Response to the editorial on "Defining vitamin D deficiency, using surrogate markers"

Sir,

We read with great interest the editorial on vitamin D deficiency (VDD) by Garg and colleagues.[1] It is apparent on biochemical analysis that subclinical VDD is a rapidly increasing global problem and needs urgent attention, as vitamin D has a major role in immune modulation, and VDD is associated with several communicable and noncommunicable diseases.[2,3] The editorial is timely, as more and more Indians are getting their vitamin D levels tested and are finding that they have VDD. There are no clear evidence-based guidelines regarding the long-term management of such incidentally detected VDD. Differentiating a clinically significant VDD from an incidental biochemical finding is a major clinical challenge. Although the editorial has attempted to provide some guidelines, clinical recommendations must be based on high quality studies in the present era of evidence-based guidelines.

We wish to draw the attention of your readers to some issues related to simultaneous testing of 25-hydroxyvitamin D (25OHD) with parathyroid hormone (PTH) levels. First, the editorial is rather silent on the important question, namely measuring 25OHD in place of 1,25-dihydroxyvitamin D (1,25-DOHD, the functional hormone). Measurement of 25OHD as a biomarker of VDD is better than measuring 1,25-DHOD in day-to-day clinical practice because the former has a longer half-life and is the principal circulating form in blood.[3] 1,25-DHOD can be normal or elevated in VDD patients and is not truly indicative of vitamin D status.[3] Second, the authors have recommended measuring PTH along with 25OHD. Measuring PTH in a clinical laboratory is challenging: PTH circulates in blood as biologically active hormone and also as several inactive peptides. Currently, assays are not specific for biologically active PTH and can detect the inactive fragments as well.[4] Third, the set point of PTH secretion in response to serum calcium varies among individuals and is the result of a complex interaction of factors including age, gender, genetics, renal function, mobility level, calcium intake, and phosphate and magnesium status, which makes selection of a single inflection point challenging at best.[5] Last but not the least, the association of VDD in various disease states are modified by vitamin D receptor gene polymorphisms.[6] Fixing a clinically relevant cut-off value for the trophic and the target hormones needs rigorous testing in real-life clinical situations, with adequate sample sizes and across age-groups. Use of such a combination testing in acute illness, chronic illness, and other comorbid conditions (e.g. diabetes) will require further analysis before being accepted into routine practice.

We wish to reiterate that 25OHD analysis is currently the best screening test available for VDD. Screening is just the beginning of a triage. If screening is indicative of VDD, a clinical pathway can be followed. In the current conundrum of inaccuracy and imprecision of the assays, absence of validated PTH reference material, unstandardized cut-offs,[4] and the multifactorial nature of bone metabolism,[2] a cointerpretation of PTH and 25OHD could result in net harm. It will also cause financial loss to the patients or their caregivers.

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