personally accountable for the individual’s own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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References


Vitamin D and Parathyroid Hormone Levels in CKD

To the Editor:

Chronic kidney disease–bone mineral disorder (CKD-MBD) includes multiple interrelated abnormalities, including hypocalcemia, hyperphosphatemia, hypovitaminosis D, and elevated levels of fibroblast growth factor 23 (FGF-23) and parathyroid hormone (PTH).1-3 Calcitriol (1,25(OH)2D), the activated form of vitamin D, is a central regulator of mineral metabolism. In CKD-MBD, metabolic abnormalities are augmented by 1,25(OH)2D and 25-hydroxyvitamin D (25(OH)D) deficiency, resulting in secondary hyperparathyroidism. Multiple studies have demonstrated that maintaining 25(OH)D levels at ≥30 ng/mL is associated with lower PTH levels in early stages of CKD,3-6 but efficacy in late-stage CKD is unclear. The most recent KDIGO guideline recommends that vitamin D deficiency in CKD patients be treated similarly as in the general population.4

The effects of calcium, phosphorus, vitamin D, and glomerular filtration rate (GFR) on PTH are profoundly interdependent. Currently available data clearly answer whether vitamin D supplementation benefits patients with advanced CKD. We therefore examined the relationships of serum calcium, 25(OH)D, phosphorus, and estimated GFR (eGFR) with PTH among a large national sample of patients evaluated during routine clinical practice.

The data were extracted from a set of adult patients who had GFR estimated at a Labcorp facility in the United States from November 2011 through June 2014; the earliest set of simultaneously obtained calcium, phosphorus, 25(OH)D, and PTH values was used (Item S1). Assay platforms were constant over the entire study. To eliminate primary hyperparathyroidism cases, individuals with elevated PTH levels were excluded if serum calcium exceeded 10.2 mg/dL. eGFR values were stratified using KDIGO criteria. 25(OH)D levels were categorized as adequate (>40 ng/mL), low (20-40 ng/mL), and depleted (<20 ng/mL). The research was approved by the Western–Copernicus Group Institutional Review Board, with informed consent waived for use of de-identified data. Analyses used SAS, version 9.4 (SAS Institute Inc).

Entry criteria were met by 153,611 individuals; 56.6% were female; mean age was 65.9 ± 14.0 years (Table 1).

Figure 1 illustrates the relationship between calcium and PTH, stratified by CKD stage and 25(OH)D level. At all levels of serum calcium in all eGFR categories, vitamin D levels ≥30 mg/dL (vs <20 mg/dL) were associated with 20%-40% lower PTH levels; patients with 25(OH)D levels 20-<40 mg/dL had intermediate PTH levels. PTH levels were greater at greater CKD stage, and patients in CKD stages 3-5 with 25(OH)D levels of ≥40 mg/dL had PTH levels comparable to 25(OH)D-depleted patients with more normal kidney function. Results were similar when we included patients with calcium levels up to 12 mg/dL (Fig S1).

Our findings illustrate the interdependencies of calcium, vitamin D, and eGFR in their association with PTH level in CKD. Two main points were apparent: 25(OH)D levels ≥40 mg/dL were associated with lower PTH among patients in every eGFR category at every level of serum
calcium. Nonetheless, eGFR was the strongest determinant of PTH. These observational data generate a hypothesis that repleting 25(OH)D levels to ≥40 ng/mL could be a possible intervention to prevent the development of secondary hyperparathyroidism during CKD stages 3-5, despite lack of evidence for vitamin D to reverse established hyperparathyroidism.

In CKD, PTH induces CYP27B1, a gene encoding the 1α-hydroxylase that converts 25(OH)D to 1,25(OH)2D; counter-regulation of CYP27B1 by FGF-23 is inhibited by the loss of necessary cofactors, α-klotho and FGFR1. Despite reduced renal 1α-hydroxylation, the oxyphil cells of the parathyroid gland may see 10-fold induction of 1α-hydroxylase in secondary hyperparathyroidism. Excess 1α-hydroxylase in the hypertrophied gland, along with reduction in cytosolic vitamin D binding protein (DBP), may promote a state of “vitamin D hunger” in the parathyroid gland. Maintenance of higher serum 25(OH)D levels could increase intraparathyroid 25(OH)D, overcome deficient DBP, and restore normal vitamin D responsiveness in the gland.

Our results are consistent with a trial of oral calcifediol in CKD stages 3-4 in which 25(OH)D levels of ≥50.8 ng/mL were required to reduce PTH and other bone turnover markers. PTH was maximally suppressed at a mean 25(OH)D level of 92 ng/mL, without hypercalcemia, hyperphosphatemia, or rising FGF-23 levels. Our group observed reduction of PTH among 14,289 CKD patients, with no plateau in effects until 25(OH)D levels reached 42-48 ng/mL. Taken together, these data suggest that correcting 25(OH)D deficiency according to general population guidelines may be overly conservative. Limitations include no information on medication use, use of a single specimen per patient, and lack of certainty.
that dialysis patients were excluded from this cohort. Our results constitute associations rather than causation. We cannot conclude that raising 25(OH)D levels in individual patients would reduce PTH. Despite these limitations, nutritional vitamin D remains an inexpensive intervention with a favorable risk-benefit profile, compared to calcitriol and other activated vitamin D products. Studies to assess the impact of interventions to raise 25(OH)D levels in CKD stages 3-5 are warranted.

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Supplementary Material
Supplementary File (PDF)
Figure S1; Item S1.

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