Inadequate levels of D: not a D-elicious perspective

Quesada Gómez JM, Navarro Valverde C

Unidad de Metabolismo Mineral - Servicio de Endocrinología y Nutrición - Hospital Universitario Reina Sofía de Córdoba - Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC) - RETICEF - Córdoba

Correspondence: José Manuel Quesada Gómez - Servicio de Endocrinología y Nutrición - IMIBIC - Hopital Universitario Reina Sofía - Avda. Menendez Pidal, s/n - 14004 Córdoba (Spain)
e-mail: jmquesada@uco.es

In the last few decades clinical research in large population studies has revealed the high prevalence of insufficient levels of vitamin D across the globe[1], which, combined with its effects on bone, the muscular-skeletal system, innate and acquired immunity, the cardiovascular system, and the development and function of cells, makes this a first order problem in public health. In fact, low levels of vitamin D are associated significantly with all the causes of morbimortality[2].

The description in this number of the Review of Osteoporosis and Mineral Metabolism of inadequate levels of vitamin D in patients with spinal injury in Las Palmas de Gran Canaria, a city in Spain which, due to its climate, is a paradigm for the ease of obtaining vitamin D_3 by cutaneous synthesis throughout the year, again challenges us[3]. Due to its high prevalence, its ease of detection, its associated adverse consequences, and its simple, cheap and efficacious means of treatment, vitamin D insufficiency should be an urgent and immediate priority for health services in general and for every medic, irrespective of their specialism.

Blood levels of 25 hydroxyvitamin D are considered to be a marker for the status of vitamin D in the body, including endogenous synthesis from to exposure to the sun, dietary ingestion of foods with or without supplements or drug treatments[4].

However, blood levels of 25 hydroxyvitamin D are not strictly regulated, no method for their quantification is perfect, with a great variability between laboratories, even the most properly checked, which, therefore, makes the definition of normality difficult[5]. In fact those methods which do not use high pressure separation chromatography do not distinguish between the metabolites of vitamin D2 or vitamin D_3[6]. Although in Spain this is not a problem since vitamin D_2 is not used in normal clinical practice, many metabolites of vitamin D are quantified as 25 hydroxyvitamin D, 24,25 dihydroxyvitamin D_3, its epimer C-3, or sulphated forms, etc., and this problem persists even when using high pressure liquid chromatography separation and mass measurement[7].

Nevertheless, while they need to improve substantially, the methods available in our normal practice of treatment or research are adequate enough and should be used more in our clinical practice for the diagnosis and follow up of treatment.

So, in the face of the variability of the different laboratories and different testing methods, the controversy regarding cut off points for normal blood levels of 25 hydroxyvitamin D proposed by different scientific societies, above 20 ng/ml for the Institute of Medicine[3] and above 30 ng/ml for the International Osteoporosis Foundation (IOF)[8], supported by the recommendation of the Endocrinology Society in the US[9], is a byzantine argument, and only one way of approaching the problem.

In any case, we could agree that the objective should be to achieve blood levels higher than 20 ng/ml as a bare minimum, and preferably higher than 30 ng/ml. So, if our patients have levels of 25 hydroxyvitamin D above 30 ng/ml we will be in agreement with existing recommendations .

Blood levels higher than 30 ng/ml will foster proper bone health and an effective response to antiresorptive treatments for osteoporosis[10,11], in addition to its more than likely beneficial impact on practically all the body's organs and systems[2,12].

Defining the maximum values is more critical. Although for some time it has been proposed that high values of vitamin D, except above toxic values, would not be damaging, there is currently

an open debate as to whether high levels of 25 hydroxyvitamin D may be associated with risk of cardiovascular death, or death by other causes[13]. Therefore, some authors have proposed a recommended cut off point blood levels of 25 hydroxyvitamin D of 60 to 70 ng/ml quantified by the usual measurement methods, which are values present in the Summer in agricultural workers, fishermen, lifeguards at the beach or swimming pool etc., who have a high exposure to ultraviolet rays and an intense epidermic production of vitamin D_3, but who never exhibit toxicity[3].

In the treatment of vitamin D insufficiency/deficiency, after the optimisation of 25 hydroxyvitamin D levels within the range of 30 to 70 ng/ml, we should not forget its maintenance once this range is reached.

To achieve this objective, in Spain we may use vitamin D_3 or 25 hydroxyvitamin D_3 (calcifediol), which means that we must remember that contra to what we have come to believe for many years, these metabolites are not equipotent, but that the latter is approximately three times more powerful than the former[14,15].

