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Con: Nutritional vitamin D replacement in chronic kidney disease and end-stage renal disease

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ABSTRACT

Insufficiency of 25-hydroxyvitamin D [25(OH)D] is highly prevalent among patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD) and is a critical component in the pathogenesis of secondary hyperparathyroidism. Accordingly, current National Kidney Foundation—Kidney Disease Outcomes Quality Initiative and Kidney Disease: Improving Global Outcomes guidelines recommend the correction of hypovitaminosis D through nutritional vitamin D replacement as a first-step therapeutic approach targeting secondary hyperparathyroidism. In this Polar Views debate, we summarize the existing evidence, aiming to defend the position that nutritional vitamin D replacement is not evidence-based and should not be applied to patients with CKD. This position is supported by the following: (i) our meta-analysis of randomized controlled trials shows that whereas nutritional vitamin D significantly increases serum 25(OH)D levels relative to placebo, there is no evidence either in predialysis CKD or in ESRD that parathyroid hormone (PTH) is lowered; (ii) on the other hand, in randomized head-to-head comparisons, nutritional vitamin D is shown to be inferior to activated vitamin D analogs in reducing PTH levels; (iii) nutritional vitamin D is reported to exert minimal to no beneficial actions in a series of surrogate risk factors, including aortic stiffness, left ventricular mass index (LVMI), epoetin utilization and immune function among others; and (iv) there is no evidence to support a benefit of nutritional vitamin D on survival and other 'hard' clinical outcomes. Whereas nutritional vitamin D replacement may restore 25(OH)D concentration to near normal, the real target of treating vitamin D insufficiency is to treat secondary hyperparathyroidism, which is untouched by nutritional vitamin D. Furthermore, the pleotropic benefits of nutritional vitamin D remain to be proven. Thus, there is little, if any, benefit of nutritional vitamin D replacement in CKD.

Keywords: cholecalciferol, CKD, nutritional vitamin D, secondary hyperparathyroidism

INTRODUCTION

Among people with chronic kidney disease (CKD) or end-stage renal disease (ESRD), 25-hydroxyvitamin D [25(OH)D] insufficiency or deficiency is common and has been proposed to contribute to the pathogenesis of secondary hyperparathyroidism and other alterations related to the CKD–mineral and bone disorder (CKD-MBD) [1–3]. The National Kidney Foundation—Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) [4] and Kidney Disease: Improving Global Outcomes (KDIGO) [1] guidelines recognize the potential role of low serum 25(OH)D levels and both guidelines recommended that 25(OH)D deficiency or insufficiency should be corrected as a first-step therapeutic approach targeting secondary hyperparathyroidism in people with non-dialysis-requiring CKD; no such recommendation was provided for people with ESRD. If this approach is ineffective, then guidelines recommend the utilization of vitamin D receptor activators (VDRAs) [1, 4]. The use of nutritional vitamin D supplements in CKD and ESRD is an issue surrounded by substantial controversy, given that NKF-KDOQI and KDIGO recommendations were based mainly on expert opinion instead of supporting evidence from properly designed, randomized controlled trials (RCTs) [2].

In this Polar Views debate, we review the existing evidence, aiming to support the position that the use of nutritional vitamin D supplementation has little or no beneficial effect in the management of people with CKD, including ESRD. We conclude that the scientific basis of the use of nutritional vitamin D among people with CKD and ESRD rests on weak evidence.

OBSERVATIONAL EVIDENCE

Over the past years, numerous observational studies conducted in CKD and ESRD populations have associated low serum

