (20-25 µg/day) being required to achieve this threshold in most of the population, although it was thought that vitamin D supplementation could reach 2,000 UI/day in certain individuals, among others, those who were obese, osteoporotic, with limited exposure to sunlight (for example, institutionalised), or with absorption problems, etc[2].

Position document on the necessities and optimum levels of vitamin D

Some years after the earlier declaration, and this time led by the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM) and including representatives from up to 11 other scientific societies involved in the management of this issue (Spanish Association for the Study of the Menopause [Asociación Española para el Estudio de la Menopausia], Hispanic Foundation for Osteoporosis and Bone Metabolic Diseases [Fundación Hispana de Osteoporosis y Enfermedades Metabólicas Oseas], Spanish Society for Orthopaedic Surgery and Traumatology [Sociedad Española de Cirugía Ortopédica y Traumatología], Spanish Society for Endocrinology and Nutrition [Sociedad Española de Endocrinología y Nutricion], Spanish Society for Osteoporotic Fractures [Sociedad Espanola de Fracturas Osteoporóticas], Spanish Society for Geriatrics and Gernotlology [Sociedad Española de Geriatría y Gerontología], Spanish Society for Primary Care Doctors [Sociedad Española de Médicos de Atención Primaria], Spanish Society forFamiily and Community Medicine [Sociedad Española de Medicina Familiar y Comunitaria], Spanish Society for

Internal Medicine [Sociedad Española de Medicina Interna], Spanish Society for Rheumatology [Sociedad Española de Reumatología], Spanish Society for Rehabilitation and Physical Medicine [Sociedad Española de Rehabilitación y Medicina Física] and the IberoAmerican Society for Osteoporosis and Mineral Metabolism [Sociedad Iberoamericana de Osteoporosis y Metabolismo Mineral]) produced a document in which were recommended optimum concentrations of 25(OH) vitamin D of between 30 and 75 ng/ml, and which considered as clearly pathological levels those below 20 ng/ml. The existence of insufficient levels in wide sections of the population were recognised (from 30% in young people to 87% in institutionalised older people) in the absence of supplementation in food commonly consumed and with limited exposure to sun. In this document, supplements of vitamin D_2 or D_3 of 800-1,000 UI/day were recommended for older people and those with osteoporosis (600-800 UI/day for postmenopausal women)[3].

Recommendations of the Institute of Medicine (IOM)

Amid growing interest in the beneficial effects of the D hormone in bone, muscular and even extra-skeletal health, in which progressively larger doses of dietary supplements were being proposed – reaching an intake of 2,000 UI/day or more – the body responsible for setting the reference levels for dietary intake in the United States, the Institute of Medicine (IOM) published recommendations which were clearly restrictive and which cooled the general euphoria associated with vitamin D. These were based on the estimated average requirements (EAR) to achieve a concentration of 25OH vitamin D of 16 ng/ml, which would be sufficient for the needs of 50% of the population, and the recommended dietary allowance (RDA) to achieve 20 ng/ml of 25OH vitamin D which would be sufficient to meet the needs of 97.5% of the apparently healthy population of the USA[4-6]. The IOM's recommended dietary allowance to reach such levels was only 600 UI/day for most of the American population, reaching 800 UI/day for people over 70 years of age, while recognising that the maximum tolerable intake was 4,000 UI/day. These recommendations were based on the absence of proven benefits of blood concentrations of 25OH vitamin D above 20 ng/ml and the potential risks – nephrolithiasis and tissue damage – putting an end to the theory "more is better" which prevailed at that time[4].

In terms of the daily necessary intake to reach these sufficient blood levels the IOM indicated a dose response curve between intake and associated blood levels which are summarised in the following formulae[4,7,8]:

25OH vitamin D in the blood (nmol/l) = 9.9 x ln (total intake of vitamin D [UI/day])

25OH vitamin D in the blood (ng/ml) = 24.75 x ln (total intake of vitamin D [UI/day])

Which means that 100 UI/day of vitamin D_2 (ergosterol) or D_3 (colecalciferol) would raise the concentration of 25OH vitamin D by approximately 3.25 ng/ml, and 800 UI/day of vitamin D_2 or D_3 would raise concentrations of 25OH vitamin D by 26 ng/ml.

