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Vitamin D and Clinical Outcomes in Dialysis

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Abstract

Most dialysis patients are vitamin D deficient, including deficiencies in both activated vitamin D (1, 25-dihydroxyvitamin D) and the less active 25-hydroxyvitamin D. These and other abnormalities associated with chronic kidney disease (CKD), if they remain untreated, lead to secondary hyperparathyroidism and bone changes, such as osteitis fibrosa cystica. Activated vitamin D has been proven to decrease parathyroid hormone (PTH) levels in dialysis patients and is currently used for this indication. There are multiple other potential "pleotrophic" effects associated with vitamin D therapy. These include associations with lower all-cause and cardiovascular mortality, lower rates of infections and improved glycemic indexes. Meta-analyses of multiple observational studies have shown activated vitamin D therapy to be associated with improved survival. Observational data also suggest fewer infections and better glucose control. There have been no randomized clinical trials powered to evaluate mortality or other clinical outcomes. Small trials of nutritional vitamin D (ergocalciferol and cholecalciferol) showed increases in 25-hydroxyvitamin D levels without hypercalcemia or hyperphosphatemia, even when given in addition to activated vitamin D therapy. While activated vitamin D therapy is associated with improved outcomes, it also leads to higher fibroblast growth factor 23 (FGF-23) levels, which may be detrimental in dialysis patients. Further research is needed to evaluate whether activated or nutritional vitamin D therapy are beneficial in dialysis patients for outcomes other than secondary hyperparathyroidism.

Chronic kidney disease – mineral bone disorder (CKD-MBD) is a systemic disorder that involves abnormal biochemical tests, abnormal bones and vascular calcification. The pathophysiology of CKD-MBD is complex and our understanding of it is rapidly evolving. Vitamin D plays a central role in CKD-MBD as the 1-α hydroxylase enzyme is found in abundance in the kidney. Thus, dialysis patients without working kidneys are deficient in activated vitamin D, and are also often deficient in nutritional vitamin D (1). Patients who are on dialysis are treated with activated vitamin D primarily for secondary hyperparathyroidism. Some dialysis patients are also prescribed nutritional vitamin D supplementation. In this review, we will discuss the evidence behind the use of various forms of vitamin D in patients on dialysis.

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Conflicts of Interest

None of the authors have conflicts of interest to declare.

CKD-MBD and Vitamin D pathophysiology

Vitamin D is obtained either through eating vitamin D rich foods (oily fish, dairy products), supplements or through the skin's exposure to UVB radiation producing vitamin D. This vitamin D is then converted to 25-hydroxyvitamin D in the liver. 25-hydroxyvitamin D (25(OH)D) circulates in the blood stream and is used to evaluate an individual's vitamin D nutritional status because of its relatively long half-life (2–3 weeks). Circulating vitamin D is bound to vitamin D binding protein (DBP) (80–90%) and albumin (10–15%), with less than 1% existing in a free, unbound form; free and albumin bound vitamin D constitute the bioavailable 25(OH)D (2). This bioavailable 25(OH)D may correlate better with some clinical outcomes, but is not routinely measured in clinical practice (3, 4). The 1-α hydroxylase enzyme converts 25(OH)D into the more active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)2D), which has a half-life of only 8–12 hours. While 25(OH)D can stimulate the vitamin D receptor (at 100 fold higher concentrations) *in vitro*, it is unclear whether it has effects *in vivo* (5, 6). Finally, both 25(OH)D and 1,25(OH)2D are made inactive by the 24-α hydroxylase enzyme, whose activity may be reduced as kidneys fail (7).