Finally, we would like to stress that, regarding the already recognised high prevalence in Spain of insufficient levels of vitamin D in all sections of the population studied[16,17], which is always greatest in patients with conventional risk factors for having low blood levels of vitamin D, the increase in obesity and poverty[18] will presumably make the current critical situation worse in the coming years.

Unfortunately, current public health policies do not auger well for effective change in the face of this serious problem, which is why we must end our comments with a quote from Robert Heaney, ending one of his interventions at the VI Symposium of SEIOMM held in Granada in October 1997 on the problem of vitamin D deficiency: "....we have the evidence; but when will we see the action.".

Bibliography

1. Van Schoor NM, Lips P. Worldwide vitamin D status. Best Pract Res Clin Endocrinol Metab 2011;25:671-80.
2. Norman AW, Bouillon R. Vitamin D nutritional policy needs a vision for the future. Exp Biol Med 2010;235:1034-45.
3. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96:53-8.
4. Rivero González L, Méndez Suárez JL, Miranda Calderín G, Bárbara Bataller E, Sánchez Enríquez J, Sosa Henríquez M. Prevalencia de hipovitaminosis D e hiperparatiroidismo secundario en la Unidad de Lesionados Medulares de Gran Canaria. Estudio preliminar. Rev Osteoporos Metab Miner 2013;5;2:67-72.
5. Binkley N, Krueger DC, Morgan S, Wiebe D. Current status of clinical 25-hydroxyvitamin D measurement: an assessment of between-laboratory agreement. Clin Chim Acta 2010;411:1976-82.
6. Thienpont LM, Stepman HC, Vesper HW. Standardization of measurements of 25-hydroxyvitamin D3 and D2. Scand J Clin Lab Invest Suppl 2012;243:41-9.
7. Lensmeyer G, Poquette M, Wiebe D, Binkley N.The C-3 epimer of 25-hydroxyvitamin D(3) is present in adult serum. J Clin Endocrinol Metab 2012;97:163-8.
8. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int 2010;21:1151-4.
9. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30.
10. Díez-Pérez A, Olmos JM, Nogués X, Sosa M, Díaz-Curiel M, Pérez-Castrillón JL, et al. Risk factors for prediction of inadequate response to antiresorptives. J Bone Miner Res 2012;27:817-24.
11. Peris P, Martínez-Ferrer A, Monegal A, Martínez de Osaba MJ, Muxi A, Guañabens N. 25 hydroxyvitamin D serum levels influence adequate response to bisphosphonate treatment in postmenopausal osteoporosis. Bone 2012;51:54-8.
12. Bouillon R, Bischoff-Ferrari H, Willett W. Vitamin D and health: perspectives from mice and man. J Bone Min Res 2008;23:974-9.
13. Durup D, Jørgensen HL, Christensen J, Schwarz P, Heegaard AM, Lind B. A reverse J-shaped association of all-cause mortality with serum 25-hydroxyvitamin D in general practice: the CopD study. J Clin Endocrinol Metab 2012;97:2644-52.
14. Burild A, Lauridsen L, Jakobsen J. Bioavailability and storage of oral 25-hydroxy D3 and D3 in relation to plasma 25 hydroxy-D3. Abstract book. Sesion XIV, pag 31. 16th Vitamin D Workshop. June 11-14th, 2013. San Francisco, California (USA).
15. Bischoff-Ferrari HA, Dawson-Hughes B, Stöcklin E, Sidelnikov E, Willett WC, Edel JO, et al. Oral supplementation with 25(OH)D3 versus vitamin D3: effects on 25(OH)D levels, lower extremity function, blood pressure, and markers of innate immunity. J Bone Miner Res 2012;27:160-9.
16.- Quesada Gómez JM. Insuficiencia de calcifediol. Implicaciones para la salud. Drugs Today 2009;45:1-31.
17. Quesada-Gómez JM, Díaz-Curiel M, Sosa-Henríquez M, Malouf-Sierra J, Nogués-Solán X, Gómez-Alonso C, et al. Low calcium intake and inadequate vitamin D status in postmenopausal osteoporotic women. J Steroid Biochem Mol Biol 2013;136:175-7.
18. Navarro M del C, Saavedra P, Jódar E, Gómez de Tejada MJ, Mirallave A, Sosa M. Osteoporosis and metabolic syndrome according to socio-economic status, contribution of PTH, vitamin D and body weight: The Canarian Osteoporosis Poverty Study (COPS). Clin Endocrinol (Oxf) 2013;78:681-6.