Active Vitamin D and Survival

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Vitamin D is more than just a therapeutic tool for lowering elevated levels of parathyroid hormone (PTH) in patients on dialysis. Deficiencies in the vitamin D axis cause osteomalacia, rickets, and myopathy and are associated with a variety of extraskeletal problems, including cardiovascular disease, infection, malignancy, and death.1–2 Interestingly, the growing awareness of a potential link among vitamin D deficiency, active vitamin D therapy, and survival emanated, in large part, from the nephrology literature, where observational studies of dialysis cohorts were the first to report a survival benefit of therapy versus no therapy.3–6 In retrospect, dialysis was the ideal setting for such studies given the common and profound deficiencies in the vitamin D axis,7 frequent treatment with active vitamin D, and high mortality rates, all of which are captured prospectively in clinical databases maintained by large dialysis providers and available to clinical investigators.

In this issue of JASN, Shoben et al.8 extend these observations to earlier stages of chronic kidney disease (CKD). They report a survival benefit of therapy with calcitriol versus no therapy in a Pacific Northwest Veterans Affairs (VA)-based study of patients with stages 3 and 4 CKD. To be eligible for the study, patients had to be calcitriol naive, have a PTH level >70 pg/ml during the year before starting therapy, and have had a nephrology clinic visit during that window. In other words, there needed to be an indication for therapy, an opportunity to receive therapy, but no previous therapy. Using a clever approach to help minimize bias, calcitriol users and nonusers were defined using the same criteria at baseline such that patients who ultimately received calcitriol but began therapy at a subsequent clinic visit were nonetheless included in the control group (accounting for 17% of the “untreated” control subjects). In the primary analysis—the multivariable-adjusted “intention-to-treat” analysis—patients who were treated with calcitriol had a 26% lower mortality compared with those who were untreated. The results were unchanged in “as-treated” analyses in which the late-starting calcitriol users were censored at the time therapy began rather than remaining in the control group. The magnitude of risk reduction with calcitriol was similar to the previous dialysis studies, and these current results corroborate those from an East Coast VA cohort of predialysis patients in which calcitriol therapy was also associated with significantly decreased mortality.9

Secondary findings in this study are also noteworthy. The mean baseline serum calcium and phosphate levels of approximately 9.0 and 3.8 mg/dl, respectively, were well within the normal range, yet PTH levels were already two- to four-fold above normal. Although this constellation was reported previously,10 it reemphasizes the need for routine PTH screening in CKD to help identify patients for earlier and more aggressive management of secondary hyperparathyroidism with active vitamin D. We must exercise caution, however, because there was a 52% greater risk for hypercalcemia among the calcitriol users. Unfortunately, the severity of these episodes and whether any patients required hospitalization are not reported.

Despite the investigators’ meticulous analytical approach, this study, like all of its dialysis predecessors, has important limitations. The study period of 1999 through 2007 spanned the 2003 publication of the Kidney Disease Outcomes Quality Improvement (K/DOQI) guidelines for bone and mineral metabolism.11 Although the guidelines undoubtedly had a significant impact on clinical practice, we are not told whether the calcitriol effect was homogeneous over time or whether the number of patients screened for PTH and treated with calcitriol increased in the latter part of the study period. This could be an important source of unmeasured confounding if improved CKD awareness and more aggressive screening for PTH after 2003 yielded a healthier population of calcitriol-treated patients.

A more important issue that is not unique to this study is the fundamental problem that limits observational studies of clinical interventions: confounding by indication and selection bias. For example, when studying the effect of calcitriol on risk for mortality, the very reasons a patient is chosen to receive calcitriol may place him or her at an a priori lower risk for death than patients who go untreated. In addition, certain patients may go untreated because they receive substandard care in general. Either way, therapy could simply be the marker of lower risk patients destined to survive longer rather than a causal mechanism for their greater survival. Although multivariable analysis, matching, restriction, stratification, and propensity scoring aim to minimize these sources of bias by homogenizing the baseline risk for death among the treatment groups, only a randomized, controlled trial is capable of completely leveling the playing field by equally balancing both known and unknown confounders.

In the absence of clinical trials, there cannot be definitive proof of the superiority of certain treatments over others; however, randomized trials are costly, are logistically challenging, and, on the basis of the inclusion and exclusion criteria, can yield results that may not always translate into day-to-day clinical practice. Thus, among the biggest questions remaining in this area are whether a placebo-controlled mortality...
trial of active vitamin D will be done and, if so, will the results from the observational studies hold up? Although these certainly are critical questions, the more pressing question is practical. What should clinicians do now for the patients in their ever-expanding dialysis units and CKD clinics while we await (hopefully) definitive trials? In the interim, are there enough data to advocate routine active vitamin D therapy in patients with CKD and secondary hyperparathyroidism, acknowledging the limitations of the literature?

Recent randomized trials in CKD have yielded disappointing results despite well-formulated, scientifically based hypotheses.12-14 Although this would argue against changing clinical practice in the absence of confirmatory trials, the nephrology community has embraced treatment paradigms in other aspects of mineral metabolism on the basis of less evidence. For example, although high serum phosphate levels are associated with increased mortality,15 there are no data—randomized or even observational—that reducing serum phosphate levels improves survival. Likewise, phosphorus binders clearly lower serum phosphate levels, but placebo-controlled studies of clinical outcomes are lacking. Nevertheless, the totality of the data on phosphate has offered a convincing argument in favor of an aggressive clinical approach to phosphate reduction in the absence of such studies. Is not a similar approach warranted for active vitamin D given the totality of its data? Does the lack of any published report of increased mortality with active vitamin D in CKD help tip the balance in favor of treatment? Finally, as favorable observational data continue to mount, might there be ethical resistance to placebo-controlled survival studies of active vitamin D in the future?

Highlighting the strengths and limitations of the vitamin D literature is a far easier task than successfully addressing these and the many other complicated questions that lie ahead. Although the risks and benefits of vitamin D continue to be featured in the lay press and thoughtfully debated by experts in the field, what is clear is that further high-level scientific inquiry into the biology of vitamin D and its therapeutic effects, such as by Shoben et al., is needed to bring us closer to the answers that will ultimately help us best help our patients with CKD.

DISCLOSURES
M.W. has received honoraria from Abbott Laboratories and Genzyme, makers of commercially available active vitamin D products.

REFERENCES