25(OH)D with higher parathyroid hormone (PTH) levels and various adverse health-related outcomes, such as acceleration of vascular calcifications, higher incidence of bone fractures, early glomerular filtration rate loss, faster CKD progression and increased risk of cardiovascular morbidity and mortality [5–10]. A previous meta-analysis of 10 prospective observational studies with an overall sample of 6853 CKD patients suggested that each 10 ng/mL increase in serum 25(OH)D levels is associated with a 14% reduction in the risk of all-cause mortality [relative risk (RR): 0.86; 95% confidence interval (CI): 0.83–0.91] [11]. Another meta-analysis by Kandula *et al.* [12] including 17 non-randomized interventional studies suggested that among those with CKD, nutritional vitamin D can successfully restore serum 25(OH)D levels [mean difference (MD): 24.1 ng/mL; 95% CI: 19.6–28.6], exerting in parallel a significant PTH-lowering effect (MD: −47.1 pg/mL; 95% CI: −55.8 to −27.7). However, these positive effects should be interpreted within the context of the inherent methodological limitations of the individual studies included in this meta-analysis; these studies were observational in nature and of low-to-moderate quality [12]. Although the observational evidence seems to be positive, causality between nutritional vitamin D replacement and improvement in outcomes cannot be established through observational association studies. Observational studies are rife in nephrology and often used to make guidelines. However, without properly designed, RCTs we cannot fully elucidate whether nutritional vitamin D has a role in people with CKD. We will therefore review the randomized evidence next, to explore the possibility of whether nutritional vitamin D is valuable in CKD.

RANDOMIZED EVIDENCE

Effect of nutritional vitamin D on 25(OH)D status and PTH levels

A previous meta-analysis of five RCTs comparing the effects of nutritional vitamin D with placebo suggested a significant increase in serum 25(OH)D levels with cholecalciferol or ergocalciferol supplementation (MD: 13.9 ng/mL; 95% CI: 5.6–22.4); restoration of vitamin D status was shown to be accompanied by a modest, but statistically significant reduction in PTH levels (MD: −32.5 pg/mL; 95% CI: −57.0 to −6.1) [12]. This meta-analysis was published in 2010 and combined data from only three available RCTs reporting data on 25(OH)D (71 patients) and only four RCTs reporting data on PTH levels (90 patients) [12]. From that time-point and onwards, additional randomized evidence has accumulated. To provide a more conclusive answer to the question of whether nutritional vitamin D has a role in management of secondary hyperparathyroidism among people with CKD, we performed an updated meta-analysis of the currently available evidence on these two outcomes.

As shown in Figure 1, we identified 4 RCTs including 130 CKD participants not yet on dialysis [13–16] and 14 RCTs including 888 ESRD participants on maintenance dialysis [16–28] that compared inactive vitamin D with placebo and reported data on serum 25(OH)D levels. The study of Marckmann *et al.* [16] is reported twice in Figure 1, because this study included patients with stage 3–5D CKD; accordingly, the outcome of 25(OH)D was analyzed separately for predialysis CKD and ESRD subgroups. In predialysis CKD, the weighted MD in the change of 25(OH)D levels during follow-up between nutritional vitamin D and placebo groups was 12.5 ng/mL (95% CI: 8.48–16.52) using an inverse-weighted, fixed-effect model and 21.19 ng/mL (95% CI: 8.87–33.51) using a random-effects model. In ESRD, the weighted MD in change of 25(OH)D between nutritional vitamin D and placebo groups was 16.01 ng/mL (95% CI: 13.31–18.71) using an inverse-weighted, fixed-effect model and 20.89 ng/mL (95% CI: 15.76–26.03) using a random-effects model. There was no evidence of heterogeneity between CKD and ESRD subgroups (P = 0.156).

With regards to the pooled PTH-lowering effect of nutritional vitamin D, we identified four RCTs including 122 predialysis CKD participants [14–16, 29] and seven RCTs including 568 ESRD participants on dialysis [17, 20, 22, 24, 25, 27, 28] that reported data on PTH levels (Figure 2). In predialysis CKD, the weighted MD in the change of PTH levels during follow-up between nutritional vitamin D and placebo groups was not significant either using an inverse-weighted, fixed-effects model (MD: −4.01 pg/mL; 95% CI: −26.67 to 18.65) or using a random-effects model (MD: −28.22 pg/mL; 95% CI: −105.8 to 49.35). Consistent with the above observation, in ESRD, nutritional vitamin D did not significantly improve PTH levels as compared with placebo either when an inverse-weighted, fixed-effects model (MD: −24.43 pg/mL; 95% CI: −53.27 to 4.42) or when a random-effects model was used (MD: −25.33 pg/mL; 95% CI: −57.28 to 6.62). There was no evidence of heterogeneity between the predialysis CKD and ESRD subgroups (P = 0.275). In contrast to the smaller earlier meta-analysis, the above data suggest that a significant PTH-lowering effect with inactive vitamin D is supported neither in the predialysis CKD nor in the ESRD setting.

