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Moving Points in Nephrology

Clinical Outcomes with Active *versus* Nutritional Vitamin D Compounds in Chronic Kidney Disease

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Increasing confusion exists as to which vitamin D compounds are more appropriate for persons with chronic kidney disease (CKD). Some opinion-based guidelines recommend administration of such nutritional vitamin D agents as ergocalciferol or cholecalciferol as the first therapy in hyperparathyroidism associated with low circulating levels of 25-hydroxy vitamin D (<30 ng/ml) in nondialysis dependent CKD patients. Insufficient to deficient levels of 25-hydroxy vitamin D have been reported in the majority of individuals with CKD, including both nondialysis dependent and maintenance dialysis patients. Epidemiologic studies have almost consistently indicated the survival benefit of active vitamin D agents across all stages of CKD, including among dialysis patients with 25-hydroxy vitamin D deficiency. To date, no large observational or interventional studies have shown any survival advantage of nutritional vitamin D in CKD patients. Several recent (postguideline) small studies have yielded mixed results regarding the potential benefits of ergocalciferol in CKD, including satisfactory to inadequate lowering of PTH level to target ranges, improving response to erythropoietin stimulating agents, and salutary effects on glycemic controls. Compared with nutritional vitamin D agents, active vitamin D compounds appear to more effectively lower the circulating levels of alkaline phosphatase, a conveniently available biomarker associated with increased mortality and coronary artery calcification in CKD patients. The ideal vitamin D therapy for CKD patients should be the one that improves survival irrespective of suggested or imposed target ranges for arbitrary or opinion-based surrogate end points. Randomized controlled trials are needed to verify which agents offer superior survival advantages.

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The kidney is the most abundant source of 1-alpha hydroxylase in the body for the conversion of 25(OH) vitamin D_3, to *active* vitamin D hormone (calcitriol), *i.e.*, $1,25(OH)_2D_3$ (1). While 1-alpha hydroxylase also exists in many nonrenal tissues for paracrine activation of vitamin D (see below), the circulating level of $1,25(OH)_2D_3$ decreases significantly with diminishing renal function across worsening stages of chronic kidney disease (CKD) contributing to hypocalcemia, secondary hyperparathyroidism (SHPT) and subsequent renal osteodystrophy (2). Hence, replacement of active vitamin D has been considered an essential step in the management of SHPT and its associated disorders in CKD (3).

Although there is no consistent vitamin D terminology, we have used the term "prepro-hormone" for such pharmacologic compounds as ergocalciferol and cholecalciferol, which lack both 25-hydroxy (25[OH]) and 1-hydroxy groups; these compounds are sometimes also known as "nutritional" vitamin D, since they can be supplemented by oral intake of vitamin D rich or fortified diets (4). The term "prehormone" refers to 25(OH) vitamin D, also known as *calcidiol*, which lacks a 1-hydoxy group. The term "hormone" is utilized exclusively for 1,25 $(OH)_2$ vitamin D, also known as *calcitriol*. We have used the term "vitamin D receptor activator" (VDRA) for any compound that can activate vitamin D receptors; such compounds have also been referred to as "active vitamin D." Furthermore, based on the presence of a double or single bond between carbons 22 and 23 of the vitamin D side chain, all vitamin D compounds can be subdivided into D_2 (such as ergocalciferol, paricalcitol and doxercalciferol) or D_3 (such as cholecalciferol, calcitriol, 1-α-calciferol), respectively. Among nutritional vitamin D compounds, D_2 agents are mostly from plants whereas D_3 derivatives are usually from animal sources (see Table 1) (5).

