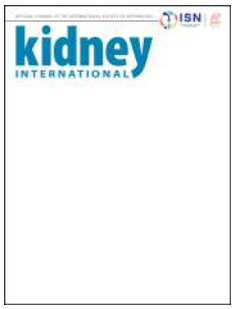

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Vitamin D supplementation in people with CKD

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Abstract

Vitamin D supplements have long been advocated for people with chronic kidney disease (CKD) based on data from observational studies among the general population and also people with CKD. These data consistently suggested that higher circulating concentrations of 25-hydroxyvitamin D are associated with improved fracture, cardiovascular, cancer, and mortality outcomes. In the last few years, large clinical trials have been conducted to assess the effects of vitamin D supplements on a range of clinically relevant outcomes. Most of these studies were performed in the general population but also enrolled people with CKD. Virtually all these trials were negative and contradicted the observational data. In this review, the key observational data and clinical trials are summarized and potential explanations for the discrepancies between these studies are discussed.

Introduction

Prior to the discovery of vitamin D and the therapeutic potential of cod oil and UV light, rickets was a typical feature of chronic kidney disease (CKD), now recognized as the consequence of the combined deficiency of calcium and vitamin D[1]. Since then, vitamin D supplements, usually cholecalciferol (vitamin D3), has been a mainstay of therapy, especially in children with a growing skeleton. Fortification of dairy products with vitamin D induced a dramatic decline in the prevalence of rickets.

Cholecalciferol undergoes two post-translational metabolic steps to yield its active form, 1,25-dihydroxycholecalciferol ($1,25(OH)_2D3$), with the final activating step most abundantly occurring in the kidney under physiological conditions (**Figure 1**).[2] The nearly ubiquitous expression of the vitamin D receptor (VDR), the recognition that many tissues other than the kidneys can also generate $1,25(OH)_2D3$, and the demonstration of pleiotropic effects of $1,25(OH)_2D3$ in animal models and experimental systems fueled the hypothesis that much more comorbidity, besides mineral and bone disorders, could be ascribed to vitamin D deficiency.

Definition and prevalence of vitamin D insufficiency and deficiency

Vitamin D deficiency is defined as a value below a certain 25-hydroxyvitamin D (25(OH)D) threshold, which varies across guidelines. The National Academy of Medicine defines 50 nmol/l as the minimum value[3], while the Endocrine Society defines insufficiency as 30-50 nmol/l and deficiency as values below 30 nmol/l for children and young adults, while for older adults a minimum concentration of 75 nmol/l is recommended[4] based on studies

examining fall and fracture risk prevention[5]. Despite the widespread use of vitamin D supplements, vitamin D deficiency (<30 nmol/l) is not rare, with a prevalence ranging from 6-13% in western countries [6]. The prevalence of vitamin insufficiency is even 4-fold higher.

For most people with CKD the prevalence of vitamin D deficiency is similar to those without CKD[7,8], although one report from South Korea observed twice the prevalence of vitamin D deficiency for stage 5 CKD compared to stage 3, from 40.7% to 85.7%[9].

Alternative biomarkers of vitamin D status

Circulating 25(OH)D concentration is the current standard clinical marker of vitamin D status. However, it is imperfect because 25(OH)D itself is not a potent activator of the VDR, not all 25(OH)D is readily available for use by cells, and 25(OH)D reflects vitamin D available for metabolism rather than functional vitamin D activity. As a result, biomarkers of vitamin D status beyond 25(OH)D have been proposed. $1,25(OH)_2D$ is the most potent activator of the VDR, but its circulating concentrations are tightly regulated and thus do not reflect long-term vitamin D exposure from UV sunlight and diet in the general population.[10] Bioavailable 25(OH)D, another proposed measure, refers to the 10-15% of serum total 25(OH)D that is unbound to vitamin D binding protein and therefore able to enter cells and undergo conversion into $1,25(OH)_2D3$ to perform biological actions.[11] 24,25-dihydroxyvitamin D3 ($24,25(OH)_2D3$) and parathyroid hormone (PTH) concentrations may reflect functional vitamin D activity. The catabolism of 25(OH)D3 into $24,25(OH)_2D3$ is induced in tissues by $1,25(OH)_2D$ and occurs in nearly all cells with that express the VDR,[2] while PTH production and secretion is directly suppressed by $1,25(OH)_2D3$ and used clinically to adjust vitamin D-

related therapies in kidney failure.[12] Aside from PTH, none of the biomarkers other than 25(OH)D are currently used to assess vitamin D status in clinical care.

