Díaz Curiel M, Arboiro Pinel RM
Enfermedades Metabólicas Óseas - Fundación Jiménez Díaz - Grupo Quirón-Salud - Madrid (España)

Prevalence of hypovitaminosis D in our environment

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Correspondence: Manuel Díaz Curiel - Fundación Jiménez Díaz - Avda. Reyes Católicos, 2 - 28040 Madrid (Spain)
e-mail: mdcuriel@fjd.es

Introduction

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

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

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

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

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

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

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

Daily vitamin D requirements

According to the United Nations Food and Agriculture Organization (FAO) recommendations[6], the minimum requirements for vitamin D would be 200 IU/day (5 µg) in childhood and adults up to 50 years of age, 400 IU (10 µg) in people aged 51 to 65 years and 600 IU/day (15 µg) in those over 65 years. In Spain, the recommended intake in people aged 65 and over is practically the same, of 10-15 µg/day. According to new evidence suggesting that previous recommendations are conservative, the US Department of Health now counts as a minimum requirement for vitamin D 400 IU/day (10 µg), which should be increased to 1000 IU/day (25 µg) People older than 70 years or those with dark skin and limited sun exposure (institutionalized)[7]. The Institute of Medicine (IOM) and the Endocrinology Society's recommended doses are listed in Table 1.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 2. Prevalence of vitamin D deficiency in Spain

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

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

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

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

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

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

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

Bibliography

1. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357:266-81.
2. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001;22:477-501.
3. Bischoff-Ferrari HA, Dawson-hughes B, Willet WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA. 2004;291: 1999-2006.
4. Quesada Gómez JM, Alonso J, Bouillon R. Vitamin D insufficiency as a determinant of hip fractures. Osteoporos Int. 1996;6 Suppl 3:42-7.
5. Bischoff-Ferrari HA, Giovannucci E, Willett WC. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006;84:18-28.
6. Human vitamin and mineral requirements. Report of a joint FAO/WHO expert consultation. Bangkok, Thailand. Rome: World Health Organization, Food and Agriculture Organization of the United Nations, 2002. Chapter 8.
7. Department of Health and Human Services and the Department of Agriculture. Dietary guidelines for Americans 2005. Disponible en: http://www.healthierus.gov/dietaryguidelines/index.html.
8. Lips P, Chapuy MC, Dawson-Hughes B, Pols HA, Holick MF. An international comparison of serum 25-hydroxyvitamin D measurements. Osteoporos Int. 1999;11:394-7.
9. Lensmeyer GL, Wiebe DA, Binkley N, Drezner MK. HPLC method for 25-hydroxyvitamin D measurement: comparison with contemporary assays. Clin Chem. 2006;52:1120-6.
10. Binkley N, Krueger D, Cowgill C, Plum L, Lake E, Hansen KE, et al. Assay variation confounds hypovitaminosis D diagnosis: a call for standardization. J Clin Endocrinol Metab. 2003;89:3152-7.
11. Binkley N, Krueger D, Gemar D. Correlation among 25-Hydroxy-Vitamin D Assays J Clin Endocrinol Metab. 2008;89:3152-7.
12 Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int. 2005;16:713-6.
13. Roux C, Bischoff-Ferrari HA, Papapoulos SE, de Papp AE, West JA, Bouillon R. New insights into the role of vitamin D and calcium in osteoporosis management: an expert roundtable discussion. Curr Med Res Opin. 2008;24:1363-70.
14. Quesada-Gómez JM and Díaz-Curiel M. Vitamin D Deficiency and consequences for the health of people in Mediterranean Countries from: Nutrition and Health: Vitamin D. Edited by: M.F. Holick, DOI 10.1007/978-1-60327-303-9_23, Springer Science+Business Media, 2010, Totowa, NJ, USA pag:453-67.
15. van der Wielen RP, Lowik MR, van den Berg H, de Groot LC, Haller J, Moreiras O, et al. Serum vitamin D concentrations among elderly people in Europe. Lancet. 1995;346:207-10.
16. McKenna MJ. Differences in vitamin D status between countries in young adults and the elderly. Am J Med. 1992;93:69-77.
17. Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, et al. The SUVIMAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Arch Intern Med. 2004;164:2335-42.
18. González Padilla E, Soria López A, González Rodríguez E, García Santana S, Mirallave Pescador A, Grova Marco M, et al. Elevada prevalencia de hipovitaminosis D en los estudiantes de medicina de Gran Canaria, Islas Canarias (España). Endocrinol Nutr. 2011;58(6):267-73.
19. Quesada JM, Jans I, Benito P, et al. Vitamin D status of