The invention of the synthetic forms of active vitamin D, also known as VDRA, available since the late 80s in most countries (6), has been considered a turning point in the history of nephrology (7), especially after the relatively unsuccessful use of

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Table 1. Vitamin D compounds used in CKD patients. All cited studies are observational/epidemiological

Vitamin D Preparation	Type	Serum Calcium & Phosphorus	Urinary Calcium & Phosphorus	Serum Alkaline Phosphatase	Survival Advantage	Availability (and brand name in the USA/Canada)
Ergocalciferol	D_2, prepro-hormone, inactive	↑	↑	?	No data (see also Tables 2 and 3)	Generic (Drisdol™)
Cholecalciferol	D_3, prepro-hormone, inactive	↑	↑	?	No data (see also Tables 2 and 3)	Generic (Calciol, Vitamin D3)
25(OH)D (calcidiol, calcifediol)	D_3, prehormone	↑	↑	?	No data	Currently not yet available in the USA (Calderol™)
1-alfa-calcidiol	1-α(OH)D_3, missing 25(OH)	↑	↑	?	Lower cardiovascular mortality among Japanese HD patients [84]	Not available in the USA (one-alpha™)
Doxercalciferol	1-α(OH)D2, missing 25(OH)	↔ to ↑	↑	↓	Potential survival advantage in ESRD (29)	PO & IV (Hectorol™)
Calcitriol	D_3 hormone, non-selective VDRA	↑	↑	↔ to ↓	Potential survival advantage in NDD-CKD (23, 24) and ESRD (28)	IV and PO (Calcijex™, Rocaltrol™)
22-oxacalcitriol	22-oxa-1,25$(OH)_2$ vitamin D_3	↔ to ↑	↔ to ↑	↓	No data	Not available in the USA
Paricalcitol	D_2, 19-Nor, selective VDRA	↔ to ↑	↔ to ↑	↓	Same or superior survival to calcitriol in ESRD (54). Higher dose per PTH associated with better outcome. (33)	IV & PO (Zemplar™)
Maxacalcitol	1,25-dihydroxy-22-oxa-vitamin D3 selective VDRA	↔ to ↑	↔ to ↑	↓	No data	Not available in the USA

CKD, chronic kidney disease; HD, hemodialysis; PD, peritoneal dialysis; KDOQI, Kidney Disease Outcomes Quality Initiative; iPTH, intact parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; 1,25$(OH)_2$D, 1,25-dihydroxyvitamin D; ESA, erythropoiesis stimulating agent; AP, alkaline phosphatase; MSM, marginal structural model; HbA1c, hemoglobin A1c; VDRA, vitamin D receptor activators; (OH), hydroxyl.

the nutritional vitamin D compounds in CKD patients before this era (8,9). However, in recent years there has been resurgent interest toward the use of nutritional vitamin D agents in CKD patients, especially since the Kidney Disease Outcome Quality Initiative (KDOQI) guidelines recommended measuring 25(OH)D levels in all individuals with nondialysis dependent (NDD) CKD and concurrent SHPT and administering ergocalciferol or cholecalciferol as the first choice of therapy before VDRA, although these recommendations were mostly opinion-based (10). As a result, there has been increasing confusion as to whether vitamin D agents are more or less appropriate for CKD patients or which type—nutritional *versus* active vitamin D preparations—should be used. Intense marketing battles among major pharmaceutical companies have intensified the confusion and uncertainties among both physicians and CKD patients (7).

Physiologic Underpinnings of Vitamin D Deficiency in CKD

There are fundamental differences in how the physiologic actions of vitamin D are affected in patients with CKD, compared with persons with normal kidney function (11). A series of changes occur in parallel with deteriorating kidney function that affect how vitamin D is handled in these patients, central of which is a decrease in renal 1α-hydroxilase activity, not only by the deterioration in kidney function *per se*, but also by the early and marked elevation of FGF-23 in response to derangements in phosphate metabolism (12). As a consequence, patients with CKD suffering from 25(OH)D deficiency also display circulating 1,25$(OH)_2$D deficiency (1). What is less well described is how the activity of nonrenal 1α-hydroxilase is affected under these circumstances. Experimental data suggests that peripheral 1α-hydroxilation occurs in CKD in response to 1,25$(OH)_2$D

deficiency, and that increased PTH levels may not stimulate the activity of this enzyme (13). It remains unclear although if FGF-23 can exert an inhibitory effect on peripheral 1α-hydroxilase activity, but one could speculate that the marked increase in mortality associated with elevated FGF-23 levels (that appear to be independent of serum phosphorus levels) may be related to their effects on vitamin D metabolism (14).

