Calcium, Calcimimetics and Clinical Outcomes

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The introduction of less-calcemic vitamin D analogs in 1998 was the beginning of a fundamental change in the management paradigm for secondary hyperparathyroidism in patients with chronic kidney disease (1). Until that time, the prevailing treatment strategy involved maintaining serum calcium (Ca) at the upper limit of normal to facilitate calcium-induced suppression of parathyroid hormone (PTH) synthesis and secretion. The inevitable transient episodes of hypercalcemia were viewed as a clinical management "nuisance" requiring temporary interruption of vitamin D therapy. Concurrent with the availability of this new therapeutic agent, which suggested the promise of having fewer episodes of hypercalcemia, observational evidence emerged, which suggested that patients with a lower calcium × phosphorus (P) product (Ca × P), lower serum Ca, and lower serum P had a survival advantage as compared with those with higher serum levels of these ions (2,3).

There have been a number of distinct data sets examining the relationship between serum Ca and clinical outcomes. Data from a large dialysis chain in the United States reveal that for each 1 mg/dl increase in Ca there is an observed 18 to 25% increase in the risk of death ($P < 0.0001$) (4). Multivariable adjusted data from the international Dialysis Outcomes and Practice Patterns (DOPPS) study suggest a 12% increase in all-cause mortality ($P < 0.0001$) and a 13% increase in cardiovascular specific mortality ($P < 0.0001$) per 1 mg/dl increase in albumin-adjusted serum Ca (5). However, data from the Canadian Patient Registration, Management and Outcome Information System (PROMIS) database and from the Netherlands COoperative Study into the Adequacy of Dialysis treatment (NECOSAD) database do not find an independent relationship between serum Ca and mortality (although both report a relationship with Ca × P) (3,6).

Though important, these observations had limited practical applicability until the introduction of calcimimetic agents in 2004. This new class of therapeutic agents acts as allosteric modulators of the Ca-sensing receptor and allow for suppression of PTH synthesis and secretion while simultaneously lowering serum Ca and P (7).

As shown by Srinivas *et al.*, calcimimetic agents can effectively suppress serum Ca in patients who have persistent secondary hyperparathyroidism and hypercalcemia after kidney transplant (8). Using low-dose cinacalcet, the investigators were able to effectively treat hypercalcemia while modestly suppressing PTH. Importantly, the serum P rose significantly, an effect predicted by the effects of PTH on P resorption. These results are similar to other small case series reported in the posttransplant population.

Chertow *et al.* studied the simultaneous reduction of active vitamin D to "physiologic levels" and the introduction of cinacalcet to subjects with controlled PTH and elevated Ca × P (9). These investigators report a significant improvement in the proportion of subjects achieving Kidney Disease Outcomes Quality Initiative (K/DOQI) PTH and Ca × P targets despite the discontinuation of active vitamin D in 21% of subjects and a reduction of active vitamin D dose by nearly 50% in the remainder. The proportion of subjects given Ca-containing phosphate binders increased from 62% to 79% and the mean dose of elemental Ca prescribed rose to 1847 mg/d.

These clinical trials provide ongoing evidence that the introduction of calcimimetic drugs represents a real opportunity to improve the paradigm of managing the biochemical variables associated with secondary hyperparathyroidism. However, neither of these clinical trials demonstrates a tangible effect of Ca reduction on clinical outcomes. While the effective treatment of hypercalcemia and secondary hyperparathyroidism is of considerable clinical interest, it remains to be seen whether this will translate into improvement in bone health or cardiovascular outcomes. The increase in serum P seen in patients with chronic kidney disease stages 2 to 4 and the increase in Ca burden associated with cinacalcet use in stage 5 warrant further investigation as they may significantly modify the independent effect of cinacalcet.

Despite the robust body of observational data supporting the hypothesis that lower serum Ca is associated with improved clinical outcomes, there have been no randomized clinical trials to test this hypothesis. The same can be said for serum P and Ca × P. It is reassuring that Cunningham *et al.* (10) report significantly improved meaningful clinical outcomes such as fracture and hospitalizations and a trend toward improved mortality in patients studied during the clinical development of cinacalcet; however, the question remains: Will interventions that specifically lower serum Ca, serum P, and PTH improve cardiovascular outcomes and alter all-cause survival in patients with end-stage renal disease? (10)

A very large, international, prospective, randomized, clinical trial to test this hypothesis is currently being developed. I

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believe this to be a critical step to establish a causal role for abnormalities of mineral metabolism in the burden of cardiovascular disease in subjects with chronic kidney disease. Until the time that such a study is completed, the current weight of evidence supports that serum Ca and serum P should be maintained in the low normal range and that the introduction of cinacalcet offers a unique opportunity to do so.

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Please see the related articles, "Improvement in Hypercalcemia with Cinacalcet after Kidney Transplantation," on pages 323–326 and "Cinacalcet Hydrochloride (Sensipar) in Hemodialysis Patients on Active Vitamin D Derivatives with Controlled PTH and Elevated Calicum × Phosphate," on pages 305–312.

Clinical use of the calcimimetic cinacalcet in hemodialysis (Chertow *et al*.) and transplant patients (Srinivas *et al*.) with the corresponding editorial by Block are featured in this month's *CJASN*. A study in experimental animals on another congener by Lopez *et al*. in this month's *JASN* (pages 795–804) shows a decrease in extraosseous calcifications, even in calcitriol-treated animals.