Parathyroid hormone (PTH) levels are elevated at lower glomerular filtration rates (GFRs) (8). PTH is made in the parathyroid gland chief cells in response to fluctuations in calcium via the calcium-sensing receptors on the chief cells. PTH promotes release of phosphorus and calcium from bone, increased vitamin D production in the kidney and urinary secretion of phosphorus. The signals for elevation of PTH in CKD are numerous including low calcium levels, high phosphate levels and low 1,25-dihydroxyvitamin D levels. At the same time, or earlier, FGF-23 levels become elevated (9). FGF-23 is a hormone made by the bone that causes phosphaturia (leading to lower serum phosphate levels) and decreased 1-alpha hydroxylase activity in the kidney (leading to lower 1,25-dihydroxyvitamin D levels).

Available Formulations of Vitamin D

Vitamin D is available for supplementation in several formulations. In the United States, nutritional vitamin D (that becomes 25(OH)D *in vivo*) is available as either ergocalciferol or cholecalciferol. Activated forms of vitamin D (analogs of 1,25(OH)2D) are available as either calcitriol (1,25(OH)2D) or its analogs, paracalcitol and doxercalciferol. Other analogs not available in the United States include alfacalcidol, maxacalcitol, and falecalcitriol. Analogs of calcitriol were developed due to concerns about hypercalcemia. It has been proposed that the mechanism of any lessened calcemic effects of these analogs is due to reduced activation of calcium uptake proteins in the intestines (10). This effect was also found in hemodialysis patients (11). However, more recent studies have shown that hypercalcemia with paricalcitol use may actually be similar in magnitude to that seen with calcitriol use (12, 13). This review will focus on the activated vitamin D formulations because there is more available data about their use.

Activated Vitamin D Use and Bone Parameters

Prior to the development of activated vitamin D therapy, patients with end-stage renal disease frequently had uncontrolled PTH levels with its associated bone changes, osteitis fibrosa cystica, a manifestation of renal osteodystrophy. In patients with CKD these bone changes, a consequence of increased bone formation and resorption, improve after daily administration of calcitriol for one year (14). In a study of dialysis patients with proven osteitis fibrosa, intravenous calcitriol was effective in improving the bone disease and lowering alkaline phosphatase and PTH levels (15). These two studies utilized bone biopsies for their outcomes, a technique that has not been used in large studies of vitamin D therapy. Thus, calcitriol therapy was shown to improve bone turnover parameters, and clinicians currently utilize lowering of PTH levels to guide therapy.

Current guidelines suggest keeping PTH levels in dialysis patients at two to nine times normal levels (16). A meta-analysis of clinical trial data shows that activated vitamin D use in dialysis patients lowers PTH and alkaline phosphatase levels (17). Vitamin D compounds also consistently increase serum phosphate and calcium levels (17). This meta-analysis concluded that there were not enough data on clinical outcomes such as fractures. Interestingly, while activated vitamin D compounds decrease PTH levels, they increase FGF-23 levels (18). The clinical significance of this increase in FGF-23 levels is currently unknown.

Vitamin D and Non-Bone Outcomes in Dialysis

Observational data have suggested that vitamin D levels and/or activated vitamin D use in dialysis patients have significant associations with various health outcomes (1, 19). These include overall (1, 20, 21) and cardiovascular mortality, (22, 23) infections, (24) and insulin resistance (25). Other outcomes that have been hypothesized to be improved with vitamin D therapy including allo-immunity (26), AVF maturation (27), and anemia (28). We will review the literature regarding some of these outcomes.

Bone mineral markers and Mortality

High PTH levels have clearly been associated with adverse outcomes in dialysis patients. One study in over 40,000 dialysis patients showed that levels of PTH >600 pg/mL were associated with a higher risk of mortality (29). Other studies showed similar associations between high PTH levels and mortality (30) and cardiovascular mortality (31). The ideal PTH level in dialysis patients is still not known (32). An analysis of the international Dialysis Outcomes and Practice Patterns Study (DOPPS) showed a higher all-cause mortality risk with PTH levels >300 pg/mL. Further complicating an analysis of this issue is the well-documented association between elevated phosphate levels and all-cause and cardiovascular mortality (21, 29–31). In addition, higher FGF-23 levels have been associated with a higher mortality risk in dialysis patients (33). Thus it is not obvious that the use of activated vitamin D, which lowers PTH levels but increases phosphate and FGF-23, will yield a survival advantage.