Postulating the presence of peripheral 1α-hydroxilase that is regulated differently from renal 1α-hydroxilase in CKD raises the possibility that replacing 25(OH)D may alleviate the consequences of vitamin D deficiency even in the absence of renal 1α-hydroxilase activity, including the correction of circulating $1,25(OH)_2D$ levels, corrections of biochemical abnormalities such as SHPT, and even alleviation of the clinical consequences of vitamin D deficiency. It is important to note, although, that this postulate is based on *in vitro* studies, animal and small human experiments; hence, it is important to examine the effects of 25(OH)D in properly conducted large clinical trials, and to compare its actions to those of $1,25(OH)_2D$ in CKD patient populations.

Vitamin D Agents Available for Therapeutic Interventions

As listed in Table 1, there are currently a number of vitamin D-related pharmacologic agents in the United States and other countries for use in CKD patients. Although there is no uniform approach to classify these agents, the structural designation of D_2 *versus* D_3 has been used to distinguish two main categories, as described above (5). The most commonly used nutritional forms of vitamin D are ergocalciferol (D_2) and cholecalciferol (D_3). The first series of KDOQI Mineral and Bone Disorder (MBD) guidelines recommended that in all NDD-CKD patients who suffer from SHPT, total circulating 25(OH)D level, which usually includes both D_2 and D_3 in the plasma, should be measured if intact PTH level is above 70 pg/ml in stage 3 or above 110 pg/ml in stage 4 CKD (10). If blood 25(OH)D level is below 30 ng/ml, then first a nutritional vitamin D compound, *e.g.*, ergocalciferol 50,000 units per week, is to be administered according to the severity of vitamin D deficiency, followed by a VDRA if SHPT persists (3,10).

Calcitriol, an active vitamin D_3, was the first synthetic and commercially available VDRA for the treatment of SHPT, while one of its originally approved indications is the treatment of hypocalcemia (15–17). Expectedly, calcitriol administration is invariably associated with increasing serum calcium level, and in some instances, even worsening hyperphosphatemia and hypodynamic (low turnover) bone disease, especially in maintenance dialysis patients without residual renal function (15). These less favorable effects of $1,25(OH)_2D_3$ therapy have spurred the development of active vitamin D analogues that retain the therapeutically important properties of VDRA but have less calcemic activity (18). The term "selective" VDRA, usually applied to paricalcitol and maxacalcitol (19), indicates that the vitamin D receptors in the gastrointestinal (GI) tract are less activated than in other organs, leading to lower GI absorption of calcium and phosphorus with subsequent less hypercalcemic or hyperphosphatemic effects, while the salutary vitamin D receptor activation in other organs is maintained.

Nutritional Vitamin D Replacement and Clinical Outcomes in CKD Patients

To the best of our knowledge, there are currently neither well designed, randomized clinical trials nor large epidemiologic studies to optimally examine the effects on clinical outcomes of nutritional vitamin D administration in CKD patients (20). Although a number of epidemiologic studies have indicated an association between low serum 25(OH)D level and poor outcomes in the general population (1), it is not known whether correction of such low levels by administering nutritional vitamin D agents improves survival or other relevant outcomes in CKD patients (21). Indeed, a recent large prospective cohort study showed that lower serum levels of 25(OH)D were associated with increased mortality in incident hemodialysis patients who were not receiving VDRA, but in those who received intravenous VDRA, the detected 25(OH)D deficiency did not have any bearing on survival (22). The latter finding might indicate that in patients treated with VDRA, measuring serum level of 25(OH)D may not be necessary at least in maintenance hemodialysis patients, but randomized controlled trials need to verify this notion. It is, however, important to note that the same study showed clearly that over 80% of new hemodialysis patients suffer from both 25(OH)D deficiency and 1,25 (OH)2 D deficiency (22).

