The paradox of vitamin D deficiency in sunny regions, in young people or in osteoporotic patients treated with vitamin D, could be explained by common genetic variations. Have we found the Rosetta Stone of this apparent contradiction?

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The "epidemics" of rickets which devastated humanity appeared to have ended with the discovery of vitamin D at the start of the last century. However, severe and prolonged deficiency of vitamin D, with clinical manifestations of rickets and osteomalacia is rising again, above all in ethnic minorities, in Western countries[1].

At present, vitamin D deficiency constitutes a pandemic which affects more than half the population of the whole world[2], and is a significant factor in age-related loss of bone and muscle mass , falls and fractures[2,3].

In addition, in developed societies, vitamin D deficiency is associated with a higher risk of degenerative and chronic diseases, such as autoimmune diseases: diabetes mellitus, multiple schlerosis; cancer: colon and breast; infectious diseases, such as tuberculosis and seasonal flu; cardiovascular diseases, cardiac insufficiency, hypertension, and acute myocardial infarction, and even a higher risk of cardiovascular death, or death by any other cause[2,3]. Although, the great majority of the studies are associative and not interventional, the biological plausability generated by knowledge of non-hormonal actions, intracrines and paracrines of the endocrine system of vitamin D, give consistency to the potential problem which, for the public health system, a deficiency or insufficiency of vitamin D may constitute[3].

"Vitamin D" in circulation is made up of vitamin D_3 and D_2, the first mainly acquired by subcutaneous formation by ultraviolet B radiation, and in smaller qualities by ingesting the few natural dietary sources which contain it, as well as fortified foods or supplements, the second solely from these last two sources[4]. Once acquired, the vitamin D, and later its metabolites, are transported by means of a vitamin D transporter protein, also known as "gc-globulin (group-specific component)", which also participates in transport within cells[2,3].

In the liver, by the action of, above all, the microsomal enzyme CYP2R1, the "vitamin D" is converted in to 25 hydroxyvitamin D (calcifediol), the most stable and abundant metabolite, biomarker for the status of the organism of vitamin D[2,3].

An adequate blood level of calcifediol is critical for human health because it is a substrate for the formation of 1-25-dihydroxyvitamin D_3 (1-$25(OH)_2D_3$ or calcitriol), through the action of the enzyme CYP27B1-hydroxylase in the kidneys. This enzyme is stimulated by the parathyroid hormone and inhibited by phosphorus and by the fibroblastic growth hormone 23 (FGF23), produced by the osteoblasts and osteocytes.

Calcitriol is a key hormone in the homeostasis of bone and calcium which controls the regulation

of the transcription of the genes involved by binding them to a high affinity receptor (HAR) in the classic target organs: intestine, kidneys, bone (osteoblasts-osteocytes)[2,3].

Calcitriol is also synthesised in other organs and tissues, such as muscle, heart, brain, breast, colon, pancreas, prostate, skin, immune system. Those which possess the enzyme CYP27B1-hydroxylase activator for the synthesis of calcitriol and the inactivator enzyme (24-hydroxylase, CYP24A1), which favours its catabolism, and the HAR receptor.

Calcitriol regulates approximately 3% of the human genome, with three generic effects: regulation of hormonal secretion, inhibiting rennin, stimulating the secretion of insulin and its action; it regulates the growth and proliferation of cells and modulates acquired and innate immunity[2].

At present, there is a significant controversy regarding three aspects related to calcifediol. Its quantification; the establishment of minimum adequate, and optimum, levels; and the apparent paradox of vitamin D deficiency in sunny regions, in young people from these regions, and in osteoporotic patients, treated, or not, with vitamin D.

Despite its importance, the measurement of 25(OH)D has always been problematic and even now generates concerns[5]. In fact, until relatively recently it was restricted to research centres, which used methods based on protein competition or high resolution liquid chromatography (HRLC). At the end of the last century other methods were validated for use in care, such as RIA, ELISA or chemiluminescence. The spread of availability of the CLAR technologies, coupled in tandem with mass spectrometry (LC-MS/MS) has improved the performance of the measurement of 25(OH)D and is allowing the standardisation of the result obtained with conventional techniques[6].

Even nowadays, there is no unanimous consensus on the recommended minimum blood levels of 25(OH)D to ensure bone health, and other health objectives mediated through vitamin D. Last October, in Bruges, Belgium, during the 14th "Workshop" on vitamin D a round table was convened to reach a consensus on this matter[7].

The debate became focussed around two options, the European one, led by Roger Bouillon and Paul Lips, who proposed minimum blood levels of calcifediol of 20 ng/ml, and the American, defended in presentations by Robert Heaney and Reinold Vieth, both proposing levels of 25(OH)D higher than 40 ng/ml[7], without an agreement being reached. In any case, these levels should always be higher than 20ng/ml, which would suppose average blood levels in the population to be higher than 30 ng/ml. Surprisingly, a target for minimum levels was proposed, but not one for maximum blood levels.