Recommendations and guide to clinical practice of the North American Endocrine Society

Only a few weeks before the report of the IOM referring to apparently healthy people, the North American Endocrine Society released a guide to clinical practice which was much more interventionist and more favourable to supplementation when looking for benefits for the skeleton[9]. They recommended supplements of vitamin D_2 (ergosterol) or D_3 (colecalciferol) - after measuring 25OH vitamin D with a reliable test – in all deficient subjects. For adults over 18 years of age an intake of at least 600 UI/day of vitamin D_2 or D_3 was recommended in order to maximise bone and muscle function. However, optimum levels of 25OH vitamin D were considered to be those above 30 ng/ml, for which an intake of at least 1,500-2,000 UI/day of vitamin D would be necessary[10]. From the age of 70, the Endocrine Society would recommend at least 800 UI/day, recognising that to reach its objective of 25OH vitamin D above 30 ng/ml, 1,500 to 2,000 UI/day of vitamin D_2 or D_3 could be required. In special populations such as those who are obese, or using anticonvulsants, glucocorticoids, antifungals or antivirals for HIV, the requirements could be 2 to 3 times higher.

The aforementioned guide[9] recommends as therapy for people deficient in vitamin D the following doses:

- Babies up to 1 year old deficient in vitamin D: 2,000 UI/day of vitamin D_2 or D_3, or 50,000 UI of vitamin D_2 or D_3 weekly over 6 weeks to reach the target levels of 25OH vitamin D, followed by a maintenance dose of 400-1,000 UI/day.
- For children from 1 to 18 years of age deficient in vitamin D: 2,000 UI/day of vitamin D_2 or D_3, or 50,000 UI of vitamin D_2 or D_3 weekly over 6 weeks to reach the target levels of 25OH vitamin D, followed by a maintenance dose of 600-1,000 UI/day.
- For adults deficient in vitamin D: 50,000 UI of vitamin D_2 or D_3 weekly over 8 weeks to reach the target levels of 25OH vitamin D, followed by a maintenance dose of 1,500-2,000 UI/day.
- For those with obesity, patients with malabsorption and patients treated with drugs which affect vitamin D metabolism: 6,000 to 10,000 UI/day of vitamin D_2 or D_3 to reach the target levels of 25OH vitamin D, followed by a maintenance dose of 3,000-6,000 UI/day.
- The maximum tolerable maintenance dose of vitamin D_2 or D_3 – which ought not be exceeded without medical supervision – would be 1,000 UI/day for babies up to 6 months, 1,500 for children of 6 to 12 months, at least 2,500 UI/day for children between 1 and 3 years, 3,000 UI/day for children between 4 and 8 years and 4,000 UI/day for those older than 8 years of age. However, the guide itself recognises that a dose of 2,000 UI/day may be required in children up to 1 year, 4,000 UI/day for those

between 1 and 18 and up to 10,000 UI/day in those over 18 in order to correct vitamin D deficiency.

These recommendations are based on the assumption that the relationship between the dose received of vitamin D_2 and/or D_3 and the response of blood 25OH vitamin D fits a regression line with a constant relationship in which for every 100 IU/day vitamin D intake, vitamin D increases 25OH 1 ng/ml (2.5 nmol/L)[9,11].

The controversy between the recommendations of the Endocrine Society and the Institute of Medicine

In the months following the appearance of the recommendations of the IOM and the Endocrine Society an argument commenced which still remains and which centres on the values of 25OH vitamin D recommended as targets, and on the recognition, or not, of the extra-skeletal effects of higher intakes of vitamin D[5,11,12].

The fundamental difference between the two associations is in reference to the populations for which the recommendations are made, which for the Institute of Medicine are apparently healthy people without pathologies or known deficient in whom there is little proof of benefits, especially extra-skeletal, of a high intake of vitamin D, while the Guide to Clinical Practice of the Endocrine Society focuses on patients with osteoporosis or other conditions of risk of vitamin D deficit for whom it seems reasonable that the targets and doses are higher. The Endocrine Society, furthermore, interprets more favourably the evidence of the bone, muscle and extra-skeletal benefits, while recognising that the proof of the last is not sufficient to recommend vitamin D supplements in the prevention or treatment of conditions such as arterial hypertension, diabetes, different cancers or multiple autoimmune diseases.