Hierarchy of evidence to assess vitamin D adequacy

Historically, vitamin D deficiency was defined using cross-sectional studies examining associations of circulating 25(OH)D concentration with intermediate markers of bone and mineral metabolism. For example, in early studies of people without kidney disease, it was noted that there was little or no association of 25(OH)D with PTH or bone mineral density (BMD) above a 25(OH)D threshold of approximately 75 nmol/L, but an inverse association with PTH and a direct association with BMD existed below this threshold.[13,14] However, a clear 25(OH)D threshold could not be established in a literature review of 70 studies in the general population, which revealed significant variability in 25(OH)D cutpoints above which the association with lower PTH was absent, ranging from 25 nmol/L to 125 nmol/L.[15] Additionally, eight of the studies showed no evidence of a plateau of PTH values, and three studies showed no association between 25(OH)D and PTH. In people with CKD, the inverse association of 25(OH)D with PTH was more consistent across studies and extended beyond concentrations of 25(OH)D generally thought of as sufficient (**Figure 2**)[16]. Indeed, in a cross-sectional study of 14,289 participants with stage 1-5 CKD, Ennis et al. found that PTH concentrations were lowest with 25(OH)D concentrations of 104-120 nmol/L.[17] Cross-sectional studies were followed by longitudinal cohort studies that assessed associations of 25(OH)D with clinical events, often including larger, more diverse populations and using adjustment to better account for confounding.

However, for clinical decision-making, adequacy is best determined in the context of treatment, using response to supplementation as the outcome of interest. For example, the Multi-Ethnic Study of Atherosclerosis Individualized Response to Vitamin D Treatment Study treated a diverse population of US adults with 2000 IU/d of cholecalciferol (or placebo) and found that this intervention significantly reduced PTH only when baseline 25(OH)D was <52.5 nmol/L (95% CI 32.5, 77.5 nmol/L, **Figure 2**), near the 50 nmol/L frequently recommended.[10] Ideally, adequacy would be defined using baseline characteristics that modify the effect of vitamin D supplementation in large clinical trials using clinical outcomes, using rigorous methods to identify subgroups of participants who derive benefit. Such trials represent the top of a "hierarchy of evidence" for assessing treatment targets, ranging from cross-sectional studies to cohort studies to trials with intermediate outcomes to trials with clinical outcomes (**Figure 3**).

Observational studies on vitamin D concentrations and mortality risk in CKD

Observational studies consistently show associations of low 25(OH)D concentrations with poor clinical outcomes. In a large observational study of US adults starting dialysis, baseline 25(OH)D concentration was independently and negatively associated with all-cause and cardiovascular mortality[18]. Of note, the risk was mitigated regardless of baseline vitamin D status by treatment with active vitamin D in the first months on dialysis. A meta-analysis among people on dialysis revealed 22% and 29% lower risks for all-cause and cardiovascular mortality, respectively, for each 25 nmol/l higher 25(OH)D[19]. In general, heterogeneity was high among the studies included, to a large extent driven by differences in baseline cardiovascular disease (CVD), dialysis duration, diabetes, and baseline PTH.

Among people with non-dialysis CKD, the largest cohort analysis was the Third National Health and Nutrition Examination Survey (NHANES-III)[20]. In this study of 3011 non-institutionalized US adults, with intentional oversampling of Black, Hispanic and older individuals, a lower 25(OH)D concentration (<37.5 nmol/l, lowest tertile) was significantly associated with all-cause mortality (hazard ratio [HR] 1.56; 95% confidence interval [CI]: 1.12, 2.18) compared with the highest tertile (>75 nmol/l). The effect size was of similar magnitude for cardiovascular and non-cardiovascular mortality and consistent across a range of subgroups (**Figure 4a**)[20]. A meta-analysis that included four studies of non-dialysis patients[21] found a 14% lower all-cause mortality for each 25 nmol/l higher 25(OH)D concentration, regardless of stage of CKD. Of note, 3011 of the 3552 participants in this meta-analysis originated from NHANES III described above, but magnitudes of association were comparable across the included studies.