Nutritional vitamin D versus vitamin D receptor activators for PTH-lowering

VDRAs such as paricalcitol or doxercalciferol have been approved by the US FDA for the prevention or treatment or both of secondary hyperparathyroidism in CKD. Thus, their value in treating these conditions in those with CKD is firmly established using rigorous double-blind RCTs [30–32]. However, head-to-head comparisons with nutritional vitamin D are few.

In a single-blind randomized trial, Moe *et al.* [33] performed a head-to-head comparison between cholecalciferol (4000 IU/day for 1 month and then 2000 IU/day for the next 2 months, $n = 22$) and the active vitamin D analog doxercalciferol (1 μg/day, $n = 25$) in 47 vitamin D deficient patients with stage 3–4 CKD and secondary hyperparathyroidism. After 3 months of therapy, a significant reduction in PTH levels of 27 ± 34% (P = 0.002) was noted in the active vitamin D group, and a non-significant reduction of 10 ± 31% (P = 0.16) in the cholecalciferol group; the between-group difference in the proportional change of PTH was not significant (P = 0.11), possibly due to the small sample size. A significant increase of 23 ng/mL in serum 25(OH)D levels from pre- to post-treatment (P < 0.001) was noted in cholecalciferol-treated patients, but not in those treated with doxercalciferol [33].