Recommendations subsequent to the Institute of Medicine-Endocrine Society controversy

In 2012, many of the signatories of the guide to clinical practice of the Endocrine Society published a new revised version of their recommendations[13] in which was discussed the best parameter for defining the optimum concentration of 25OH vitamin D – probably the better the concentrations in populations maintaining ancestral lifestyles such as the Aboriginals or the Masai, the lower the osteiod volume that the values of PTH highly dependent on age, sex and renal function, among others – the benefits for the skeleton, muscle and to health in general of concentrations of 25OH vitamin higher than 30 ng/ml, and indicated the differences between recommendations for the general healthy population and those for osteoporotic patients.

Subsequent to the exchange of the aforementioned articles, a recommendation related to the use of calcium and vitamin D was made by the US Preventive Services Task Force (USPSTF)[14]. The USPSTF is the North American body responsible for making recommendations on the efficacy of preventative services specifically for patients without signs or symptoms of these pathologies. Its recommendations, based on systematic reviews of publications available and their meta-analysis for people with neither osteoporosis nor known vitamin D deficit, are that:

- There is no proof of the efficacy of calcium or vitamin D supplements in preventing fractures.
- Nor is there proof for the recommendation of doses higher than 400 UI/day of vitamin D_2 or D_3 combined with a gram of calcium in the primary prevention of fractures, except in older people admitted to residential homes for chronic patients.

Rules for the calculation of the replacement dose for vitamin D

As has already been said, the IOM and the Endocrine Society base their recommendations for the replacement of vitamin D on different assumptions about the relationship that exists between the dose of vitamin D received and the response of 25OH vitamin D in the blood (see above). In a study with low intakes of vitamin D (800 UI/day) administered to institutionalised older people over 16 months with severe hypovitaminosis D, the dose response curve found was 3.6 ng/ml per each 100 UI/day, nearly 4 times higher than that predicted by the Endocrine Society. Using the IOM's regression equation, the predicted value was 26 ng/ml for an intake of 800 UI/day, similar to that observed, of 31.9 ng/ml, and clearly higher than that predicted by the Endocrine Society rules (an increase of 8 ng/ml)[7,8].

Following this observation, and with the aim of confirming the appropriateness of the rules for the dose-response relationship from the two associations, 41 available works have been studied in which the daily doses administered were lower than 2,000 UI/day, with a duration greater than 3 months and with baseline and final measurements of 25OH vitamin D. The changes in these levels were compared with those predicted by the IOM and Endocrine Society formulae (see above), as well as the regression equation for Vitamin D Supplementation in Older Subjects (ViDOS) (25OHD (nmol/l) = 54.5 + 24.6 x dose/1,000 – 2.5 x $dose^2/1{,}000^2$)[15]. The constant for the relationship observed was 2.12 (1.76-2.48) ng/ml (5.3 nmol/l) for each 100 UI/day of intake. This is, on average, double that predicted by the rule of the Endocrine Society. The differences in percentages between the expected and observed values were: IOM -7%; ViDOS + 2% and ES - 21%, which is why the authors propose that the Endocrine Society rule should be doubled (an increase of 2 ng/ml for each 100 UI/day[16].

In any case, most of the recommendations for the replacement of vitamin D make mention of the use of daily, weekly or monthly doses, given that recent evidence has shown that the administration of annual mega-doses of vitamin D (500,000 UI/annually of colecalciferol) is associated with an increase in the risk of falls of 15% and of fractures of 26% in women over 70 years of age[17]. Similar data have been published for apparently healthy older men[18].

Most of the available data, and the recommendations of the scientific societies, are based on the administration of oral supplements of vitamin D_3 (colecalciferol) or D_2 (ergocalciferol). However, the formulations available in each country are different. A study in the general population has evaluated the efficacy and safety of the administration of 50,000 UI/monthly of vitamin D_3. In the group of patients the vast majority achieved concentrations higher than 20 ng/ml, and in more than ¾ of them, values of between 20 and 50 ng/ml. In this study, no significant adverse effects were identified[19]. On the other hand, in healthy subjects it has been confirmed that calcifediol is between 4 and 5 times more effective than vitamin D_3 in increasing blood concentrations of 25OH vitamin D[20], which means that in cases where calcifediol is chosen doses between 4 and 5 times lower should be given. It should be remembered that in order to obtain health benefits from vitamin D supplements it is indicated that treatment with vitamin D_2, D_3 or calcifediol should be sustained while factors which predispose to the development of this deficit persist, which in most cases means indefinite treatment.