Efficacy of Vitamin D supplementation to raise 25(OH)D

Clinical trials consistently show that vitamin D supplementation is effective in raising 25(OH)D concentrations among people with or without CKD. Of 11 placebo-controlled or head-to-head randomized clinical trials designed to examine biomarkers of vitamin D metabolism in both non-dialysis CKD and hemodialysis (**Table 1**), 9 used either vitamin D2 or vitamin D3, the most common forms of supplementation.[22-30] All reported significant increases in total 25(OH)D concentrations from baseline. Armas et al. showed a significant $25(OH)_2D3$ increase was detectable as soon as 7 days after an initial weekly vitamin D_3 dose in patients on hemodialysis.[22] Wetmore et al. compared identical doses of weekly vitamin D_2 and D_3 and found vitamin D_3 treatment led to a greater increase in total 25(OH)D at 12

weeks without changes to serum calcium.[29] Two randomized, placebo-controlled trials by Sprague et al. (N = 78 and 429) tested extended-release oral 25(OH)D3 and found that 25(OH)D3 treatment raised total 25(OH)D concentrations in both studies.

Vitamin D supplementation and fractures and falls

Given the well-established role of vitamin D in mineral metabolism, several large placebo-controlled trials studied whether vitamin D supplementation may reduce the risk of fracture in the general population (**Table 2**)**.** In a study over 30 years ago, Chapuy and coworkers recruited 3270 institutionalized women with very high risk for fracture (mean age 84 ± 6 years, and body weight of 56 ± 12 kg).[31] They were randomized to placebo or a combination of 1200 mg calcium plus 800IU vitamin D3 and followed for 18 months. Those allocated to active treatment had 43% less hip fractures and 32% less non-hip non-vertebral fractures, both statistically significant. Trivedi et al. recruited 2686 older participants form the UK (mean age 76 years, 76% male) who were randomized to receive either 100 000 IU vitamin D3 every four months or placebo[32]. The HR after 5 years of follow-up for the active treatment group for any fracture was 0.78 (95% CI: 0.61, 0.99), and for major osteoporotic fracture was 0.67 (95% CI: 0.48, 0.93). This study was followed by a large study from the US that recruited 36282 postmenopausal women, who were randomized to 400 IU vitamin D3 plus 1000 mg calcium every day or placebo[33]. The study did not meet its primary endpoint: the HR was 0.88 (95% CI: 0.72, 1.08) for hip fracture and 0.96 (95% CI: 0.91, 1.02) for any fracture. There were signals of benefit of vitamin D3 in this study: BMD was higher (1.06%) in the active treatment group, and in an on-treatment analysis the HR for hip fracture was

0.71 (95% CI: 0.52, 0.97). In turn, there was a higher incidence of renal calculi in the group receiving active treatment.

Recently, results from the VITAL trial on fracture risk were published[34]. In this study 25871 adults were randomized to either 2000 IU/d vitamin D3 or placebo. Previous CVD was an exclusion criterion, and there was no requirement for the existence of vitamin D deficiency or osteoporosis at baseline. After 5.3 years of follow-up, the study was negative on its outcome of total fractures with a HR of 0.98 (95 % CI: 0.89, 1.08), and also negative for both nonvertebral and hip fractures. In addition, there was no effect modification for any subgroup, including those with the lowest baseline concentrations of 25(OH)D (<30 nmol/l), although the number of events in this subgroup was small.