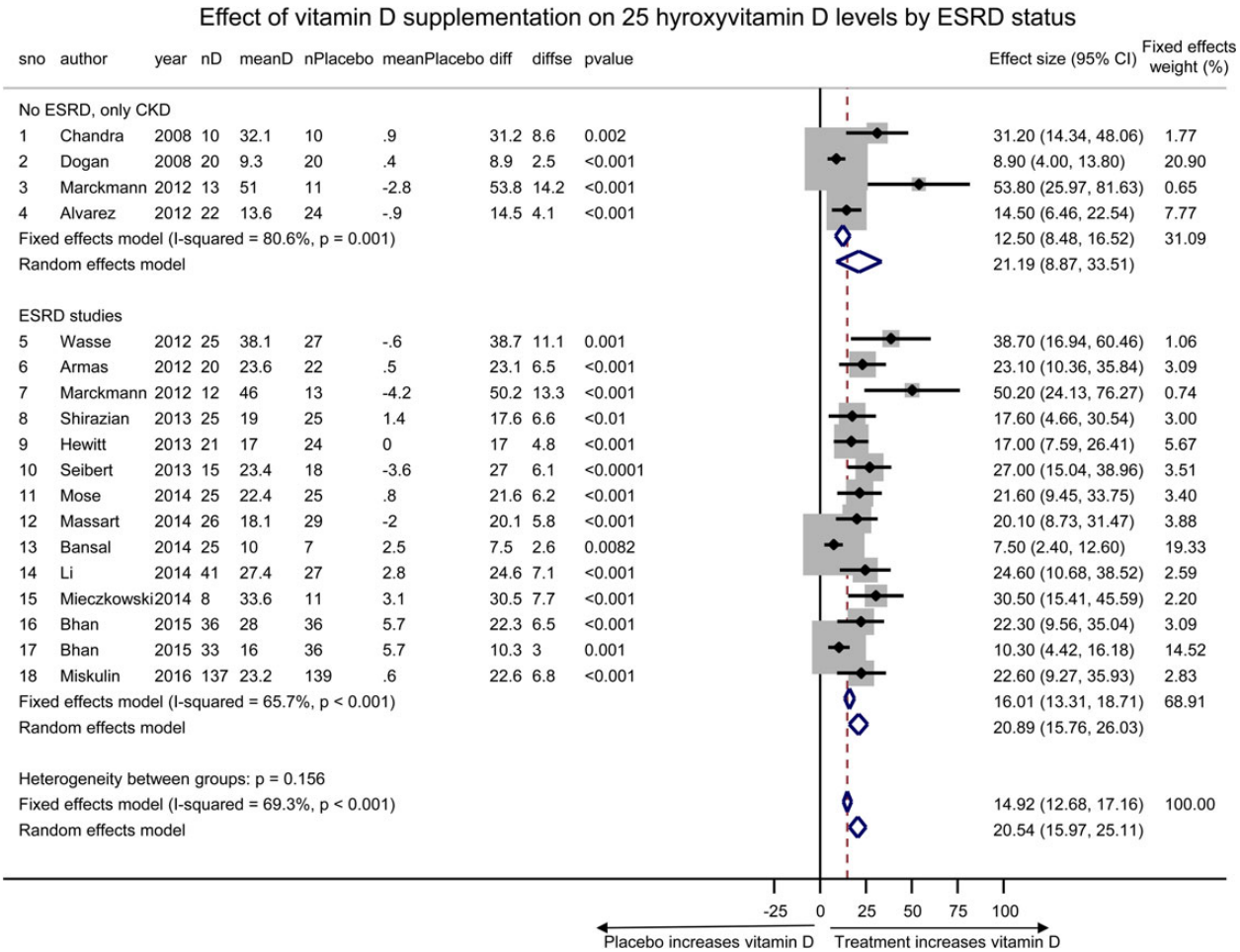

FIGURE 1: Forest plot depicting the change from baseline in 25(OH)D levels in the 'nutritional vitamin D group' minus the change from baseline in the 'placebo group'.

Kovesdy *et al.* [34] randomized 80 stage 3–4 CKD patients with vitamin D deficiency and secondary hyperparathyroidism to ergocalciferol (50 000 IU weekly-to-monthly) or paricalcitol (1–2 μg/day) for 4 months. Ergocalciferol was shown to be inferior to active vitamin D in causing PTH reduction, since the proportion of patients reaching the primary study endpoint (defined as the occurrence of two consecutive PTH levels decreased by at least 30% from baseline) was significantly lower in ergocalciferol-treated than in paricalcitol-treated participants (18 versus 58%, P = 0.002) [34]. To the extent that this inferiority is true, the use of nutritional vitamin D in CKD is not only ineffective, but may also result in delayed institution of other effective therapies against secondary hyperparathyroidism, such as activated vitamin D analogs.

Effects of nutritional vitamin D on non-mineral-related intermediate endpoints

Vitamin D has numerous non-calcemic effects such as vascular effects, immunomodulatory effects, anti-inflammatory effects, suppression of the renin-angiotensin system, and effects on glucose homeostasis [35]. Therefore, it should not be surprising that numerous investigators have tested the non-calcemic benefits of vitamin D supplementation among people with CKD.

We discuss further that nutritional vitamin D has minimal to no beneficial actions on these endpoints. Effects on a series of intermediate outcomes reported in RCTs, the so-called pleotropic effects, are summarized in Table 1 and discussed in detail below.

Pulse wave velocity and left ventricular mass index. In a double-blind manner, Marckmann *et al.* [16] randomized 52 patients with stage 3–5D CKD to cholecalciferol (40 000 IU weekly) or placebo. Over a 2-month-long follow-up, changes in aortic pulse wave velocity (PWV) were comparable in both vitamin D and placebo; this effect was consistent in both predialysis CKD and ESRD subgroups. In a subsequent study, Dreyer *et al.* [29] investigated the effect of ergocalciferol (50 000 IU weekly for 1 month and monthly later) versus placebo on macro- and microcirculatory function. Over a 6-month follow-up, change in aortic PWV and LVMI was no different between groups. However, ergocalciferol significantly improved endothelium-dependent vasodilatation after iontophoresis of acetylcholine, suggesting a benefit on microcirculatory endothelial function [29]. In contrast, in a larger RCT testing