On the other hand, if vitamin D is being treated, we should understand the response to the treatment, with a view to changing the regimen or its intensity. It is necessary to take into account the seasonal variation and the use of drugs which may alter the rate of response (such as corticoids or hepatic inductors). An annual review is indicated in order to adjust the treatment regime. It has also been recently reported that there may be a greater risk of lithiasis, and greater than expected hypercalcemia[21].

In summary, although there is general agreement in terms of the high prevalence of vitamin D deficit, especially in some populations such as those who are osteoporotic, and older people, there are wide differences in terms of the recommended doses for replacement and for its supplementation. As a reasonable general rule, 800-1,000 UI/day of ergocalciferol or colecacliferol daily, or its weekly or monthly equivalent may be recommended. Calcifediol at doses 4 to 5 times less is also a reasonable approximation. Taking into account the fact that there is a correlation between the number of UIs administered and the blood levels of 25OH vitamin D achieved, the highest dose of this range (1,000UI/day) could increase the probability that those individuals achieve levels higher than 30 ng/ml. Furthermore, the administration to certain individuals and/or certain circumstances of supplementary doses of up to 2,000 UI/day could be considered.

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Sosa Henríquez M[1,2], Saavedra Santana P[3], Díaz Curiel M[4]
1 Universidad de Las Palmas de Gran Canaria - Grupo de Investigación en Osteoporosis y Metabolismo Mineral
2 Servicio Canario de la Salud - Hospital Universitario Insular - Unidad Metabólica Ósea - Las Palmas de Gran Canaria
3 Universidad de Las Palmas de Gran Canaria - Departamento de Matemáticas - Las Palmas de Gran Canaria
4 Fundación Jiménez Díaz - Hospital Nuestra Señora de la Concepción - Unidad Metabólica - Madrid

What perception do Spanish doctors have of vitamin D?

Correspondence: Manuel Sosa Henríquez - c/Espronceda, 2 - 35005 Las Palmas de Gran Canaria (Spain)
e-mail: msosa@ono.com

Introduction

The last few years have seen a notable advance in the understanding of practically all the fields of study related vitamin D, which has resulted in it being considered to be a vitamin which is recognised as a steroid hormone[1-4].

Although vitamin D is classically related with bone mineral metabolism, its effects on practically the whole organism, the so-called "extra-bone" effects of vitamin D, are becoming increasingly better understood[2,3,5-8], and which have been reviewed in another article in this Monograph[9].

In the literature consulted we found scant reference to the opinions of Spanish doctors regarding different aspects of vitamin D in the Spanish population in general or in their patients, their views on desirable levels of vitamin D, and lastly, the dose they would recommend be administered. In this study we would like to make a first approximation of these data, which will allow us to understand what knowledge Spanish doctors have of vitamin D.

Material and method

To carry out this study we obtained data on the whole population of doctors specialising in primary care, rheumatology, traumatology, internal medicine, rehabilitation and endocrinology in Spain, classified according to their respective autonomous communities. Subsequently they were grouped as primary care specialists and other specialists (the rest).

The sample size in each study group (primary care, and other specialists), was determined in order to estimate each proportion with an error quotient of 5%. To achieve this it was necessary that 381 questionnaires be completed in each of the groups.

The participants were invited to access a web page which contained a questionnaire designed for the study and where they had to enter the data directly. Each doctor could on access only one questionnaire by means of a code which had been provided earlier. The questionnaire was completed in approximately 2 minutes and the data exported to an Excel spreadsheet, and then imported into the SPSS® programme, where the statistical calculations were performed.