Discrepant findings in these trials may be explained by differences in the population studied, dosing scheme of vitamin D3, and the use of non-protocolized supplements. Compared with the VITAL trial (which was negative), the trial by Trivedi (which was positive) included older participants who more often had CVD at baseline, both factors that contribute to higher fracture risk. Additionally, the 5-year incidence of any fracture in the placebo groups differed between studies; it was 11% in the Trivedi trial, 6% in the VITAL trial, and 12% in the trial of postmenopausal women by Jackson et al.[33] These trials also differed in the maximum allowable doses of non-study vitamin D and calcium supplements, which may have dissipated results. There is a remarkable paucity of trial data studying vitamin D supplements in people with CKD on fracture risk reduction. A small study in people on hemodialysis (the VitaDial trial n=55), recruited individuals who were randomized to cholecalciferol repletion or placebo.[35] Fractures were reported as safety outcome. There were 10 fractures reported in the 9 participants in the placebo arm and none in the active

treatment group. Half of all fractures occurred in the first 13 weeks, which seems unlikely to be ascribed to the intervention. In another study, 65 people treated with peritoneal dialysis were randomized to cholecalciferol or placebo, and the primary outcome was change in left ventricular mass.[36] The study was negative on its primary endpoint. One and two fractures were observed in the vitamin D supplementation and placebo groups, respectively, and the difference was statistically non-significant.

In addition to potential effects on bone density and quality, vitamin D has been hypothesized to improve muscle function and prevent falls, the major cause of fractures. This has been a matter of debate, with studies showing higher, neutral and lower fall incidence with vitamin D supplementation. The recent STURDY trial of 688 elderly men and women at high fall risk compared low dose vitamin D3 (200 IU/d) with an adaptive variable higher dose (1000, 2000 or 4000 IU/d) treatment strategy and found no difference in the primary outcome of any falls.[37]. However, the risk of first serious fall (e.g., resulting in fracture, dislocation, or hospitalization) was twice as high in the higher dose group, drawing attention to potential risks of high dose vitamin D supplementation. A meta-analysis and the VITAL trial, described above, also failed to establish any benefit of vitamin D supplementation on risk for falls[38,39]. This includes those with baseline plasma concentration of 25(OH)D <30 nmol/L in the VITAL trial.

Vitamin D supplementation and extra-skeletal clinical outcomes

Motivated by known pleiotropic effects of vitamin D that may theoretically help prevent CVD and cancer, a number of large clinical trials of vitamin D supplementation with

cardiovascular, cancer, and mortality outcomes have been performed (**Table 2**). In general, these trials included community-based older adults (since these outcomes are highly age-related) selected without regard to kidney disease, and often without regard to baseline vitamin D status. Six large such studies[33,40-44] showed no clinical benefits of vitamin D supplementation, with hazard ratios near 1 and in some cases narrow confidence intervals around the null effect. In addition, among critically ill adults admitted to an intensive care unit, bolus vitamin D supplementation did not affect 90-day mortality.[45] Few vitamin D trials with clinical outcomes have been performed among people with kidney disease; an exception is the VITALE trial of kidney transplant recipients, which showed no effect of high- versus low-dose vitamin supplementation on a broad composite outcome that included diabetes, cardiovascular events, cancer, or death, though only 82 such events were observed.[46]

The VITAL trial, described above, had CVD and cancer as co-primary outcomes.[40] The null cardiovascular effect (**Figure 4b**) was found to be consistent across strata of eGFR (with no benefit among participants with eGFR <60 mL/min/1.73m2 despite a higher overall event rate and larger effects on PTH).[47] A meta-analysis including VITAL and prior clinical trials confirmed the absence of cardiovascular benefit (HR 1.00, 95% CI: 0.95, 1.06), with consistent results by sex, baseline 25D concentration, vitamin D dose and formulation, and concurrent calcium administration.[48] In VITAL, the effect of vitamin D on invasive cancer was also null.[40] Secondary analyses and a meta-analysis including VITAL and prior clinical trials reported a promising signal for reduced cancer mortality (without a significant effect on cancer incidence),[49] but the subsequent large D-Health Study reported no benefits on all-cause or cancer mortality.[44] The VITAL trial included assessment of a wide range of

secondary outcomes that were not positively affected by vitamin D supplementation. For example, among 1312 VITAL participants with type 2 diabetes, vitamin D did not slow loss of eGFR or blunt a rise in albuminuria over 5 years.[50]

How to reconcile contradictory conclusions form observational data and clinical trials?