VDRA and Clinical Outcomes in CKD

Virtually all contemporary epidemiologic studies with large sample sizes have consistently shown an association between administration of any dose of VDRA and greater survival in both NDD-CKD (23,24) and maintenance dialysis patients (25–29) (see Table 2). A recent study implied that the greater survival of African American dialysis patients compared with their non-Hispanic Caucasian counterparts, which is in sharp contradistinction to the general population (30), could be explained by virtue of a higher likelihood of these patients to receive VDRA as a result of their higher PTH levels (31). Such findings are epidemiologic-observational in nature, and causality is yet to be proven (32). In terms of the dose-response phenomenon, it has recently been shown that higher paricalcitol doses per unit of PTH—the so-called paricalcitol to PTH ratio—exhibited incrementally greater survival in 34,307 hemodialysis patients who were followed for up to 3 yr (Figure 1) (33).

Recently, Tentori *et al.* (34) analyzed a heterogeneous international cohort of 38,066 dialysis patients from 12 countries across four continents who received diverse forms of vitamin D agents including oral (alphacalcidol, calcitoriol and others [probably also cholecalciferol]) and intravenous (calcitriol, paricalcitol, doxercalciferol and maxacalcitol) compounds. The survival advantages of vitamin D persisted in most versions of the multivariate regression models including time-dependent and even more sophisticated marginal structural models, except for an instrumental variable model (35). While the creation of an instrumental variable in analyzing the CKD cohorts might be a legitimate effort to try to mitigate the impact of confounding by medical indication and/or nonrandom therapy assignment, the selection of an inappropriate instrumental variable may introduce new sources of error and bias, especially if the basic

Table 2. Epidemiologic studies examining survival advantages of active vitamin D agents, also known as vitamin D receptor activator (VDRA) in CKD patients

Author/Year	Number of Patients	Examined Therapy	Main Results	Comments
Shoji *et al.*, 2004 (84)	242	Oral alfacalcidol *versus* no treatment	Lower cardiovascular mortality with alfacalcidol treatment.	Prevalent HD patients from Japan; all cause mortality similar in the two groups.
Teng *et al.*, 2003 (54)	67,399	Paricalcitol *versus* calcitriol	16% lower all-cause mortality with paricalcitol.	Prevalent HD patients from Fresenius, benefit also present in patients who switched treatments.
Teng *et al.*, 2005 (25)	51,037	Any VDRA *versus* no treatment	20% lower all-cause mortality in the VDRA (IV calcitriol and paricalcitol) group.	Prevalent HD patients from a single for-profit dialysis chain; benefit present in 48 of 49 examined subgroups.
Melamed *et al.*, 2006 (28)	1007	IV calcitriol *versus* no treatment	Lower all-cause mortality associated with IV calcitriol use.	Incident HD and PD patients from CHOICE study.
Tentori *et al.*, 2006 (29)	7731	Any VDRA *versus* none, and calcitriol *versus* paricalcitol *versus* doxercalciferol	Lower mortality with any VDRA *versus* none. No difference between the three different types of VDRA after multivariable adjustment.	Prevalent HD patients from a single non-profit dialysis chain.
Kalantar-Zadeh *et al.*, 2006 (26) and Lee *et al.*, 2007 (85)	58,058	Paricalcitol *versus* no treatment	Lower all-cause mortality associated with IV paricalcitol use in time-dependent models.	Prevalent HD patients from a single for-profit dialysis chain. Benefit present in all examined subgroups.
Kovesdy *et al.*, 2008 (23)	520	Calcitriol *versus* no treatment	Lower all-cause mortality with po calcitriol.	CKD stages 2 to 5, nondialysis dependent. Also showed trend toward lower ESRD incidence with calcitriol.
Shoben *et al.*, 2008 (24)	1418	Oral calcitriol *versus* no treatment	Lower risk of all-cause mortality and combined mortality or ESRD with po calcitriol.	CKD stages 3 and 4, mostly male US veterans from the Pacific Northwest.
Naves-Diaz *et al.*, 2008 (27)	16,004	Oral calcitriol *versus* no treatment	Lower mortality with po calcitriol.	Prevalent HD patients from six Latin American countries. Lowest mortality was seen in those taking the lowest dose of calcitriol.
Shinaberger *et al.*, 2008 (33)	34,307	Paricalcitol lower dose *versus* higher dose	Higher ratio of IV paricalcitol dose to PTH level associated with greater survival.	Prevalent HD patients from a single for-profit dialysis chain. Results suggest a dose-response effect for survival benefit with VDRA.
Wolf *et al.*, 2008 (31)	9303	VDRA *versus* no treatment, stratified by race	Mortality lower with VDRA treatment in each race stratum.	Incident HD patients enrolled in a prospective cohort (ArMORR).
Tentori *et al.*, 2009 (34)	38,066 dialysis patients from 12 countries (1996– 2007)	Inactive and active vitamin D agents combined (see text)	Time-varying and MSM regression models showed 7% to 22% lower mortality. No difference in mortality in instrumental variable models.	Did not differentiate between nutritional and active vitamin D. Validity of instrumental variable not proven.