Statistical analysis. In all the groups considered, the variables were summarised as percentages, which were compared using the χ^2 test. A hypothesis test was considered statistically significant when the corresponding p value was less than 0.05. Those variables which showed a significant association with a specialism (primary care/other) were put through a multidimensional correspondence analysis. From the χ^2 distance between the categories in the Burt table a group of points was generated in a space with the dimension p -1. The first two principal components were then extracted and the variability percentages explained by each of the components were evaluated. The data were analysed using the statistical software package R.

In addition to classifying the participants as a function of their specialisms in two groups (primary care and other specialisms), a second stage addressed gender, so enabling the opinions of the men to be compared with those of the women.

Figure 1. Percentage of doctors who gave their opinion on the ideal levels of vitamin D (measured as 25-hydroxycolecalciferol – 25-HCC)

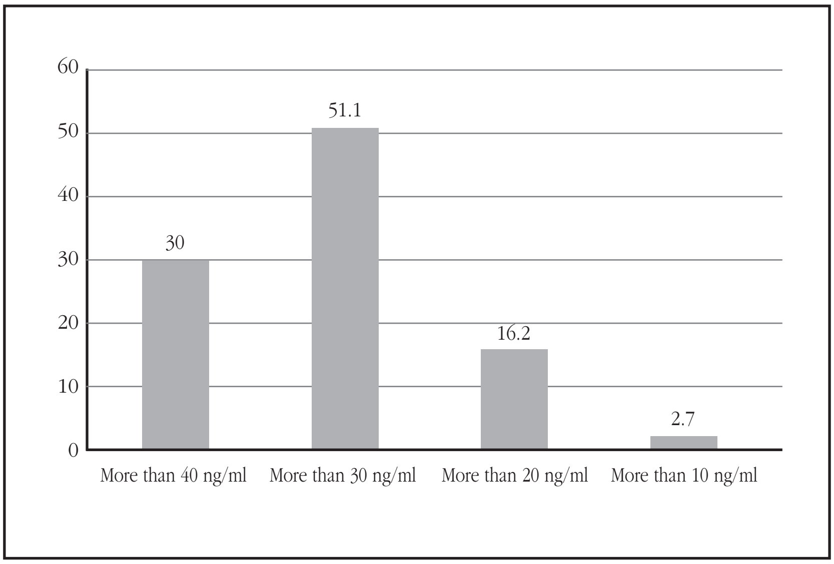
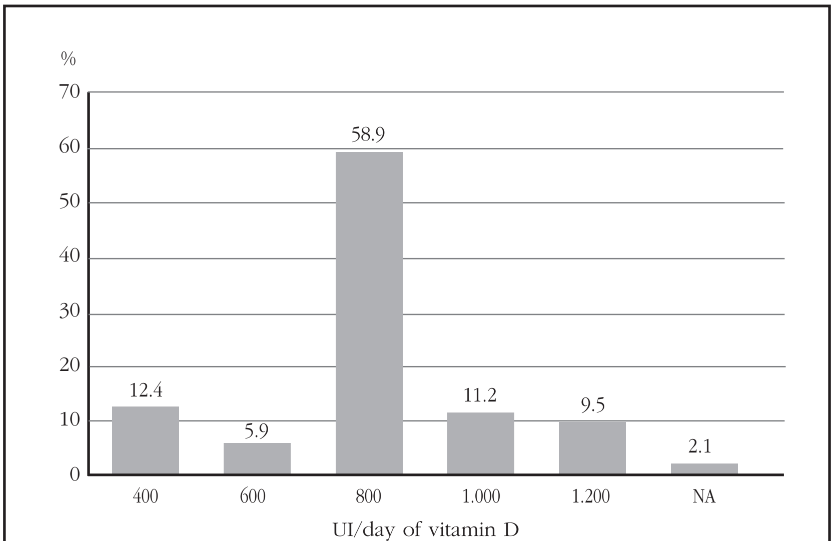


Figure 2. Ideal dose of vitamin D to be administered daily to patients according to the opinion of Spanish doctors



Results

1. Description of the participants in the study

A total of 777 doctors across Spain responded to the survey, 419 male (53.9%) and 358 (46.1%) female. The overall mean age was 46.6±8.9 years, with the males being older than the females (49.1±8.7 years vs 43.7±8.3 years, p<0.001).