Biologic plausibility and observational data support potential benefits of vitamin D supplementation on skeletal outcomes as well as CVD, cancer, and mortality. However, the results of large clinical trials comparing vitamin D supplementation with placebo have generally not found benefits on clinical outcomes despite substantially raising 25(OH)D concentrations (**Figure 4**).

What may explain these discrepancies? As with all observational studies, residual confounding may undermine conclusions. However, confounding effects must be substantial, and what these residual confounders may be remains elusive. Vitamin D has been considered to be a proxy of "overall health", not reflected by variables that were used in statistical adjustments of the observations. Identifying these factors is important because they may be alternate targets for therapeutic intervention. On the other hand, clinical trials may suffer from type 2 error, especially when a low-risk population is recruited, the dose of the intervention is too low, nonadherence to treatment assignment or concomitant supplements limit separation in treatment arms, or the observation period is too short.

The large trials with clinical outcomes included broad populations, often without selecting participants on the basis of low vitamin D status or other propensity to respond to supplementation. These trials essentially ask whether vitamin D supplementation should be

broadly applied to the unselected general population and answer that question with a resounding “no.” However, it remains possible that targeted populations may benefit, particularly for skeletal effects, for which biologic plausibility is strongest and trial data are more nuanced. Populations at high risk of fracture, such as the elderly and those with CVD, may derive skeletal benefits from vitamin D supplementation. Of note, if this presumed benefit also applies to people with CKD, is largely unknown. A recent meta-analysis studied the effects of vitamin D (both nutritional or activated) on fracture risk among people with CKD[51]. It concluded that the effects are uncertain on this endpoint. Of note, this analysis also concluded that among people with CKD, like in the general population, vitamin D supplements do not reduce the risk of all-cause mortality.

While subgroup analyses of large trials have generally not found heterogeneity of effects of vitamin D supplementation on clinical outcomes by baseline 25(OH)D concentration, trials were not designed to address these subgroups with adequate power, and 25(OH)D may not be the ideal biomarker to define vitamin D status. However, application of alternative biomarkers is understudied. Similarly, clinical risks and benefits have not been found to vary by CKD status, though power to address the CKD population was limited. Since CKD clearly alters vitamin D metabolism, unique effects in this population cannot be ruled out.

A possible exception to null clinical effects may be some benefit of vitamin D supplementation on fracture prevention in high-risk populations, like the elderly with previous CVD and at risk for fractures, based on the arguments described above. Based on the results of the STURDY trial described above, the dose of vitamin D supplements then should be restrictive and be less than 1000 IU per day.

In this review, we focused on clinical endpoints like fractures, incident CVD and cancer, and mortality because these directly affect how patients feel, function, and survive. Nephrology practice commonly also targets intermediate outcomes, such as circulating PTH concentration. Secondary hyperparathyroidism is a frequent complication of advanced CKD, and treatment options are limited[52]. The KDIGO guideline on CKD-MBD is restrictive on the use of activated vitamin D for this indication, based on the higher prevalence of hypercalcemia.[53] Whether using vitamin D supplements is an appropriate alternative is unknown because it has not been shown that its PTH suppressive properties lead to improved clinical outcomes as described above.

In the future, it is very important to assess whether targeting intermediate outcomes like PTH with vitamin D supplements or other treatments improves clinical outcomes. We also didn't address intermediate cardiovascular outcomes, such as pulse wave velocity, which reflects arterial stiffness. Clinical trials assessing such intermediate outcomes are useful for motivating and planning larger clinical trials, and some have suggested benefits for vitamin D3 as compared to placebo (and active vitamin D),[54] but benefits on such intermediate outcomes should not on their own change clinical practice. It should be emphasized that active vitamin D compounds (i.e. $1,25(OH)_2D3$ and its analogues) may have entirely different risks and benefits than vitamin D supplements. Effects of active vitamin D were beyond the scope of this review.

