correspondence

Pathology Consultation on Vitamin D Testing: Clinical Indications for 25(OH) Vitamin D Measurement

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To the Editor

I read with great interest the recent article by Krasowski[1] on the timely topic of vitamin D testing. In this review, Krasowski[1] presented a common clinical case scenario about vitamin D and provided an excellent discussion on causes of vitamin D deficiency and the challenges faced by pathologists related to 25-hydroxyvitamin D [25(OH)D] testing, including controversy about optimal and target serum 25(OH)D concentrations, variable and confusing reference intervals, various 25(OH)D assays, and misordering of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] testing. Although Krasowski[1] mentioned the dramatic increases in 25(OH)D testing volume, the article did not discuss the clinical indications for vitamin D testing, which, in my view, are even more important for pathologists in their clinical consultation on test utilization.

During the past few years, the idea that nearly everyone needs extra vitamin D has gained significant attention in the general public and lay media, thanks to the speculated health benefits of vitamin D from epidemiologic association studies. More and more people are being tested for 25(OH)D, even as part of screening during routine physical examinations. As a result, the 25(OH)D assay has become one of the most ordered, if not *the* most ordered, esoteric test and is associated with an increasing cost burden to the often strained laboratory testing budget.

Despite continued debate on the optimal 25(OH)D concentration and the cutoff values for vitamin D deficiency and insufficiency,[2] according to the recently published consensus guideline from the Endocrine Society,[3] vitamin D deficiency is defined as a 25(OH)D level less than 20 ng/mL (50 nmol/L) and vitamin D insufficiency as a 25(OH)D level of 21 to 29 ng/mL (52-72 nmol/L). Guided by systematic reviews of evidence in published literature and panel discussions, the guideline recommends screening for vitamin D deficiency only in people at risk for deficiency and unequivocally recommends against routine screening for vitamin D deficiency in people who are not at risk.[3] To follow the Endocrine Society guideline, pathologists need to educate their clinical colleagues, particularly primary care providers, about the clinical indications for 25(OH)D measurement (candidates for screening).

Pathologists need to understand that only patients with or being evaluated for certain diseases or conditions are at risk for vitamin D deficiency[3,4] and should be considered for testing. These conditions include rickets, osteomalacia, osteoporosis, chronic kidney disease, liver disease, pancreatic insufficiency, malabsorption syndromes (eg, cystic fibrosis, inflammatory bowel disease, bariatric surgery, radiation enteritis), hyperparathyroidism, obesity (body mass index >30 kg/m^2), history of nontraumatic fractures, history of vitamin D deficiency or need for replacement therapy (to monitor the efficacy of treatment), chronic obstructive pulmonary disease, granuloma-forming disorders (eg, sarcoidosis, tuberculosis, histoplasmosis), diabetes and other chronic inflammatory conditions, and some lymphomas. In addition, older adults (eg, women older than 65 years; men older than 70 years), especially with history of falls; people taking antiseizure medications (anticonvulsants) or undergoing long-term therapy with glucocorticoids; dark-skinned people (eg, African Americans); and people with a dietary history that strictly excludes dairy products (eg, vegans) may also benefit from 25(OH)D testing.

It is impractical and unnecessary, in my experience, for pathologists to enforce compliance with the 25(OH) D test order guideline. However, pathologists can have an active role in controlling test overutilization through development of a written test order guideline for the institution, good communication with care providers, and continued education of ordering providers about the guideline. Since a 25(OH)D test order guideline, jointly developed by the laboratory medicine and endocrinology services, was distributed to all providers about 6 months ago as a cost-control measure, there has been a 40% to 50% decrease in the test orders in our health care system.

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To the Editor

The elucidation of several challenges faced by pathologists, consequent to the recent awareness about high global prevalence of vitamin D deficiency,[1] would also be appropriate for pathologists and clinicians worldwide.

Synchronization of all data obtained during vitamin D assays at various levels of laboratories in different continents would be essential to maintain excellent quality control since laboratory services have continued to be a neglected component of health systems. Their central role in public health, disease control and surveillance, and patient management is not recognized by governments.[2] Moreover, lack of competent diagnostic laboratories in resource-poor countries has been alarming not only in rural and remote areas: A large number of laboratories in bigger cities are also without high levels of diagnostic competence. Very often they are the only ones to serve vast populations with different disorders.[3]

An international program of external quality assessment would be required to upgrade the competence of laboratories carrying out vitamin D_3 measurements. That program could be funded by different international philanthropic organizations concerned with human nutrition. Furthermore, commercial programs like the Randox International Quality Assessment Program (RIQAS) that already has a global network of 18,000 laboratories for regular dissemination of samples, retrieval of local results, and reporting on the performance of individual laboratories,[4] would be extremely valuable for professionals handling vitamin D deficiency in pathology[1] and would build confidence in the quality of local results among colleagues in allied disciplines.

Measurement of 25-hydroxyvitamin D (vitamin D_3) by commercially available immunoassay kits and constant internal quality control might be the only option at a few laboratories affiliated with nonacademic, nonresearch health care centers without facilities for radioimmunoassay, high-performance liquid chromatography, or liquid chromatography–mass spectroscopy. Local assays of vitamin D_3 levels have been carried out since April 2010, at the Sant Parmanand Hospital, Delhi, India, a 140-bed, tertiary care, multidisciplinary hospital using a vitamin D enzyme-linked immunosorbent assay kit (Immunodiagnostic, Bensheim, Germany). The individual assay runs were monitored by inclusion of the low- and high-level controls supplied by the manufacturer and third-party controls supplied by Randox Laboratories (Crumlin, Wales).[5]

The majority of diagnostic laboratories will not be able to measure 25-hydroxyvitamin D [25(OH)D] on their premises with existing infrastructure. Simple and rapid point-of-care assays would be indispensable to monitor vitamin D_3 levels in the general population in rural and urban areas. Point-of-care formats would assist in maintaining a watch on postsupplementation vitamin D_3 levels. A daily supplementation of 1,000 IU of vitamin D_3 may fail to bring levels to a minimum of 30 ng/mL (75 nmol/L) in 20% to 30% of cases.[6]

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The Author's Reply

I read with interest the comments by Arya and Agarwal who broadened the discussion of vitamin D testing into an international context and raised a number of important points. First, 25-hydroxyvitamin D testing is currently not accessible in many parts of the world owing to financial constraints or lack of infrastructure. In this regard, philanthropic and governmental aid efforts will be invaluable in providing access to testing. Second, 25-hydroxyvitamin D testing in resource-poor countries would logically focus on identification of severe vitamin D deficiency in communities to help target nutritional programs. In this context, accuracy and precision of assays for 25-hydroxyvitamin D may be less an issue than having inexpensive point-of-care assays that can perform in varying and often challenging environmental and transport conditions. Last, vitamin D testing will need to be done in careful conjunction with nutritional programs.

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