Approximately half of the doctors, 377 (48.5%), worked in primary care. Of the remaining 400 (51.1%), who were hospital specialists, the most common specialisms were rheumatology (15.3%), traumatology (11.3%) and rehabilitation (9.5%).

Doctors from all 17 of the autonomous communities participated. Andalucia, with 98 doctors (12.6%) was the autonomous community with the highest rate of participation, followed by Catalonia with 82 doctors (10.6%). Cantabria, with 19 doctors, was the autonomous community which had the lowest number of responses. Figure 1 shows the results obtained when the doctors were asked what they considered to be the ideal levels of vitamin D, measured by its reserve metabolite, 25-hydroxyvitamin D (25-HCC). As may be observed, more than 80% of those surveyed (81.1%) were of the opinion that patients needed to have a value of 25-HCC higher than 30 ng/ml. While only 2.7% thought that this value should be greater than 10 ng/ml.

2. Results expressed as a function of the gender of the participants

In Table 1 are recorded the opinions of Spanish doctors regarding different aspects of vitamin D, expressed globally on the one hand, and as a function of gender on the other. Only 36% thought that the Spanish population in general had sufficient levels of vitamin D, and those who thought that patients attending their clinics had sufficient levels of vitamin D amounted to less than 30% (28.8%). There were no statistically significant differences in the these opinions as a function of the doctors' gender.

When asked where they thought vitamin D exerted it beneficial effects, almost 80% (79.8%) thought that this effect occurred both in the bone and in the musculo-skeletal and immune systems. Furthermore, 72.1% of the doctors surveyed thought that there was a relationship between levels of vitamin D and falls. Again, no statistically significant differences were observed in these opinions as a function of the gender of the doctors. With regard to the way vitamin D was obtained, the majority of Spanish doctors (86.5%), thought that all available means should be used, which included exposure to sun, dietary intake or by means of drugs. So, in the specific case of older people, a great proportion of the doctors (87.5%) were in favour of the administration of vitamin D supplements to this group.

Table 1. Opinion of Spanish doctors (as a percentage) regarding levels of vitamin D, according to gender

		Total N=777	Male N=419	Female N=358	P
Suitable levels of vitamin D in	Spanish town	36.9	38.4	35.2	0.353
	Own doctor's office	28.8	31.3	26.0	0.105
Place to vitamin D is beneficial	Bone (1)	3.6	3.6	3.6	0.876
	Musculoskeletal (2)	0.8	0.7	0.8	
	Immunologic	0.1	0	0.3	
	All previous	79.8	80.0	79.6	
	Only 1 and 2	15.7	15.8	15.6	
There is an association between vitamin D and falls	Yes	72.1	69.0	75.7	0.100
	No	15.7	17.9	13.1	
	No opinion	12.2	13.1	11.2	
Obtaining source vitamin D	Sun	4.0	3.6	4.5	0.787
	Diet	3.6	3.3	3.9	
	Drug	5.3	5.5	5.0	
	All previous	86.4	87.1	85.5	
	None of the above	0.8	0.5	1.1	
Should vitamin D administered to the elderly?	Yes	87.5	89.5	85.2	0.157
	No	7.2	6.4	8.1	
	No opinion	5.3	4.1	6.7	
Is substantiated the importance assigned to the vitamin D?	Correct	81.1	81.9	80.2	0.528
	Correct but disproportionate	11.7	12.1	11.2	
	It is a fallacy of the pharmaceutical industry	0.6	0.5	0.8	
	No opinion	6.6	5.5	7.8	

With regard to whether the current interest in vitamin D is correct, disproportionate, or is a fallacy of the pharmaceutical industry, 81.1% of those surveyed though that the interest was correct, and only 0.6% though that it was an industry fallacy. On this question, 6.6% of all the doctors did not express an opinion.

Finally, in terms of the dose of vitamin D which should be administered, it was observed that even though there is a wide variety of opinions, more than 80% of the doctors thought that it was necessary to administer 800 or more UI daily of vitamin D (Figure2).

3. Results expressed as a function of the specialisms of the doctors

Table 2 records the opinions of Spanish doctors regarding the same questions, but classified according to their specialisms, grouping on the one hand primary care doctors, and on the other, the other specialisms (traumatology, internal medicine, rehabilitation, rheumatology, endocrinology and gynaecology).