Activated Vitamin D Use and All-Cause Mortality: Observational Studies of Vitamin D Use

Low vitamin D levels are associated with mortality in patients on dialysis (1). In addition, numerous observational studies have shown an association between activated vitamin D use and improved survival in dialysis patients (20, 21, 23). One early analysis evaluated 51,037 incident hemodialysis patients that survived for at least 90 days from the initiation of hemodialysis (20). Mortality rates were lower in the group receiving activated vitamin D after adjusting for multiple confounders. This was true even when activated vitamin D was administered to patients with low PTH, high calcium and high phosphorus levels (20). In the few studies comparing different activated vitamin D agents, paricalcitrol and/or doxercalciferol were associated with better survival than calcitriol (34, 35).

In contrast to the many studies showing a benefit with activated vitamin D therapy, some studies suggest there is no association with improved survival (36). It could be that the improved survival found with vitamin D is due to residual confounding, possibly treatment or other biases. Since an adequately powered randomized clinical trial has not been performed we must rely on observational studies and smaller randomized clinical trials that have been combined using meta-analysis techniques.

One such study from 2013 by Zheng et al collected data from 20 studies, of which 11 were prospective cohort studies (37). (Figure 1) Studies included met the following criteria: a cohort study with at least one year follow-up, patients with CKD or on renal replacement therapy, patients treated with active vitamin D but not native vitamin D such as ergocalciferol or cholecalciferol, outcome studied was all-cause mortality or cardiovascular mortality, and quantitative data were available to analyze. Adjusted all-cause mortality in ESRD patients was evaluated in 6 studies totaling 66,639 patients, resulted in a hazard ratio of 0.80 (0.68–0.94) (37). Data from five studies was used to elucidate cardiovascular mortality. Of 4,250 patients in the studies, the hazard ratio was 0.59 (0.41–0.86) (37). (Figure 2) This meta-analysis was limited by the underlying data including multiple different vitamin D agents used and significant heterogeneity in the studies.

Another meta-analysis from Spain yielded similar results (22). Inclusion criteria were mostly similar, but studies that had 6 months, rather than at least a year follow-up were included. In addition, studies with outcomes data and at least one death were required. Due to these and other strict inclusion criteria, no randomized controlled trials were included. Fourteen observational studies with 194,932 patients were included, consisting mostly of hemodialysis patients receiving calcitriol or paricalcitol. After 3 years of therapy, the relative risk of death was 0.72 (95% CI 0.65–0.80) and after 5 years, 0.67 (95% CI 0.45–0.98) (22). The risk reduction was greater in patients with higher PTH values. Cardiovascular mortality was also reduced (22). (Figure 2) It is important to remember that these meta-analyses mostly used data from observational studies which are subject to residual confounding. Therefore, these meta-analyses, just like the studies that they combine, do not prove causality.

One meta-analysis combining 13 randomized clinical trials including 1469 participants found no effect of vitamin D compounds on all-cause or cardiovascular mortality (38). This meta-analysis was smaller than the previous ones discussed because it only included randomized clinical trials; only 41 all-cause deaths occurred during the follow-up of the trials (38). Thus, the authors concluded that insufficient patient-level outcome data exist and that larger randomized clinical trials are required.