Conclusion

Many large clinical trials justify the conclusion that wide-spread supplementation with vitamin D does not confer clinical benefits on all cause- or cause-specific mortality, cardiovascular events, cancer or numerous other clinically relevant endpoints. The discrepancy of these trials with observational data may be the result of residual confounding in the latter studies, but we cannot exclude that some people may benefit with regard to these endpoints, potentially including some people with CKD, whom were not well-represented in the large trials. In sum, there is no strong rationale for indiscriminate use of vitamin D supplements in the general population or among patients with CKD. Supplementing vitamin D may mitigate fracture risk in high-risk populations, and this remains the most well-supported application of vitamin D.

Disclosure statement

All authors declare having no disclosures.

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Figure legends

Figure 1:

Overview of vitamin D metabolism. Intermediate metabolites are shown in boxes. Features that catalyze the metabolic steps are shown between the corresponding metabolites

Figure 2:

Relationship of 25-hydroxyvitamin D and parathyroid hormone. (A) Cross-sectional relationship in a CKD population. (B) Change in PTH from baseline after 16 weeks of 1000 IU/d of vitamin D_3 by baseline 25(OH)D in a general population without CKD. The red circle at 21 ng/mL represents the 25(OH)D concentration where a segmented threshold effect was seen. Adapted from Ravani P et al. "Vitamin D levels and patient outcome in chronic kidney disease." Kidney International. 2009;75(1):88-95 and Hsu S et al. "Clinical and biomarker modifiers of vitamin D treatment response: the multi-ethnic study of atherosclerosis." The American Journal of Clinical Nutrition. 2021;115(3):914-924.

Figure 3:

Hierarchy of quality of evidence.

Figure 4:

Contrasting effects of observational and trial data of vitamin D on mortality. (A) Adjusted hazard ratios for all-cause mortality among different subgroups of participants in the Third National Health and Nutrition Examination Survey. (B) Cumulative incidence rates of major cardiovascular events in participants treated with 1000 IU/d of Vitamin D3 versus placebo in the VITamin D and OmegA-3 TriaL (VITAL). Reprinted from Mehrotra R et al. "Chronic kidney

disease, hypovitaminosis D, and mortality in the United States. Kidney International. 2009;76(9):977-983 and Mason JE et al. “Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease.” New England Journal of Medicine. 2018;380(1):33-44.

Table 1.

Overview of randomized clinical trials of vitamin D supplementation and effects on 25-hydroxyvitamin D and parathyroid hormone in CKD

Study	Country	Study population	Intervention	Duration	Total 25(OH)D (nmol/L)[a]	
					Baseline	Final value or Δ from baseline[b]
Vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol)						
Alvarez et al.[15]	USA	46 participants with stage 2-3 CKD	50000 IU of vitamin D_3 every other week	52 weeks	66.8 ± 17	100.8 ± 40.3
Armas et al.[7]	USA	42 participants on hemodialysis	10333 IU of vitamin D_3 per week	15 weeks	33.3 (27.8, 40.5)	59 (48, 74.8)[b]
Bhan et al.[8]	USA	105 participants on hemodialysis, 25(OH)D ≤ 80 nmol/L	50000 IU of vitamin D_2 per week	12 weeks	54.5 ± 17.5	124.5 ± 5.8
			50000 IU of vitamin D_2 per month		55.8 ± 16.3	95.8 ± 6
Chandra et al.[9]	USA	34 participants with stage 3-4 CKD, 25(OH)D < 75 nmol/L and PTH > 7.4 pmol/L	50000 IU of vitamin D_3 per week	12 weeks	Mean 43.3	Mean change 80.3[b]
Dreyer et al.[10]	UK	38 participants with stage 3-4 CKD, 25(OH)D < 40 nmol/L	50000 IU of vitamin D_2 weekly for 1 month, then 50000 IU per month	6 months	-	Mean change >50[b]
Marckmann et al.[11]	Denmark	52 participants with stage 1-5 CKD and on hemodialysis, 25(OH)D < 50 nmol/L	40000 IU of vitamin D_3 per week	8 weeks	23.8 (17.2, 41.4)	117.8 (89.4, 151.9)[b]
Petchey et al.[12]	Australia	28 participants with stage 3-4 CKD	2000 IU of vitamin D_3 per day	6 months	95 ± 37	146 ± 25
Westerberg et al.[13]	Sweden	95 participants with stage 3-4 CKD, 25(OH)D < 75 nmol/L and PTH >6.8 pmol/L	8000 IU of vitamin D_3 per day	12 weeks	57.5 ± 22	161.6 ± 49
Wetmore et al.[14]	USA	44 participants with stage 3-5 CKD, 25(OH)D < 75 nmol/L	50000 IU of vitamin D_2 per week	12 weeks	51.3 ± 13.8	76.8 ± 38.3[b]
			50000 IU of vitamin D_3 per week		52.3 ± 15.8	112.5 ± 41.3[b]