On this occasion there were statistically significant differences in the perceptions the primary care doctors had in comparison with the other specialists, with 40.8% having the view that the general population had adequate levels of vitamin D, as opposed to 33.2% of the other specialists (p=0.028). Concerning levels of vitamin D among patients attending their clinics, 34.7% of the primary care doctors thought that their patients had sufficient levels of vitamin D, as opposed to 23.2% in the other specialists (p=0.001).

When asked where they thought vitamin D exerted its beneficial effects, whether there was an association between vitamin D and falls, and finally, what they thought should be the source of vitamin D, the responses did not show any statistically significant differences between the primary care specialists and the other specialists.

However, a significant difference was found with respect to their opinions on whether they thought it necessary to administer vitamin D to older people, with 84.9% of the primary care doctors believing that it was, as opposed to 90% of those of other specialisms (p=0.004).

In terms of what would be the ideal dose of vitamin D to be administered daily to patients, in general less than 20% of doctors supported the idea of using doses lower than 800 UI/day. In Figure 2 it is observed that more than 80% of those surveyed thought that it was necessary to administer 800 UI/day or even more.

Table 2. Opinion of Spanish doctors (as a percentage) regarding levels of vitamin D, according to speciality

		Speciality		
		Primary Care N=377	Other N=400	P
Suitable levels of vitamin D in	Spanish town	40.8	33.2	0.028
	Own doctor's office	34.7	23.2	<0.001
Place to vitamin D is beneficial	Bone (1)	3.2	4.0	0.567
	Musculoskeletal (2)	1.1	0.5	
	Immunologic	0	0.2	
	All previous	78.8	80.8	
	Only 1 and 2	17.0	14.5	
There is an association between vitamin D and falls	Yes	72.1	72.0	0.864
	No	16.2	15.2	
	No opinion	11.7	12.8	
Obtaining source vitamin D	Sun	4.5	3.5	0.753
	Diet	3.7	3.5	
	Drug	4.5	6.0	
	All previous	86.7	86.0	
	None of the above	0.2	1.0	
Should vitamin D administered to the elderly?	Yes	84.9	90.0	0.004
	No	10.3	4.2	
	No opinion	4.8	5.8	
Is substantiated the importance assigned to the vitamin D?	Correct	76.9	85.0	0.018
	Correct but disproportionate	14.9	8.8	
	It is a fallacy of the pharmaceutical industry	1.1	0.2	
	No opinion	7.2	6.0	

Lastly, in Figure 3 the variability of the data with respect to opinions about vitamin D is observed as a function of the specialism of the doctors surveyed. The two axes used account for 74.9% of the variability of the data. The horizontal axis has the greater importance, accounting for 59.5% of the variability of the data. The second axis explains 15.4%.

In the multiple correspondence analysis those variables are introduced which show a significant association with the specialism (primary care/other specialisms). As can be seen, the profile of the primary care doctors differs from those of the other specialists in terms of their approach to treatment with vitamin D. The hospital specialists have a stronger conviction in relation to the importance of vitamin D and its administration to older people. More of them think that levels seen in both the patients in their clinics and in the general Spanish population are inadequate. There is an association between the opinion that levels are adequate in their clinics and that this might also apply in the Spanish population. The importance given to vitamin D being administered to older people is also associated with the belief that the importance they be given it is correct.

Discussion

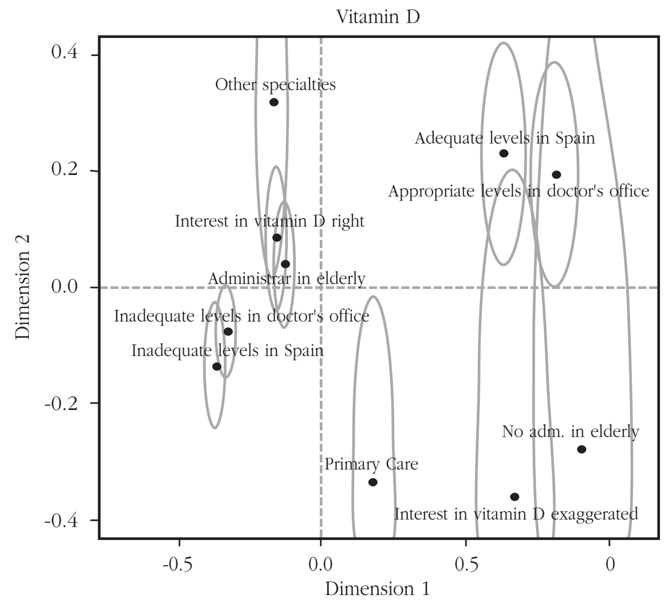
Interest in vitamin D has increased notably in recent years. We understand better its physiology and physiopathology, above all that related to the extra-bone aspects of this hormone[10-17].