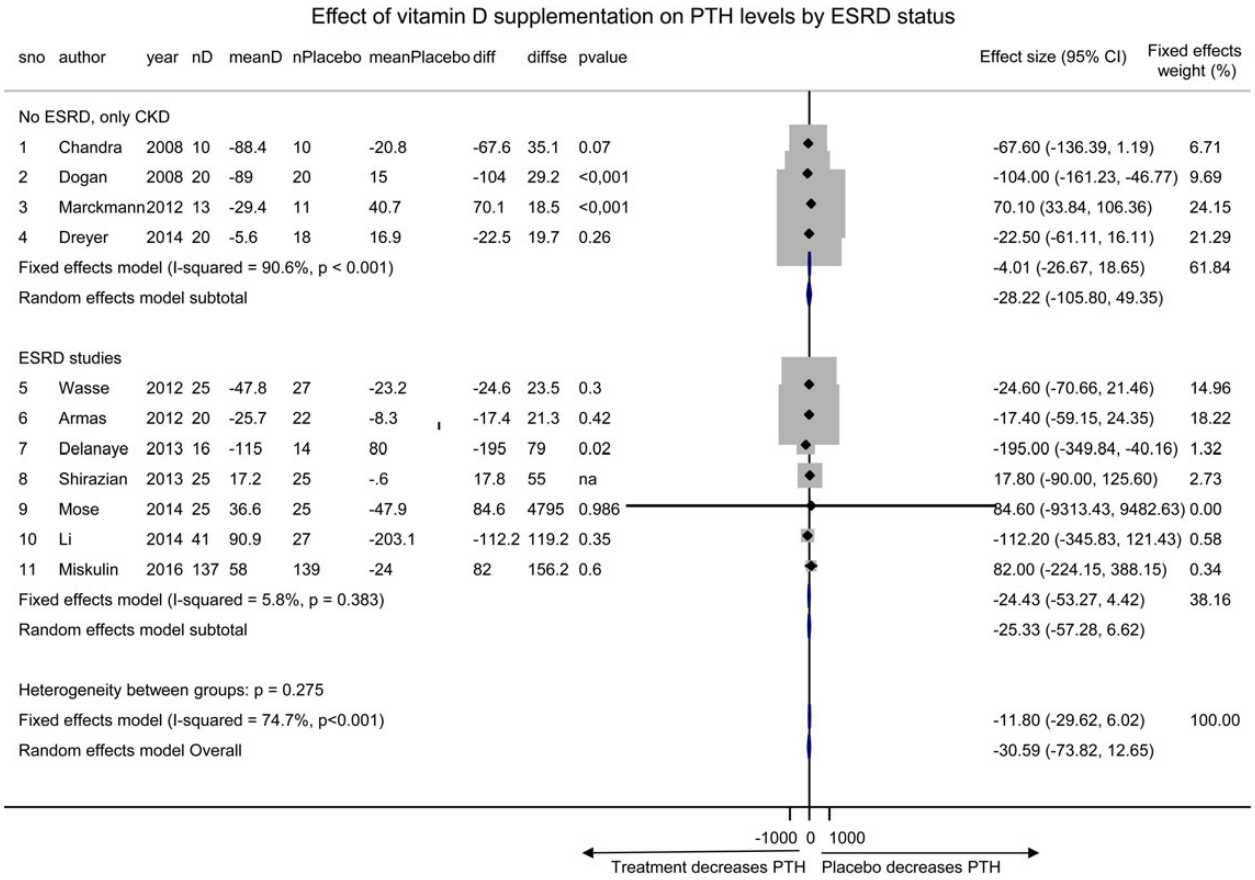

FIGURE 2: Forest plot depicting the change from baseline in PTH levels in the 'nutritional vitamin D group' minus the change from baseline in the 'placebo group'.

paricalcitol versus placebo, the endothelium-dependent vasodilatation in patients with stage 3 and 4 CKD was improved 1.8% (95% CI: 0.3–3.1%, P = 0.016) [38].

As in the case of predialysis CKD, Mose *et al.* [25] showed that among 64 ESRD patients receiving hemodialysis, 6-month-long therapy with cholecalciferol (3000 IU/day) was unable to improve aortic PWV and LVMI relative to placebo (ΔPWV: 0.8 versus 0.1 m/s, P = 0.269; ΔLVMI: 3 versus −5 g/m^2, P = 0.397) [25]. In another study, Hewitt *et al.* [21] randomized 60 hemodialysis patients with 25(OH)D deficiency to ergocalciferol (50 000 IU weekly for 8 weeks and monthly later) or placebo for 6 months; nutritional vitamin D was not superior to placebo in improving aortic stiffness.

