Serum 25-Hydroxyvitamin D Immunoassays: Recommendations for Correct Clinical Interpretation

To the Editor:

We read with interest the report by Leino et al. (1) concerning the analytical evaluation of the 25-hydroxyvitamin D₃ (25-OH-D₃)¹ assay on the Roche Modular analyzer. They used clinical samples that were almost free of 25-hydroxyvitamin D₂ (25-OH-D₂) (<10 nmol/L) as confirmed by liquid chromatography–tandem mass spectrometry (LC-MS/MS) and found a good overall agreement between the results obtained with the Roche assay and those measured with the DiaSorin RIA and by LC-MS/MS. Although they acknowledged that the Roche assay, which does not measure 25-OH-D₂, may underestimate vitamin D status in patients receiving vitamin D₂, they considered that that was probably not a clinical problem in their country (Finland), because vitamin D supplementation in adults is most commonly provided as vitamin D₃. We briefly discuss this point by reporting our own experience in France, where surveys performed in our units found that approximately 10%–15% of adult patients treated with vitamin D receive vitamin D₂.

As individuals working in university reference laboratories, we receive several telephone calls each week from physicians who are puzzled by the fact that the serum 25-OH-D concentration for their patients has not increased, or has even decreased, during treatment with vitamin D (sometimes large doses). These patients invariably received vitamin D₃ and were monitored for their 25-OH-D concentration with the Roche assay. Every time a verification measurement was done in our laboratories with the DiaSorin RIA, the concentration was typical (>75 nmol/L) and sometimes quite high (>200 nmol/L). As we recently reported (2), this situation not only generates useless and costly exploration of results but also produces a certain degree of anxiety in the patients. We are even aware of 2 patients in whom a malabsorption syndrome was suspected and an analytical problem. Furthermore, a low 25-OH-D concentration measured with the Roche assay in a patient treated with vitamin D₂ may prompt a physician to prescribe large doses of vitamin D in a patient already replete with vitamin D, thus potentially causing toxic 25-OH-D concentrations to be attained. Finally, after discussing this issue with physicians, we came to realize that many physicians prescribing vitamin D are unaware of whether they have prescribed a drug containing vitamin D₂ or vitamin D₃. We also realized that many of these physicians thought that vitamin D₂ was in fact 1,25-dihydroxyvitamin D. This confusion highlights the urgent need for providing clear and simple information about vitamin D immunoassays to the medical community.

Because some 25-OH-D assays do not measure 25-OH-D₂, one can argue that vitamin D₃ should be the only vitamin D compound to use in clinical practice. Because other commercial assays, such as the DiaSorin assay and, to a lesser extent, the Immunodiagnostics Systems kit (50%–75% cross-reactivity with 25-OH-D₃), measure both 25-OH-D₂ and 25-OH-D₃, our opinion is that this recommendation would be valid only if vitamin D₂ is clearly demonstrated to be less effective that vitamin D₃. To our knowledge, apart from a shorter half-life for 25-OH-D₂, which must be taken into account when vitamin D is prescribed in large, spaced-out doses (3), vitamin D₂ seems as potent as vitamin D₃ when prescribed as daily doses (4). We thus believe that in countries where vitamin D₂ is prescribed (even in a low proportion of patients, as in France), 25-OH-D assays should measure both 25-OH-D₂ and 25-OH-D₃ and that the only interesting information to be provided to physicians in clinical practice is the sum of the 25-OH-D₂ and 25-OH-D₃ concentrations. Separating the reporting of the 2 compounds may be misleading, as previously reported in this journal (5). This rationale is why, on behalf of the French Society of Clinical Biology and the Group of Specialized Biology (GBS) of the French Society of Nuclear Medicine, we recommend the use of a 25-OH-D assay that measures both 25-OH-D₂ and 25-OH-D₃.

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