Note that the study by Tentori *et al.* (34) included both inactive and active vitamin D agents combined (see text).

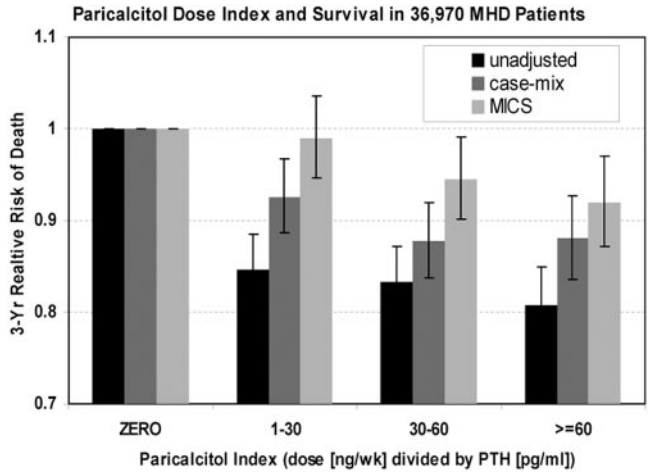

Figure 1. Survival advantages of higher doses of intravenous paricalcitol per each unit of serum PTH in 34,307 maintenance hemodialysis patients (adapted from ref. 33).

assumptions of this error-prone methodology are violated (36). Tentori *et al.* used the percentage of patients prescribed vitamin D in each dialysis clinic as the instrumental variable and stated that this arbitrarily created covariate, which was adjusted for in multivariate regressions, was not influenced by an individual patient's characteristics, which could have influenced the mortality risk (34). In addition to (inappropriately) combining various nutritional and active vitamin D agents under the uniform predicting variable "vitamin D" in the regression model, the appropriateness of the said instrumental variable remains in question, as the study's methodology section did not provide details about how and if it was subjected to necessary testing to assure its proper functioning. (34). This approach would resemble the inclusion of the percentage of individuals carrying lighters or match boxes (for lighting a fire to smoke tobacco) as an instrumental variable when examining the association between smoking and lung cancer across diverse communities. Such an adjustment may lead to the mitigation or even elimination of the association between smoking and lung cancer in a multivariate regression model.

Effects of Nutritional Vitamin D and VDRA on Biochemical End Points

In spite of the intriguing possibility that vitamin D administration might affect hard outcomes, the current routine clinical application of all these agents is largely restricted to indications comprising biochemical end points. We will examine below the evidence concerning the effects of nutritional and active vitamin D on such biochemical end points.

Vitamin D and Secondary Hyperparathyroidism

The main clinical indication for the use of both nutritional and active vitamin D in CKD to date is the suppression of SHPT. Although higher serum PTH levels are associated with worse survival in NDD-CKD patients (37,38), in North-American maintenance dialysis patients, serum PTH appears to have a U-shape association with survival (26), an observation that supported the notion of an "ideal" PTH level being 150 to 300 pg/ml in dialysis patients (10). We hypothesize that low PTH levels have a spurious association with mortality, especially since VDRAs are usually withheld when PTH level is below 150 pg/ml due to fear of adynamic bone disease (20). Furthermore, the deleterious effects of very high PTH levels are probably mitigated in US dialysis cohorts as a result of unusually high doses of VDRA that are administered to correct a more severe SHPT (33). In a Japanese dialysis patient cohort, low PTH levels (<150 pg/ml) were associated with the greatest survival (39). We recently found that low PTH is yet another facet of malnutrition-inflammation complex and that after adjusting for this confounder, a PTH level in the 100 to 150 pg/ml range is associated with the best 5-yr survival in hemodialysis patients (40).