Anemia. The effect of nutritional vitamin D on epoetin utilization was investigated in the recently reported study of Miskulin *et al.* [24], in which 276 hemodialysis patients with serum 25(OH)D levels <30 ng/mL were randomly assigned to receive double-blind therapy with ergocalciferol (50 000 IU weekly) or placebo. Nutritional vitamin D had no effect on anemia management over the 6-month follow-up, since rate of change in epoetin dose over time was no different between the ergocalciferol and placebo groups (geometric mean rate: 0.99; 95% CI: 0.95–1.03) [24]. The effect of nutritional vitamin D on anemia-related parameters was also reported in the Dialysis Infection and Vitamin D in New England (DIVINE) trial [19], in which 105 hemodialysis patients were randomized to three different arms (ergocalciferol 50 000 IU/month, ergocalciferol 50 000 IU/week or placebo). Frequency of intravenous iron use (monthly 39% versus weekly 39% versus placebo 51%, P = 0.49) and epoetin utilization (monthly 71% versus weekly 69% versus placebo 60%, P = 0.61) were not different between the three study arms [19].

Immune function. To investigate the effect of nutritional vitamin D on immune function, Li *et al.* [22] randomized 96 hemodialysis patients in a 2:1 ratio to cholecalciferol (50 000 IU weekly) or no supplementation. Change in alloreactive T-cell memory assessed by IFNγ ELISPOT-based panel of reactive T-cell assays (PRT) was no different between groups over the 12-month follow-up of the trial (ΔPRT: 104.8 ± 2330.8 versus 252.9 ± 2431.3, P = 0.25) [22]. In another double-blind RCT, Seibert *et al.* [26] showed that administration of cholecalciferol at a dose of 20 000 IU/week for 3 months had no benefit relative to placebo on monocyte subset cell count, T-cell differentiation and cytokine production.

Other outcomes. In the aforementioned study of Hewitt *et al.* [21], 6-month-long ergocalciferol supplementation did not improve muscle strength tests, functional capacity and health-related quality of life assessed with the use of the Kidney Disease Quality of Life-36 survey. Two other small RCTs

Table 1. Randomized studies comparing the effect of inactive vitamin D supplementation versus placebo or no treatment on surrogate risk factors in patients with CKD and ESRD

Author	Year	*n*	Patient characteristics	Design	Intervention	Control	Duration (months)	Outcome	Overall effect	Details
Studies in CKD patients										
Marckmann [16]	2012	52	CKD stage 3–5D	Double-blind	Cholecalciferol (40 000 IU weekly)	Placebo	2	Change in PWV	Null	PWV was unchanged over time (ΔPWV: 0.7 versus −0.3 m/s, P = NS)
Alvarez [36]	2013	46	CKD stage 2–3	Double-blind	Cholecalciferol (50 000 IU weekly for 12 weeks and then 50 000 IU every other week)	Placebo	12	Change in inflammatory biomarkers	Null	Change in serum MCP-1 over time was no different between groups (−3.0 ± 14.5 versus 2.5 ± 13.2%, P = NS)
Dreyer [29]	2014	38	Stage 3–4 CKD with 25(OH)D <16 ng/mL	Double-blind	Ergocalciferol (50 000 IU weekly for 1 month and monthly later)	Placebo	6	Change in micro- and macrocirculatory function	Null	No effect on aortic PWV (P = 0.78) and LVMI (P = 0.44)
									Positive	Ergocalciferol improved endothelium-dependent vasodilatation after iontophoresis of acetylcholine (P = 0.03)
Studies in ESRD patients										
Delanaye [20]	2013	43	HD patients with 25(OH) D insufficiency	Double-blind	Cholecalciferol (25 000 IU every 2 weeks)	Placebo	12	Change in vascular calcification score	Null	No difference between groups in change of vascular calcification score over time (Deltas: 2 ± 3 versus 2 ± 2, P = 0.89)
Hewitt [21]	2013	60	HD patients with 25(OH) D <24 ng/mL	Double-blind	Ergocalciferol (50 000 IU weekly for 8 weeks and monthly later)	Placebo	6	Change in muscle strength, PWV and HRQOL	Null	Muscle strength tests, aortic PWV and HRQOL domains were no different between groups
Seibert [26]	2013	38	HD patients with 25(OH) D insufficiency	Double-blind	Cholecalciferol (20 000 IU weekly)	Placebo	3	Change in immune function	Null	Cholecalciferol had no benefit on monocyte subset cell count, T cell differentiation and cytokine production relative to placebo
Mose [25]	2014	64	HD patients with 25(OH) D insufficiency	Double-blind	Cholecalciferol (3000 IU daily)	Placebo	6	Change in PWV and LVMI	Null	No difference between groups in change of aortic PWV (Deltas: 0.8 versus 0.1 m/s, P = 0.269) and LVMI (Deltas: 3 versus −5 g/m^2, P = 0.397) over time
Li [22]	2014	96	HD patients with 25(OH) D <20 ng/mL	Open-label	Cholecalciferol (50 000 IU weekly)	Nothing	12	Change in immune function	Null	Change in alloreactive T-cell memory assessed by IFNγ ELISPOT-based panel of reactive T-cell assays did not differ between groups (Deltas: 104.8 ± 2330.8 versus 252.9 ± 2431.3, P = 0.25)