Activated Vitamin D Use and Cardiovascular Mortality

Accepting that activated vitamin D therapy reduces all-cause mortality, the question becomes which cause of death might be altered by this therapy? Observational data show that lower cardiovascular mortality is associated with activated vitamin D use (22, 23, 37). However, cardiovascular mortality is a broad term for multiple etiologies of death in dialysis patients. Vascular medial calcification, an important underlying cause of cardiovascular disease in CKD and dialysis patients,(39) has a well established link to elevated phosphate levels (40). The link between vitamin D and vascular calcification is more complicated. In a mouse model of kidney disease, low dose activated vitamin D use (paricalcitol or calcitriol) protects against vascular calcification while use of higher doses is associated with more calcification (41). Other studies have shown that calcitriol leads to calcification but paricalcitol does not (42). It is unclear whether currently used doses of vitamin D analogs lead to or protect against vascular calcification.

Another effect of vitamin D in animal models is inhibition of the renin-angiotensin system and associated left ventricular hypertrophy (LVH) (43, 44). These animal models and patient data led to the design of the PRIMO and OPERA trials, which both evaluated the effects of paricalcitol on left ventricular hypertrophy in patients with CKD not on dialysis (45, 46). Neither of these trials showed a difference in LVH between paricalcitol and placebo. There were fewer cardiovascular hospitalizations in the paricalcitol group in both studies (45, 46). A post-hoc analysis of the PRIMO trial revealed that therapy with paricalcitol significantly decreased left atrial volume (47). Thus, while observational data show improvements in cardiovascular outcomes, randomized trial data in CKD suggest no effect on LVH in pre-dialysis CKD patients. In dialysis patients, a meta-analysis of randomized clinical trials showed no improvement in cardiovascular mortality, but there were only 13 cardiovascular deaths (38). Further studies are needed to elucidate whether activated (or nutritional) vitamin D therapy may ameliorate cardiovascular disease in dialysis patients.

Activated Vitamin D Use and Infections

Infection is the second leading cause of death in individuals on dialysis (48). Innate immunity represents a branch of host defense that responds to organisms within minutes to hours of invasion (49). Antimicrobial peptides (AMPs) are key members of the innate immune system; they have been found in many bacteria, plant, fungi, and animal species. The best studied AMPs are defensins and cathelicidins. Cathelicidins are linear structures that are represented on one gene and are expressed on all epithelial cell surfaces, circulating neutrophils, monocytes, natural killer cells, and T cells (50).

Human cathelicidin antimicrobial peptide 18 (hCAP-18) is the only identified cathelicidin in humans; low levels in dialysis patients are associated with a higher risk of infection (51). Patients with hCAP18 levels in the lowest tertile had a 2-fold increased risk of death attributable to infection even after multivariable adjustment (51). This study further showed that hCAP-18 levels had a modest correlation with active vitamin D levels, suggesting an association between the two(51). Interestingly, basic science data shows that the gene for hCAP-18 is transcriptionally regulated by the vitamin D receptor (52). A small trial in 30 ICU patients revealed that a one-time high dose cholecalciferol (200,000 IU or 400,000 IU) treatment at the initiation of sepsis was associated with a rise in 25(OH)D levels and importantly, higher cathelicidin levels (53).

Several studies have looked at the role of supplemented vitamin D in the risk of infections. Tsujimoto *et al.* found that the incidence of hospitalization because of acute respiratory infection was significantly lower in dialysis patients who had been treated with vitamin D compared to patients who had not (24). Kerschbaum *et al.*, in a retrospective study, reported that oral activated vitamin D was independently associated with a decreased risk for peritonitis in peritoneal dialysis patients (54). Whether this association with a lower risk of infection is mediated by higher cathelicidin levels requires further studies.

Activated Vitamin D and Insulin Resistance

Altered glucose metabolism and insulin resistance are recognized at all stages of CKD and ESRD (55, 56). In ESRD, insulin resistance is an independent non-traditional risk factor for cardiovascular mortality and is associated with protein energy wasting and malnutrition (57). Animal studies have demonstrated improvement in insulin resistance with administration of vitamin D with both increased insulin sensitivity and insulin secretion being affected (58–60). Studies in dialysis patients show some improvements in glucose metabolism with vitamin D supplementation in ESRD patients (61–63) but no improvement in other studies (64). A recent meta-analysis combining data from five randomized clinical trials and 12 non-randomized studies showed significantly lower glucose levels in patients treated with vitamin D (25). Although this meta-analysis used data from some randomized clinical trials, the considerable heterogeneity in the studies precluded a definitive conclusion about causality.