Properly designed clinical trials have not been conducted to show the efficacy and safety of nutritional vitamin D in the treatment of SHPT and its consequences. Before the VDRA-era, ergocalciferol or cholecalciferol were used with only modest success in CKD patients. A controlled trial by Berl *et al.* (8) found that vitamin D_3 (cholecalciferol) was not effective in decreasing serum PTH level in dialysis patients, whereas calcitriol was. In this study, nine of 12 patients on D_3 showed histologic deterioration of bone disease, whereas in six of seven patients who received calcitriol improved or had unchanged bone histology (8). In a study by Malluche *et al.* (9), vitamin D_3, in doses that normalized intestinal absorption of calcium, failed to restore bone histology to normal, although mineralization and collagen texture of osteoid were consistently improved.

As shown in Table 3, a number of small clinical trials have been conducted in the past few years to examine the biochemical effects of nutritional vitamin D in CKD patients (41–49). Most of these studies have shown either no (41,45,48,49) or minimal to inadequate changes in PTH levels, usually only in some stages of CKD (42,43), or changes that still would not satisfy the KDOQI recommended target ranges for PTH (44). Some non-MBD biochemical outcomes associated with nutritional vitamin D were an improved glycemic profile (hemoglobin A1c) (49) or greater response to erythropoietin stimulating agents (ESA) (45). Most of these studies suffer from significant flaws in the design or conduct of the study, including small sample sizes, nonrandomized assignment, lack of an appropriate control arm, and short-term follow-up periods. Larger and better designed randomized controlled trials are needed to examine whether nutritional vitamin D replacements improve SHPT across various stages of CKD.

Due to regulatory requirements in the United States, several active vitamin D analogues have undergone rigorous testing in clinical trials to prove their efficacy and safety as treatment regimens for SHPT (50–53). While head-to-head comparisons of the various VDRAs in the treatment of SHPT are few and inadequately powered to allow any statement of superiority for one *versus* the other, there are some interesting physiologic considerations regarding their differential effects that may merit further studying. Differences in survival-advantages between paricalcitol and calcitriol observed in an epidemiologic study (54) may also be explained by virtue of their differential

Table 3. Recent studies related to the use of nutritional vitamin D compounds in CKD

Author/Year	Subjects	Vitamin D Dose	Change in Serum Vitamin D Level	Change in Other Relevant Biomarkers	Comments
Shah *et al.*, 2005 (41)	29 PD patients	Ergocalciferol 50,000 IU weekly for 4 wk	<7 (6.9 to 8) to 30 (6.9 to 82) ng/ml	No change in PTH or $1,25(OH)_2D$.	Retrospective, observational study.
DeVille *et al.*, 2006 (42)	85 NDD-CKD subjects stages 3 to 5	Ergocalciferol 800 IU to 100,000 IU/ wk	17.4 to 42.1 ng/ml	Median PTH decreased by 2.8 pmol/L (95% CI 1.3-4.4, $P < 0.001$).	Decrease in PTH only observed in CKD stage 4, but not stages 3 or 5.
Al-Aly *et al.*, 2007 (43)	66 NDD-CKD subjects, stages 3 and 4	Ergocalciferol 50,000 IU weekly for 12 wk and monthly for 6 mo	16.6 ± 0.7 to 27.2 ± 1.8 ng/ml	PTH levels decreased from 231 ± 26 to 192 ± 25 pg/ml.	Decrease in PTH only in CKD stage 3.
Zisman *et al.*, 2007 (44)	52 NDD-CKD subjects	Ergocalciferol according to KDOQI recommendation	20.3 ± 1.3 to 31.6 ± 2.2 ng/ml in CKD stage 3, and 18.8 ± 1.3 to 35.4 ± 1.9 ng/ml in CKD stage 4	PTH decreased by 13% in CKD stage 3, but only by 2% in CKD stage 4.	Prospective, nonrandomized, observational study.
Saab *et al.*, 2007 (45)	119 HD patients	Ergocalciferol 50,000 IU monthly for 6 mo	16.9 ± 8.5 to 53.6 ± 16.3 ng/ml	No change in PTH.	Retrospective, observational study. Decreased ESA dose in 64% of patients
Jean *et al.*, 2008 (46)	149 HD patients	Cholecalciferol 10 to 30 μg/day	30 ± 19 to 126 ± 46 nmol/ L	Lowered PTH and AP in patients whose serum vitamin D levels increased following supplementation.	13% of patients showed partial response to replacement
Jean *et al.*, 2008 (47)	43 HD patients	Cholecalciferol) 10 to 30 μg/day	27.8 ± 18 to 118 ± 34 nmol/l	$1,25(OH)_2$ D levels increased from 7.7 ± 5 to 30.5 ± 15 pmol/l. PTH levels decreased from 144 ± 108 to 108 ± 63 pg/ml. AP unchanged.	1,25(OH)2 D levels increased in parallel with 25(OH)D levels.
Chandra *et al.*, 2008 (48)	20 NDD-CKD subjects, stages 3 and 4	Cholecalciferol 50,000 IU weekly for 12 wk *versus* placebo	17.3 (95% CI: 11.8 to 25.2) to 49.4 ng/ml (95% CI: 33.9 to 72.0)	No change in PTH or $1,25(OH)_2D$	Double-blind, randomized controlled pilot study.
Blair *et al.*, 2008 (49)	344 HD patients	Ergocalciferol 50,000 IU weekly for 24 wk	18.4 ± 9.0 to 42.0 ± 24.7 ng/ml	HbA1c levels fell 6.9 to 6.4 Hemoglobin increased 12.1 to 12.3 Decrease in serum calcium, no change in PTH.	Retrospective, observational study.