Mieczkowski [37]	2014	19	HD patients with 25(OH)D <20 ng/mL	Open-label	Cholecalciferol (2000 IU three times/week)	Nothing	12	Change in BMD	Null	Change in BMD measured in the spinal segment L1–L4 and proximal femur was no different between groups
Bhan [19]	2015	105	HD patients with 25(OH)D <32 ng/mL	Double-blind	Ergocalciferol (50 000 IU weekly or 50 000 IU monthly)	Placebo	3	Change in anemia-related parameters	Null	Frequency of intravenous iron use (monthly 39% versus weekly 39% versus placebo 51%, P = 0.49) and EPO use (monthly 71% versus weekly 69% versus placebo 60%, P = 0.61) was no different between groups
Miskulin [24]	2016	276	HD patients with 25(OH)D <30 ng/mL	Double-blind	Ergocalciferol (50 000 IU weekly)	Placebo	6 months	Change in EPO dose	Null	No significant change in weekly EPO dose over time in both groups (geometric mean rate: 0.99; 95% CI: 0.95–1.03)

HD, hemodialysis; CKD, chronic kidney disease; ESRD, end-stage renal disease; BMD, bone mass density; EPO, epoetin; PWV, pulse wave velocity; LVMI, left ventricular mass index; HRQOL, health-related quality of life; CI, confidence intervals; NS, non-significant.

showed that compared with placebo, nutritional vitamin D had no benefit on bone mass density [37] and vascular calcification score [20] among hemodialysis patients.

Effect of nutritional vitamin D on survival and clinical outcomes

The effect of nutritional vitamin D on all-cause and cause-specific morbidity and mortality remains unclear, due to the absence of adequately powered RCTs to evaluate survival and other 'hard' clinical outcomes as primary trial endpoints. Available data on clinical outcomes are derived from the study of Miskulin and co-workers, the largest RCT conduced so far, in which the incidence of all-cause hospitalizations [incidence rate ratio (IRR): 0.82; 95% CI: 0.60–1.12], cardiovascular disease hospitalizations (IRR: 0.60; 95% CI: 0.33–1.09) and infection-related hospitalizations (IRR: 1.03; 95% CI: 0.50–2.10) over the 6-month follow-up did not significantly differ between the ergocalciferol and placebo groups [24]. The authors state in the paper, and we agree, that 'estimates are imprecise given the small sample size' [24]. All-cause hospitalization and survival data were also collected in the DIVINE trial [19]. Incidence of all-cause hospitalizations over the 3-month treatment period was similar in the three study arms (monthly ergocalciferol: 11 events; weekly ergocalciferol: 14 events; placebo: 11 events, P = 0.89). Survival was assessed in an extended 12-month post-treatment follow-up; all-cause mortality was no different between ergocalciferol-treated and placebo-treated patients [hazard ratio (HR): 0.28; 95% CI: 0.07–1.19] [19]. Again, an HR as low as 0.28 together with the wide CIs indicates that the study was underpowered to detect significant differences between groups on survival.

In comparison, in the multinational, double-blind, randomized placebo-controlled trial among 227 patients with CKD, mild to moderate left ventricular hypertrophy, and preserved left ventricular ejection fraction, conducted in 11 countries, showed that the number of hospitalizations from any cause (paricalcitol, 15.7% versus placebo, 17.0%; P = 0.86) and from noncardiovascular causes (paricalcitol, 15.7% versus placebo, 11.6%; P = 0.44) did not differ between groups [39]. In contrast, there were fewer hospitalizations for cardiovascular disease events in the paricalcitol group (placebo group 8.8 per 100 person years, paricalcitol group 1.1 per 100 person years, P = 0.04). The most common cardiovascular event was congestive heart failure (paricalcitol, $n = 0$; placebo, $n = 5$). Thus, there is at least some evidence for benefit with activated vitamin D.