Nutritional Vitamin D Use and Outcomes in Dialysis Patients

A meta-analysis of 22 studies including five randomized clinical trials including patients with all stages of CKD with 25(OH)D levels less than 20–30 ng/ml revealed that supplementation with ergocalciferol or cholecalciferol resulted in higher 25(OH)D and lower PTH levels (65). Since that meta-analysis was performed, two more randomized clinical trials have been published describing the effects of nutritional vitamin D in dialysis patients. A trial of 60 patients on dialysis randomized to either cholecalciferol 50,000 IU weekly for 8 weeks, then monthly, compared to placebo revealed no episodes of hypercalcemia or hyperphosphatemia and an increase in 25(OH)D and 1,25(OH)2D levels after 6 months (66). No differences in PTH levels or muscle function or quality of life measures were noted after 6 months (66). A larger trial similarly showed increases in

25(OH)D levels with weekly or monthly ergocalciferol 50,000 IU (67). No differences were noted in PTH, hemoglobin, or 1,25(OH)2D levels or blood pressure (67). Notably, FGF-23 levels increased in all the groups including the placebo group (67). We can conclude that nutritional vitamin D (ergocalciferol and cholecalciferol) are effective in increasing 25(OH)D levels without increasing the risk of hypercalcemia or hyperphosphatemia but effects on patient outcomes are not currently known.

Conclusions and Future Directions

Dialysis patients are deficient in both nutritional and activated vitamin D. Activated vitamin D therapy with calcitriol, paricalcitol and doxercalciferol controls the secondary hyperparathyroidism associated with CKD. Vitamin D may have “pleotropic” effects in patients on dialysis, effects on organs and outcomes that are not related to bone effects. The most data on these effects are available on associations between vitamin D use and improved survival. However, these associations have only been seen in observational studies. Newer data reveal that nutritional vitamin D supplementation does not cause hypercalcemia or hyperphosphatemia in dialysis patients even when used in combination with activated vitamin D. Future research should concentrate on patient-level outcomes including mortality, cardiovascular events, infections and glucose control.

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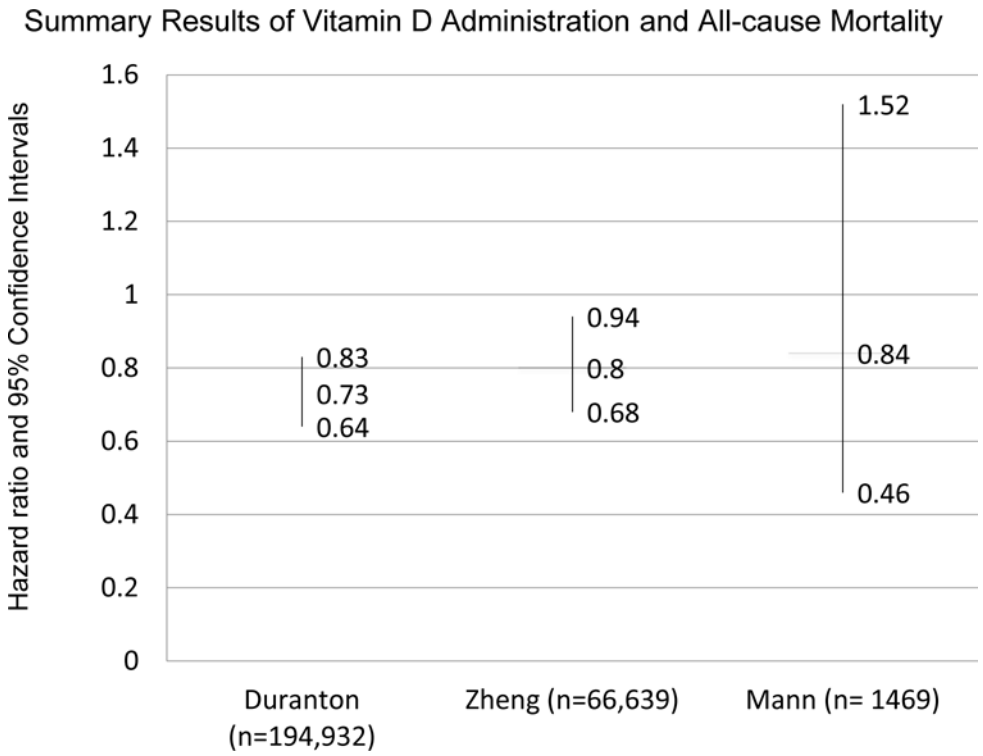