effects on diverse PTH segments, as found by Monier-Faugere *et al.* (55), the description of which is beyond the scope of this review article.

Vitamin D and Alkaline Phosphatase

Among the myriad of proposed pathophysiologic mechanisms that can explain the survival advantages of VDRA in

Table 4. Effect of active vitamin D agents on serum alkaline phosphatase (AP)

Author/Year	AP Related Outcomes	Other Findings
Moriniere *et al.*, 1985 (86)	27 HD patients randomly assigned to 1-α (OH) D_3 *versus* placebo. Although serum AP values were *not* significantly different between 2 groups, AP increased in control	Serum phosphate, Calcium- phosphate product and aluminium were higher in 1-α (OH) D_3 group.
Baker *et al.*, 1989 (76)	NDD-CKD subjects randomized to po calcitriol ($n = 8$) *versus* placebo ($n = 8$). Significant fall in serum phosphorus and AP concentrations in 13 patients who finished the study	Bone biopsy histology after 12 mo showed evidence of amelioration of hyperparathyroid changes in calcitriol group.
Przedlacki *et al.*, 1995 (77)	NDD-CKD subjects randomized to po calcitriol *versus* placebo. Mean AP was 143 (calcitriol, $n = 13$) *versus*, 180 IU/L (placebo, $n = 12$)	Increase in bone mineral density in the calcitriol group measured by DEXA.
Martin *et al.*, 1998 (52)	78 HD patients (40 Paricalcitol injection, 38 placebo) for 12 wk. Significant reduction in serum AP from 148 to 101 U/L in paricalcitol group ($P < 0.001$) compared with 120 to 130 U/L ($P =$ NS) in placebo	Paricalcitol led to significant drop in iPTH from 795 to 406 pg/ml ($P < 0.001$), but not in placebo ($P =$ NS).
Moe *et al.*, 2001 (78)	31 HD patients not receiving vitamin D because of low PTH randomized to placebo or IV paricalcitol for 12 wk. *Paricalcitol* led to significant drop in PTH and bone AP (all $P < 0.05$).	Among 20 anergic patients, four of 11 in paricalcitol and 0 of 9 in the placebo group converted to reactive ($P = 0.09$).
Coyne *et al.*, 2006 (51)	NDD-CKD subjects randomized to po paricalcitol ($n = 107$) *versus* placebo ($n = 113$). 46% reduction in bone specific AP in paricalcitol *versus* 7% in placebo.	At least two consecutive decreases in iPTH levels of 30% or greater from baseline occurred in 91% of paricalcitol *versus* 13% of placebo patients ($P < 0.001$).

