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Nutritional vitamin D in dialysis patients: what to D-iscern?

Sagar U. Nigwekar, Ishir Bhan and Ravi Thadhani

Division of Nephrology, Massachusetts General Hospital, Boston, MA, USA

Correspondence and offprint requests to: Ravi I. Thadhani; E-mail: rthadhani@partners.org

Worldwide, ~2 million patients rely on chronic dialysis therapy to sustain their life [1,2]. Despite advances in therapies and technology, mortality and morbidity in the dialysis population remain high. Cardiovascular disease is the leading cause of mortality in this population [3] and the search remains active for ‘modifiable factors’ that will improve outcomes in this patient population.

Vitamin D, traditionally thought to be involved only in bone and mineral metabolism, has been increasingly reported to have significant extraskeletal actions [4,5]. These include its effects on monocyte–macrophages (expression of the cathelicidin antimicrobial peptide), lymphocytes (cytokine release), pancreas (insulin production) and kidney (renin production). Studies have suggested that vitamin D has anticancer properties through its effects on cellular proliferation, differentiation, apoptosis and angiogenesis. It has been shown to be involved in the growth and proliferation of vascular smooth muscle cells and cardiomyocytes [4,6]. Vitamin D traditionally exerts its effects on bone and mineral metabolism in its hormone form, 1,25-dihydroxyvitamin D (1,25-D). In patients with normal renal function, inadequate supply of substrate 25-hydroxyvitamin D (25-D) will stimulate the 1-α hydroxylase enzyme in proximal renal tubular cells to maintain levels of 1,25-D, an effect mediated via an increase in parathyroid hormone (PTH) production; fibroblast growth factor 23 (FGF-23) acts as a counter-regulatory hormone, suppressing 1-α hydroxylase and reducing conversion of 25-D to 1,25-D [7]. In contrast to the endocrine effects of vitamin D on bone mineral metabolism, its extraskeletal effects are exerted as paracrine and auto-
The high prevalence of vitamin D deficiency (defined as low serum levels of 25-D) in the general population as well as in patients with end-stage renal disease requiring dialysis. In fact, a recent analysis reports that vitamin D deficiency is almost universal among chronic hemodialysis patients with hypoalbuminemia who initiate dialysis in winter months [8]. Etiologies of low 25-D levels in dialysis population have not been entirely worked out; however, reduced delivery of 25-D to target tissues will result in reduced intracellular conversion to 1,25-D independent of renal 1-α hydroxylase activity.

Medical literature is replete with studies describing the high prevalence of vitamin D deficiency (defined as low serum levels of 25-D) in the general population as well as in patients with end-stage renal disease requiring dialysis. In fact, a recent analysis reports that vitamin D deficiency is almost universal among chronic hemodialysis patients with hypoalbuminemia who initiate dialysis in winter months [8]. Etiologies of low 25-D levels in dialysis population have not been entirely worked out; however, reduced capacity of skin to produce vitamin D, limited sunlight exposure, reduced intake of foods that provide natural sources of vitamin D and increasing age of the dialysis population are some of the possible explanations [9–11]. The effects of low 25-D are compounded by reduced activity of renal 1-α hydroxylase enzyme. Thus, dialysis patients are at high risk of reduced endocrine as well as paracrine and autocrine activity of vitamin D and consequently should be at a higher risk than those in the general population for the ill effects of vitamin D deficiency. What are the implications of inadequate vitamin D in the dialysis population?

A number of studies have investigated the association between vitamin D and clinical outcomes. Studies by our group and others have suggested in association studies survival benefits from activated vitamin D preparations, such as paricalcitol and calcitriol [12–15]. Other investigators have proposed that these findings, derived from retrospective studies, may have been due to confounding factors such as younger age and other favorable case mix and laboratory characteristics that are generally associated with greater longevity [16]. Furthermore, these studies generally did not adequately evaluate the superimposed effects, if any, of 25-D levels. To address this, our group conducted a case–control study nested in a large prospective cohort of patients initiating hemodialysis [17]. In these observational studies, patients with 25-D levels <10 ng/mL were at significantly increased risk of all-cause mortality and cardiovascular mortality at 90 days compared to subjects with normal 25-D levels. A subsequent study also observed increased overall mortality in hemodialysis patients with 25-D levels <20 ng/mL [10], while a third study demonstrated an increased risk of cardiovascular events in chronic peritoneal dialysis patients with 25-D levels below ~18 ng/mL [18].

In this issue, Drechsler et al. [19] report analysis of data from the NECOSAD cohort and have further explored the association between 25-D levels and mortality in chronic dialysis patients 1 year after dialysis initiation. This analysis included 762 adult hemodialysis and peritoneal dialysis patients recruited since 1997 from 37 dialysis centers in the Netherlands. While all analyzed patients had survived their first year on dialysis, subsequent mortality rates were high (~7% at 6 months and 30% at 36 months), and cardiovascular causes were responsible for >50% of these deaths. In analyses adjusted for possible confounders, including bone mineral metabolism parameters and season, authors observed higher cardiovascular mortality in patients with baseline 25-D levels ≤10 ng/mL (also measured after 1 year on dialysis); adjusted hazard ratios (HR) for cardiovascular mortality were 2.72 (1.05–7.05, P = 0.04) and 1.61 (1.00–2.57, P = 0.048) for the 6-month and 3-year follow-up, respectively. In analyses stratified by PTH levels, patients with PTH levels above the median (123 pg/mL) appeared particularly at high risk from low 25-D levels [HR 3.37 (1.64–6.91), P = 0.001]. No association was seen between vitamin D deficiency and non-cardiovascular mortality; however, a low non-cardiovascular mortality event rate may have limited the power in these analyses.

The results of this study not only confirm the previously reported associations between 25-D levels and short-term clinical outcomes, but they also suggest that these levels may have more long-lasting implications. This effect is most prominent in patients with high PTH levels, an interaction not reported in prior studies on this topic. Thus, patients suggested to have the least amount of 1,25-D activity (as measured by PTH) appear to be at the greatest risk from 25-D deficiency. Analogously, we similarly found that the associations between 25-D and mortality were strongest among patients not treated with active forms of vitamin D [17].

In the absence of a randomized placebo controlled trial, we cannot draw any definitive conclusions regarding causality or the potential effects of supplementation with nutritional vitamin D (ergocalciferol or cholecalciferol). However, studies such as these are essential as they lay the groundwork for future intervention studies and suggest a target population in whom the yield may be greatest (e.g. patients with the highest PTH levels). These findings, when taken along with previously reported investigations, emphasize the need for trials in this population to definitively address the role of nutritional vitamin D supplementation, an inexpensive and relatively well-tolerated intervention. Such trials should also address the optimal dose and duration of such supplementation. Cardiovascular events and infections, the first and second most common causes of mortality in dialysis population, are the two highest yielding outcomes to assess. A recent review from the Institute of Medicine highlights the lack of definitive data on the health benefits of vitamin D supplementation beyond bone health [20]. The dialysis population, with its higher rates of vitamin D deficiency, cardiovascular events and infections compared to the general population, represents an ideal group in which to study further.

Conflict of interest statement. R.T. has received a research grant from Abbott Laboratories.

(See related article by Drechsler et al. Vitamin D status and clinical outcomes in incident dialysis patients: results from the NECOSAD study. Nephrol Dial Transplant 2011; 26: 1024–1032.)

References


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