The upper limit for vitamin D in the blood is also not clearly established. But in populations highly exposed to the sun, blood levels of 25(OH)D are not usually found above 60 ng/mL, and no complications of hypercalcaemia or hypercalciuria are found[8]. Therefore, reaching blood levels of calcidiol of between 20 and 30 (higher than 20 in any case) and 60 ng/mL, seems recommendable from a physiological point of view. Surprisingly, even in a country as sunny as Spain, and independently of the region we consider, the insufficiency and even the clear deficiency in vitamin D, is that described in scientific publications[9,10,11], and that which we find in normal clinical practice. On the other hand, in patients treated with calcium and vitamin D in postmenopausal osteoporosis there is evidence of insufficiencies in calcium and vitamin D in more than 60% of the population, both in Spain[11] as well as in other countries[12,13].

In this edition of the Review of Osteoporosis and Mineral Metabolism[14] a higher prevalence of insufficiency or deficiency in vitamin D is described in a group of medical students from Las Palmas de Gran Canaria, which confirm the data found in young junior doctors (Residentes) who began their specialisation at the 12th October Hospital in Madrid[15]. These data coincide with the descriptions of young people in countries or geographical regions which are sunny and have a good climate, such as Hawaii[16], or of colder and less sunny regions[17].

These descriptions and observations of low levels of vitamin D even in situations favourable to finding adequate levels, produce great perplexity among researchers and medical practitioners, because, at least theoretically, exposure to sunlight or a sufficient intake of vitamin D should be enough to maintain the status of adequate vitamin D.

We know that personal habits and socio-cultural factors, which can modify the diet and exposure to sun, are the main determinants of the availability of vitamin D in the blood. The concentration of 25(OH)D is higher in summer and autumn, and lower in spring and winter[18]. However, only a quarter of the variability in blood levels of 25(OH)D can be attributed to the season, latitude and intake of vitamin D[19,20]. Association studies of families and twins suggested that genetic factors contributed the most to the individual variability observed, with more than 50% of this variability being inherited[21]. In fact some rare Mendelian alterations, such as the Smith-Lemli-Optiz syndrome are associated with vitamin D deficiency[22].

Almost at the same time that this edition of the Review of Osteoporosis and Mineral Metabolism 14 published the apparent contradiction of being young, knowing the importance of taking sun and living in a sunny region of Spain, and having low levels of vitamin D, Wang et al. in The Lancet, give a possible explanation[23]. By means of a large consortium of experts ("SUNLIGHT consortium"), a study of some 30,00 persons in five selected epidemiological cohorts, which were then increase to 15, stated that at least 3 or 4 genes contribute to the variability in concentration of 25(OH)D in the blood[23].

The genes involved code for three key enzymes in the metabolism of vitamin D: 7-dehydro-

cholesterol (7-DHC), reductase (responsible for the availability of 7-DHC in the skin); hepatic 25-hydroxylase CYP2R1 (involved in the conversion of vitamin D to 25-hydroxyvitamin D) and CYP24A1 (key enzyme in the catabolism of vitamin D). In addition, the GC gene which codes for the vitamin D transporter protein. The polymorphisms in GC had the greatest effect on the blood concentration of vitamin D[24].

The authors propose that those patient found in the higher quartile of a "score" constructed with those genotypes studied multiply by two their risk of having vitamin D insufficiency.

This finding could constitute the Rosetta Stone to start deciphering the hieroglyphics of the variability in blood concentrations of 25(OH)D in patients who, according to environmental factors, should have high levels and "surprisingly" have low levels. If confirmed, it would help us to understand the "inexplicable" variations in the corporal status of vitamin D cited earlier, and would demonstrate that some polymorphisms could protect or accelerate the step to deficiency or insufficiency in vitamin D. Posing the following question: do these genes modify the response to supplementation with vitamin D?, the answer has important pharmacological or nutrigenomic implications.

In any case, the battle against vitamin D deficiency continues, and while we know, in depth, the mechanisms involved, we should propose as an unrenounceable public health objective, the correction of vitamin D deficiency, from infancy and throughout life, to prevent its impact on bone and to achieve other health objectives, and in osteoporotic women treated with anticatabolic drugs, to optimise their therapeutic response[25].