CONCLUSIONS

In conclusion, correction of hypovitaminosis D with the use of nutritional vitamin D supplements in people with CKD and ESRD is not justified by the currently available evidence for the following reasons: (i) a meta-analysis of 11 RCTs comparing cholecalciferol or ergocalciferol with placebo does support a significant PTH-lowering effect both in the predialysis CKD and ESRD settings; (ii) RCTs comparing head-to-head nutritional vitamin D supplements with VDRAs have shown that

inactive vitamin D is inferior to activated vitamin D analogs in reducing PTH levels; (iii) currently available evidence from RCTs suggests that nutritional vitamin D is ineffective in improving several intermediate endpoints, such as aortic stiffness, LVMI, epoetin utilization, immune function, functional capacity and health-related quality of life; and (iv) in the absence of adequately powered RCTs, it remains unclear whether nutritional vitamin D supplementation improves survival and reduces cause-specific morbidity and mortality in people with CKD and ESRD. Correction of secondary hyperparathyroidism and improvement in outcomes and not simply hypovitaminosis D are the major targets of therapy for the benefit of our patients. There is little evidence to support the practice of nutritional vitamin D use in CKD. We believe that VDRA use is evidence-based and should replace nutritional vitamin D use in CKD.

CONFLICT OF INTEREST STATEMENT

R.A. has received fees for chairing event adjudication committees of Abbvie, a manufacturer of activated vitamin D receptor activator. P.I.G. has no conflicts of interest to disclose.

(See related articles by Goldsmith. Pro: Should we correct vitamin D deficiency/insufficiency in chronic kidney disease patients with inactive forms of vitamin D or just treat them with active vitamin D forms? *Nephrol Dial Transplant* 2016; 31: 698–705; Zoccali and Mallamaci. Moderator's view: Vitamin D deficiency treatment in advanced chronic kidney disease: a close look at the emperor's clothes. *Nephrol Dial Transplant* 2016; 31: 714–716)

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Opponent's comments

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I am very impressed to see a fresh meta-analysis from my learned and expert opponent, delivered just for this debate.

However, I am very concerned that such activities can be misleading.

What is needed is two things—first, a decent set of trials. This must involve first some preparatory 'dose ranging' work, to see how responsive plasma parathyroid hormone (PTH) is to the administration of natural vitamin D compounds. This would be akin to phase 2 work in preparing a regulatory submission for drug approval. It is important to understand that the impact of daily, weekly, monthly and 3/12ly oral (or im) supplements need to be considered separately—these cannot be assumed to produce the same outputs. The stimulation of counter-regulatory enzymes to degrade 1,25 di(OH)vitamin D3 is much greater with higher doses, and, with intermittent boluses. Also, we need to know whether to aim for simple repletion (so, >75 nmol/L), or to aim a little higher than that. We simply don't know yet [1].

In addition, and more worrying still to me, is the simplistic assumption that all people respond, and to the same extent. The reality of all treatment, especially in a more diverse recipient population, is that you might see, and have to tease out, 'responder' versus 'non-responder' populations. This would of course apply to any form of vitamin D compound used in this clinical situation. This type of analysis is of course destroyed by simplistic 'yes or no' metrics, so beloved of many in this field.

Finally, we do not actually know the real PTH range to aim for (we know what is too low, probably, and, what is too high, probably). This is akin to the correction of low hematocrit using erythropoiesis-stimulating agents in renal anemia. This is a serious problem, as also is the sole reliance on a most unreliable biomarker, PTH, in our trials and interventions [2].

Until we truly know what we are doing in a rather complex biological situation, we would be better advised to attempt gently holistic vitamin D repletion with natural compounds which then require activation. If these fail, as judged by reasonable and reliable tests of success, then it may need the addition of more powerful, more toxic, and more expensive treatments. This I feel is especially the case in the context of chronic kidney disease, not yet requiring dialysis.

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