Vitamin D deficiency: are we identifying it properly?

Martínez Díaz-Guerra G[1], Aramendi Ramos M[2]

1 Servicio de Endocrinología y Nutrición - Hospital Universitario 12 de Octubre - Universidad Complutense de Madrid (España)

2 Unidad de Hormonas y Marcadores Tumorales - Laboratorio de Bioquímica - Hospital Universitario 12 de Octubre - Madrid (España)

e-mail: guillermo.martinez@salud.madrid.org

Subclinical deficiency of vitamin D or vitamin D deficiency is prevalent throughout the world, and there is great variability depending on the geographic region, genetic factors and lifestyle considerations.

Moreover, researchers now believe that serum 25-hydroxyvitamin D (25OHD) levels are the best indicator of vitamin D, although there are methodological issues that limit comparability between studies and how to establish deficiency cutoffs.

There are several criteria to establish the optimal level of 25OHD, which include the degree of maximal suppression of PTH, the intestinal absorption of mediated calcium $1,25(OH)_2$ vitamin D or reduction of fractures. Regarding the former, several studies have analyzed 25OHD concentration required for maximum suppression of PTH and offer variable results. This has led some researchers and scientific entities to recommend 25OHD levels above 20 ng/ml (Institute of Medicine, IOM) while others advise over 30 ng/ml (Endocrine Society, International Osteoporosis Foundation). The application variable for these recommendations has generated considerable confusion in clinical practice.

The article by López-Ramiro et al.[1] investigates 25OHD levels and PTH serum in 4,063 patients with a mean age of 60.6 years (70% women), and analyzed by ROC curves 25OHD value that allows us to predict optimal sensitivity and specificity to a value of high PTH (>70 pg/ml). In both cases automated methods used well-standardized electrochemiluminescence, especially in the case of 25OHD, wherein the method is validated against reference technique (liquid chromatography/mass spectrometry tandem, LC-MS/MS). The study's most important conclusion is that, to avoid inducing secondary hyperparathyroidism, 25OHD levels should be higher than 24 ng/ml. Strikingly, less than half of patients with low 25OHD levels according to the cutoff point used by the authors presented secondary hyperparathyroidism. This was even lower (24%) in the group of younger patients (18-40 years). Although the patients' clinical characteristics are not detailed in the study (concomitant diseases, or if they received treatment with vitamin D, etc), these data are relevant in our view. They confirm what other authors have already noted: 1) although the general recommendation is that the desirable range for 25OHD is 20-40 ng/ml, somewhat lower levels (15-20 ng/ml) may be sufficient in some cases, and 2) 25OHD determination should be reserved for patients who are considered at risk of deficiency because of their age, lifestyle or concomitant[2] diseases.

Moreover, the authors point out the importance of using a method quantification 25OHD sufficiently standardized. In 2010, the vitamin D Standardization Program (VDSP) proposed establishing LC-MS/MS (liquid chromatography/tandem mass) as the reference method. The various 25OHD tests must be referenced and made available to the approved reference manufacturers using this technique[3].

Although commercial methods exist that meet this requirement, there is still variability in determining 25OHD, whereby one patient can be considered deficient or not, depending on the method used. This high variability may be attributed to several factors[4]:

1) Concentration of vitamin-D binding protein (DBP). Levels of 25OHD may be low when there is a decrease in DBP concentrations.

2) The immunoassay used (competitive towards binding protein, capture Ac).

3) Forms detected vitamin D: percentage of cross-reactivity to 25 OHD_2 and 25 OHD_3, and metabolites 24,25 $(OH)_2$ D_2 and 24,25 $(OH)_2$ D_3.

4) Detection of epimers 3-epi-25 and 3-epi OHD_3 25-OHD_2.

5) Determining complexity due to the lipophilicity of the molecule, with nonspecific interference by the presence of other lipids.

In view of the methodological limitations that still exist and involving clinical implications has been proposed that concentrations of free 25OHD or free $1.25(OH)_2D$ could be a better marker of vitamin D status[5]. In fact, it is accepted that free (or bioavailable) concentrations of other hormones such as T4 or testosterone are more relevant from a physiological point of view.

Finally, the extensive information and published literature that indicate the benefits of vitamin D in bones and extra-osseous have led to an exponential increase in laboratory applications to quantify 25OHD levels. It has reached the point that in

some areas this has been become almost a routine determination. Clinically we should be cautious when interpreting 25OHD levels under the established ranges as desirable, especially in patients with no risk factors for vitamin D deficiency.

Bibliography

1. López-Ramiro E, Rubert M, Mahillo I, de la Piedra C. Hiperparatiroidismo secundario al déficit de vitamina D. Rev Osteoporos Metab Miner. 2016;8(2):55-60
2. Fuleihan GEH, Bouillon R, Clarke B, Chakhtoura M, Cooper C, McClung M, et al. Serum 25-hydroxyvitamin D levels: variability, knowledge gaps, and the concept of a desirable range. J Bone Miner Res. 2015;30:1119-33.
3. Phinney KW. Development of a standard reference material for vitamin D in serum. Am J Clin Nutr. 2008;88(suppl):511-2.
4. Wallace AM, Gibson S, de la Hunty A, Lamberg-Allardt C, Ashwell M. Measurement of 25-hydroxyvitamin D in the clinical laboratory: Current procedures, performance characteristics and limitations. Steroids. 2010;75(7):477-88.
5. Bouillon R. Free or total 25OHD as a marker for vitamin D status? J Bone Miner Res. 2016;31:1124-7.