Bibliography

1. Prentice A, Vitamin D deficiency: a global perspective, Nutr Rev 2008;66:153-64.
2. Holick MF. Vitamin D deficiency, N Engl J Med 2007; 357:266-81.
3. Bouillon R, Bischoff-Ferrari H, Willett W. Vitamin D and health: perspectives from mice and man. J Bone Min Res 2008;23:974-9.
4. Holick MF, Biancuzzo RM, Chen TC, Klein EK, Young A, Bibuld D, et al. Vitamin D_2 is as effective as vitamin D_3 in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab 2008;93: 677-81.
5. Carter GD, Carter R, Jones JJB. How accurate are assays for 25-hydroxyvitamin D? Data from the international vitamin D External Quality Assessment Scheme. Clin Chem 2004;50:2195-7.
6. Binkley N, Krueger D, Gemar D, Drezner MK. Correlation among 25-Hydroxy-Vitamin D Assays J Clin Endocrinol Metab 2008;89:3152-7.
7. Henry HL, Bouillon R, Norman AW, Gallagher JC, Lips P, Heaney RP, et al. 14th Vitamin D Workshop consensus on vitamin D nutritional guidelines. J Steroid Biochem Mol Biol In Press, Corrected Proof, Available online 24 May 2010.
8. Barger-Lux MJ, Heaney RP. Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. J Clin Endocrinol Metab 2002; 87:4952-6.
9. Quesada Gómez JM. Insuficiencia de calcifediol. Implicaciones para la salud. Drugs today. 2009;45:1-31.
10. Quesada Gómez JM, Diaz Curiel JM. Vitamin D deficiency consequences for the health of people in Mediterranean countries en vitamin D. Physiology, Molecular Biology, and Clinical Applications. Holick, Michael F. (Ed.) 2a ed. 2010, pp 453-68.
11. Quesada Gómez JM, Mata Granados JM, Delgadillo J, Ramírez R. Low calcium intake and insufficient serum vitamin D status in treated and non-treated postmenopausal osteoporotic women in Spain. J Bone Miner Metab 2007;22:S309.
12. 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 osteoporosis therapy. J Clin Endocrinol Metab. 2005;90:3215-24.
13. Lips P. Vitamin D status and nutrition in Europe and Asia. J Steroid Biochem Mol Biol 2007;103:620-5.
14. Groba Marco MV, Mirallave Pescador A, González Rodríguez E, García Santana S, González Padilla E, Saavedra Santana P, et al. Factores relacionados con insuficiencia de Vitamina D en estudiantes de Medicina de Gran Canaria. Rev Osteoporos Metab Miner 2010;2;2:11-8.
15. Calatayud M, Jodar E, Sánchez R, Guadalix S, Hawkins F. Prevalencia de concentraciones deficientes e insuficientes de vitamina D en una población joven y sana. Endocrinol Nutr 2009;56:164-9.
16. Binkley N, Novotny R, Krueger D, Kawahara T, Daida YG, Lensmeyer G, et al. Low vitamin D status despite abundant sun exposure. J Clin Endocrinol Metab 2007; 92:2130-5.
17. Haney EM, Stadler D, Bliziotes MM. Vitamin D insufficiency in Internal Medicine Residents. Calcif Tissue Int 2005;76:11-6.
18. Livshits G, Karasik D, Seibel MJ. Statistical genetic analysis of plasma levels of vitamin D: familial study. Ann Hum Genet 1999;63:429-39.
19. Shea MK, Benjamin EJ, Dupuis J, Massaro JM, Jacques PF, Dágostino RB, et al. Genetic and non-genetic correlates of vitamins K and D. Eur J Clin Nutr 2009; 63:458-64.
20. Hunter D, De Lange M, Snieder H, MacGregor AJ, Swaminathan R, Thakker RV, et al. Genetic contribution to bone metabolism, calcium excretion, and vitamin D and parathyroid hormone regulation. J Bone Miner Res 2001;16:371-8.
21. Lauridsen AL, Vestergaard P, Hermann AP, Brot C, Heickendorff L, Mosekilde L, et al. Plasma concentrations of 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D are related to the phenotype of Gc (vitamin D-binding protein): a cross-sectional study on 595 early postmenopausal women. Calcif Tissue Int 2005; 77:15-22.
22. Rossi M, Federico G, Corso G, Parenti G, Battagliese A, Frascogna AR, et al. Vitamin D status in patients affected by Smith-Lemli-Opitz syndrome. J Inherit Metab Dis 2005;28:69-80.
23. Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet 2010; published online June 10. DOI:10.1016/S0140-6736(10)60588-0.
24. Fu L, Yun F, Oczak M, Wong BY, Vieth R, Cole DE. Common genetic variants of the vitamin D binding protein (DBP) predict differences in response of serum 25-hydroxyvitamin D [25(OH)D] to vitamin D supplementation. Clin Biochem 2009;42:1174-7.
25. Adami S, Giannini S, Bianchi G, Sinigaglia L, Di Munno O, Fiore CE, et al. Vitamin D status and response to treatment in postmenopausal osteoporosis. Osteoporos Int. 2009;20:239-44.