Figure 1.

Summary of results of meta-analyses evaluating the administration of vitamin D and all-cause mortality in patients with chronic kidney disease. Duranton et al. and Zheng et al. include observational studies. Mann et al. includes only randomized clinical trials.

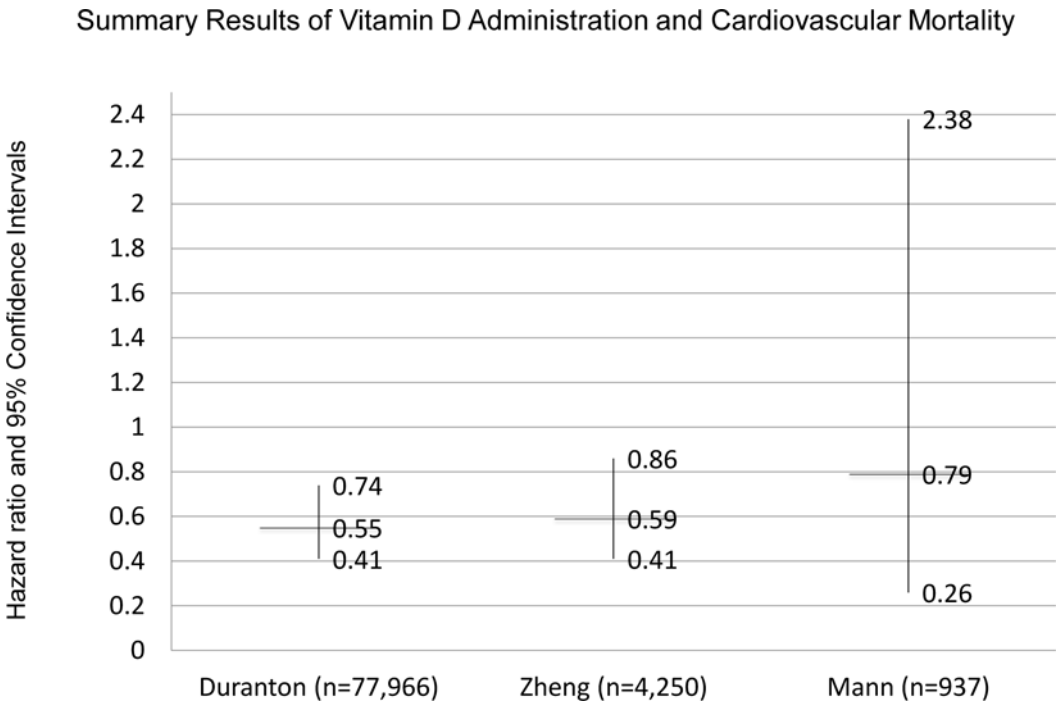

Figure 2.

Summary of results of meta-analyses evaluating the administration of vitamin D and cardiovascular mortality in patients with chronic kidney disease. Duranton et al. and Zheng et al. include observational studies. Mann et al. includes only randomized clinical trials.