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Vitamin D deficiency in Spain. Reality or myth?

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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 35°N 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	75±85	197	15±8	31% 79%	10 20	RIA
	(Residence)			83±7	146	17±7	32% 91%	10 20	
Quesada (38)	Osteoporotic women PM Not Treated	All Spain 43-28º	Final Spring	71±5	190	22±10	11% 44% 76%	10 20 30	HPLC
	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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