CKD patients, the revisited role of alkaline phosphatase (AP) warrants special attention. Increased serum AP level (hyperphosphatasemia or hyperphosphatasia) in CKD patients is usually resulting from excesses of the bone isoforms of the enzyme (62,63). Although the first KDOQI guidelines did not recommend monitoring serum AP (10), a recent epidemiologic study showed a robust association between serum AP >120 U/L and poor survival in hemodialysis patients (64). Indeed, compared with serum PTH, which has a U-shaped association with mortality, serum AP appears to have a linear and incremental association with both all-cause and cardiovascular mortality, and this association appears to hold across different PTH strata including PTH level below 150 pg/ml (26).

Higher AP has indeed been shown to result in increased hydrolysis of pyrophosphate (65,66), which is a potent inhibitor of vascular calcification (67–69). The effect of AP on pyrophosphate could be the link that explains why lower levels of the former are associated with a linear decrease in mortality (70). Indeed, a recent epidemiologic study found that higher levels of AP, but not other biomarkers such as PTH or minerals, were associated with coronary artery calcification in hemodialysis patients (71). A recent study also suggested that the lower serum AP, the better is the response of dialysis patients to erythropoietin stimulating agents during anemia management (72). Another possible explanation for the observed association is a link between higher AP and lower 25(OH)D levels (73–75), which is *per se* associated with increased mortality (22). AP is also a marker of bone turnover, and as such it is closely associated with PTH levels. It is thus of interest to examine how various (nutritional and active) vitamin D agents fare in suppressing elevated AP levels, although such an application for these agents has not yet reached mainstream.

Similar to the effects on SHPT, mixed results have been reported on the impact of nutritional vitamin D agents on serum AP in a small number of flawed studies (46,47). Conversely, as shown in Table 4, the level of circulating AP can be effectively decreased by active vitamin D products (51,52,76–78) (and possibly also calcimimetics [79], further description of which is beyond the scope of this focused review paper). Indeed a recent meta-analysis, which questioned the PTH lowering effect of active vitamin D analogs, showed that these agents can decrease serum AP effectively (80). As therapeutic tools for

treatment of hyperphosphatasemia, VDRAs appear to be effective agents. Better studies will be needed to judge the efficacy of nutritional vitamin D.

Epilogue

SHPT is engendered, at least in part, as a result of the progressive decline in circulating level of $1,25(OH)_2D_3$. Replacement of active vitamin D has thus become the main strategy in the treatment of SHPT. Assuming that PTH is a uremic toxin and associated with poor survival in CKD, normalization of PTH levels using active vitamin D agents or calcimimetics appears prudent, provided that reliable PTH assays can be used (81). Currently there is not enough evidence to suggest that nutritional vitamin D compounds can achieve a similar control of SHPT or of elevated AP. To that end, we question the wisdom of opinion-based KDOQI recommendations on administering nutritional vitamin D compounds without adequate evidence from CKD population-based studies. The failure of statin trials in improving outcomes of dialysis patients (82,83) clearly shows that general population-based paradigms should not be blindly extrapolated as guidelines for CKD patients. Similarly we question the utility of measuring 25(OH) vitamin D level for management of dialysis patients, especially since the vast majority of patients appear to be deficient, and (somewhat analogously) over the past three decades, anemia management has been accomplished successfully without measuring the erythropoietin level in the same patient population.

We believe that ultimately the best vitamin D agents for CKD patients will be the ones that improve survival irrespective of suggested or imposed target ranges for arbitrary or opinion-based surrogate end points. Since, to date, clinical trials do not exist to show which vitamin D agent(s) might achieve this, our interventions at this point appear limited to controlling biochemical targets by using agents that have been proven to do this in properly designed clinical trials with such surrogate end points, which means VDRA, among others. Notwithstanding the potential upside of nutritional vitamin D stemming from physiologic considerations, we would advise that patience and good science should preempt premature enthusiasm about their clinical application in the CKD population before proper proof from clinical trials becomes available.

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