Vitamin D: How much hope? How much hype?

By Eleanor Lederer

O f longstanding interest to nephrologists, vitamin D has now become a hot topic in the general medical and lay literature. While the beneficial effects of vitamin D on mineral metabolism have been appreciated for a century, a burgeoning body of literature attests to a multitude of other effects including modulation of the immune system, anti-infectious and anti-neoplastic effects, anti-proteinuric effects, antagonism of the renin angiotensin system with attendant cardiovascular benefits, and insulin-sensitizing effects.

Low vitamin D levels have been correlated with a greater incidence of several cancers including prostate and breast; autoimmune diseases such as multiple sclerosis; and metabolic syndrome. The majority of these claims stem from animal studies or epidemiologic association studies in humans. In parallel with these studies, a large number of reports document the very high incidence of low vitamin D levels in multiple populations including the elderly, the chronically ill, African Americans, and even generally healthy young people. Naturally, the intuitive response to these findings is to raise vitamin D levels under the assumption that normalizing the level will diminish the risk of the associated illnesses.

But how strong are the data supporting aggressive vitamin D replacement? Until very recently, vitamin D deficiency was defined as 25-hydroxy vitamin D levels (D2 or D3) less than 10 ng/mL, but an optimal vitamin D level was not established. The methodology for measuring 25-hydroxy vitamin D has only recently been standardized, allowing comparisons between different laboratories. Based on data demonstrating that vitamin D levels lower than 30–32 ng/mL in adults were associated with the development of secondary hyperparathyroidism and less efficient intestinal absorption of calcium, the ADA recommended targeting 32 ng/mL as the optimal vitamin D level with suggestions that higher levels are being considered. The Institute of Medicine (IOM) reviewed this subject and recently presented a consensus statement. The report supports the ingestion of 600 IU cholecalciferol daily for the mineral benefits, but did not find sufficient evidence that vitamin D supplementation can benefit conditions such as cancer, autoimmune diseases, and metabolic syndrome. Furthermore, the institute concluded that levels of 20 ng/mL were sufficient and that there was inadequate evidence to support pushing for higher levels. So who is right? The ADA or the IOM? It is too early to say.

Clearly, more well-designed large studies examining the effect of vitamin D in selected populations are needed. What about the dialysis and chronic kidney disease populations, populations with a high incidence of vitamin D insufficiency/deficiency and a high incidence of cardiovascular disease and insulin resistance? A number of studies suggest that dialysis patients receiving active vitamin D supplementation such as paracalcitrol or calcitriol enjoy a survival benefit over dialysis patients who are not receiving calcitriol or its analogs, without differences in biochemical measures of calcium, phosphate, and parathyroid hormone. However, no mechanisms for the survival advantage have been identified—it is only postulated. As these studies have been predominantly observational, the association between vitamin D or calcitriol/analog administration and survival is correlative only. No cause and effect conclusion can be made. The consensus reached by the committees responsible for the KDOQI and KDIGO guidelines has taken these studies into consideration and recommends the monitoring and maintenance of vitamin D levels throughout the stages of chronic kidney disease. A fall in 1,25 dihydroxy vitamin D is the first measurable change in mineral metabolism noted during the course of chronic kidney disease, long before the onset of hyperparathyroidism, hyperphosphatemia, or hypocalcemia. The nearly universal prevalence of bone mineral disorders in this population suggests strongly the need for vitamin D replacement.

One very interesting discovery regarding vitamin D replacement in this population is that administration of the precursor molecule, cholecalciferol, can result in significant increases in active 1,25 dihydroxy-vitamin D, even in patients on dialysis, perhaps owing to autocrine conversion at extra-renal sites. While the hope is that maintenance of normal vitamin D status will result in superior cardiovascular outcomes for our patients, those answers will not come for several years. Questions regarding the effect of vitamin D, calcitriol/analog replacement on bone metabolism, vascular calcification, insulin resistance, and cardiovascular disease will require long-term controlled studies in large numbers of patients. In the meantime, our best approach is to use the data that we have now, embark on the needed studies, and adjust our guidelines as better data emerge.

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