elderly people in Spain. Age and Ageing. 1989;18:392-7.
20. Mata-Granados JM, Luque de Castro MD Quesada JM. Inappropriate serum levels of retinol, tocopherol, 25 hydroxyvitamin D3 and 24,25 dihydroxy vitamin D3 levels in healthy Spanish adults: simultaneous assessment by HPLC. Clinical Biochemistry. 2008;41:676-80.
21. Mezquita-Raya, P, Muñoz-Torres, M, Luna, JD, Luna V, López-Rodríguez F, Torres-Vela E, et al. Relation between vitamin D insufficiency, bone density, and bone metabolism in healthy postmenopausal women. J Bone Miner Res. 2001;16:1408-15.
22. Aguado P, del Campo MT, Garces M, González-Casaús ML, Bernad M, Gijón-Baños J, et al. Low vitamin D levels in outpatient postmenopausal women from a rheumatology clinic in Madrid, Spain: their relationship with bone mineral density. Osteoporos Int. 2000;11:739-44.
23. Larrosa M, Gratacòs J, Vaqueiro M, Prat M, Campos F, Roqué M, et al. Prevalencia de hipovitaminosis D en una población anciana institucionalizada. Valoración del tratamiento sustitutivo. Med Clin (Barc). 2001;117:611-4.
24. Vaqueiro M, Baré ML, Antón E. Valoración del umbral óptimo de vitamina D en la población mayor de 64 años. Med Clin (Barc). 2006;127:648-50.
25. González-Clemente JM, Martínez-Osaba MJ, Miñarro A, Delgado MP, Mauricio D, Ribera F, et al. Hipovitaminosis D: alta prevalencia en ancianos de Barcelona atendidos ambulatoriamente. Factores asociados. Med Clin (Barc). 1999;113:641-5.
26. Gómez-Alonso C, Naves-Díaz ML, Fernández-Martín JL, Díaz-López JB, Fernández-Coto MT, Cannata-Andía JB, et al. Vitamin D status and secondary hyperparathyroidism: the importance of 25-hydroxyvitamin D cut-off levels. Kidney International. 2003;63:S44-S48.
27. Docio, S, Riancho JA, Pérez A, Olmos JM, Amado JA, González-Macías J, et al. Seasonal deficiency of vitamin D in children: a potential target for osteoporosis-preventing strategies? J Bone Miner Res. 1998;13:544-8.
28. Perez Castrillón JL, Niño Martin V. Niveles de vitamina D en población mayor de 65 años. Rev Esp Enf Metab Oseas. 2008;17:1-4.
29. Quesada Gomez JM, Díaz Curiel M, Sosa Henríquez M, Malouf-Sierra J, Nogués-Solan X, Gómez-Alonso C, et al. Low calcium intake and insufficient serum vitamin D status in treated and non-treated postmenopausal osteoporotic women in Spain. J Steroid Biochem Mol Biol. 2013;136:175-7.
30. Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosistherapy. J Clin Endocrinol Metab. 2005;90:3215-24.
31. Holick MF. High Prevalence of Vitamin D Inadequacy and Implications for Health Mayo Clin Proc. 2006;81:353-73.
32. Quesada Gómez JM, Blanch Rubio J, Díaz Curiel M, Díez Pérez A. Calcium Citrate and Vitamin D in the Treatment of Osteoporosis. Clin Drug Investig. 2011;31(5):1-14.
33. Sosa Henríquez M, Gómez de Tejada Romero MJ, Recker RR, Cannata Andía JB, Del Pino Montes J. Díaz Curiel M, et al. Papel del calcio y la vitamina D en el tratamiento de la osteoporosis. Rev Osteoporos Metab Miner. 2010;2:61-75.
34. Giovannucci E, Liu Y, Hollis BW Rimm EB. Independent Association of Low Serum 25-Hydroxyvitamin D and risk of myocardial infarction in men. Arch Intern Med. 2008;168:1174-80.
35. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, et al. 25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D levels with all-cause and cardiovascular mortality. Arch Intern Med. 2008;168:1340-9.
36. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Inter Med. 2007;167:1730-7.
37. Díaz Curiel M. Recomendaciones para una ingesta adecuada de calcio y vitamina D en la población española. Disponible en: htpp://ib02.4doctors.science/vitamina-d/2016.