The metabolite which determines the status of the reserves of vitamin D is 25-hydroxycolecalciferol (25-HCC). There is a consensus in recommending blood levels of vitamin D higher than 30 ng/mL of 25-HCC, so avoiding an increase in blood PTH and the development of secondary hyperparathyroidism[18-23]. A figure lower than 30 ng/mL is considered to be insufficient, while it has been agreed to establish vitamin D deficiency as a level of 25-HCC below 20 ng/mL[22]. The doctors surveyed knew of and agreed with these figures, with more than 80% of those surveyed (81.1%) giving the view that patients should have a value of 25-HCC higher than 30 ng/mL, as is seen in Figure 1. It is worth noting that up to 30% of the doctors thought that optimum levels were even higher, more than 40 ng/mL, which coincides with similar views of recognised and prestigious authors such as Professors Heaney or Holick[19,20,22].

When we compared the doctors' opinions on various topics related to vitamin D, we observed that there were no differences as a function of their gender. We obtained no statistically significant differences in their opinions in any of the survey questions. In general terms, the Spanish doctors thought that both the general Spanish population, as well as their patients, were deficient in vitamin D. In fact they thought that more than 63% of the population and 70% of their patients had low levels of vitamin D. This is precisely what has been reported in various series carried out in our country, both in the healthy population and in patients with different pathologies[24-28].

There is a widely-held opinion, in around 80% of those surveyed, regarding the beneficial effects of vitamin D in the bone, and in the musculo-skeletal and immune systems. Similarly, 72.1 % of the doctors thought that there was an association between vitamin D and falls, a fact that has been confirmed in various studies and meta-analyses[29-31].

Figure 3. Variability of data with respect to the opinions as a function of the specialism of the doctors surveyed



The horizontal axis has the greater importance, accounting for 59.5% of the variability of the data. The second axis explains 15.4%

Also, the vast majority of the doctors (87.5%) thought, independently of their gender, that it was necessary to administer vitamin D to older people, and more than 80% believed that the importance which is currently being given to vitamin D was justified. It is, therefore, interesting to highlight the fact that some studies have shown that is it precisely those Spanish patients affected by osteoporosis who received little vitamin D. Thus, in a telephone study it was confirmed that older people over 75 years of age took daily amounts of 120 UI of vitamin D, a quantity clearly insufficient for their needs[32]. In another study, carried out in younger Spanish women, of between 16 and 60 years of age, it was confirmed that 72.6% of them did not achieve the recommended intake of either calcium or vitamin D[33].

In another section of our work we compared the opinions of the doctors as a function of whether they were primary care specialists or specialists of another discipline, but related to osteoporosis. We found statistically significant differences in 3 questions. Thus, 40.8% of the primary care doctors considered that the Spanish population in general had adequate levels of vitamin D, while 33.2% of the doctors of the other specialisms had this view (p=0.028). Similarly, 34.7% of the primary care doctors believed that the patients in their clinics had adequate levels of vitamin D, with 23.2% of the other specialists believing this (p<0.001). There were also statistically significant differences in the opinions they had as to whether it is necessary or not to administer vitamin D to older people, with the proportion of doctors who believed that it is necessary higher among the other specialists than among the primary care specialists (90% as against 84.9%, p=0.004).

The opinions of Spanish doctors coincide with those published for doctors from New Zealand, where a survey carried out in 1,089 primary care doctors came to practically the same conclusions as ours[34].

In conclusion, Spanish doctors are highly aware of vitamin D and its beneficial effects both in bone and for the whole organism, and their opinions coincide in general terms with the position documents published on this issue.

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