$25(OH)D_3$ (calcifediol)						
Sprague et al.[19]	USA	78 participants with stage 2-4 CKD, 25(OH)D < 75 nmol/L and PTH > 7.4 pmol/L	30, 60, or 90 μg of extended-release $25(OH)D_3$ per day	6 weeks	55.8 ± 13	161 ± 62.3
Sprague et al.[20]	USA	429 participants with stage 3-4 CKD	30 or 60 μg of extended-release $25(OH)D_3$ per day	26 weeks	49.8 ± 13.3	Mean change >100[b]

All trials were placebo-controlled, except Wetmore et al., which compared vitamin D_2 to vitamin D_3. CKD, chronic kidney disease; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

[a]25(OH)D and PTH concentrations are in the vitamin D-treated groups only and reported in median (interquartile range) or mean ± standard deviation unless otherwise stated.
[b]Cells marked with this superscript indicate change from baseline and not final concentration

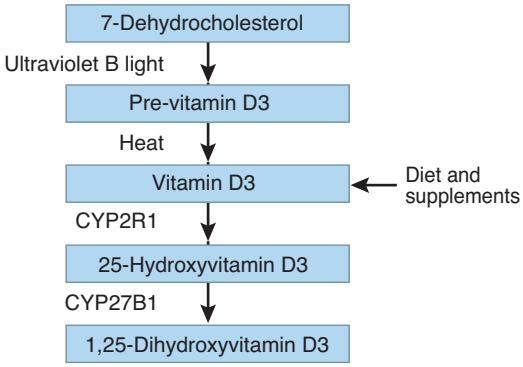
Table 2.

Overview of randomized clinical trials of vitamin D supplementation on risk of fractures, falls, cardiovascular disease, cancer and mortality

year	author	participants	N	Intervention	Outcome	Follow-up	result
Fractures							
1992	Chapuy	Postmenopausal woman	3270	Ca 1200 plus D800 or placebo	Hip and nonvertebral fracture	18 months	43% less hip fractures and 32% less non-hip fractures for active treatment
2006	Jackson	postmenopausal woman	36282	Ca1000 plus D400 or placebo	fracture	7 years	HR 0.88 (0.72-1.08) for hip; 0.90 (0.74-1.10 for clinical spine; 0.96 (0.91-1.02) total
2022	LeBoff	older adults (man>50;woman>55)	25871	2000D or placebo	fracture	5.3 years	HR 0.98(0.89-1.08)
2003	Trivedi	65-85(more men), many docters	2686	100000 D3/4 month or placebo	fracture	5 years	HR 0,78 (0.61 to 0.99) any fracture and 0.67 (0.48-0.93) for MOF
Falls							
2021	Apple (Sturdy)	community-dwelling ≥ 70 years (77 mean); at risk for falling	688	1000, 2000 or 4000 IU vs 200 IU plus dietary intake	falls (or mortality)	22 months	HR=0.94, 95%CI:0.76–1.15;
2020	LeBoff	older adults (man>50;woman>55)	25871	2000D or placebo	2 or more rctures leading to doctor visit	5.3 years	odds ratio [OR] = 0.97; 95% CI, 0.90-1.05
Cardiovascular disease							
2017	Scragg (Vitamin D Assessment Study)	adults 50-84 years (New Zealand)	5110	200000 IU then 100000 IU monthly or placebo	CVD events (very broad definition)	3.3 years	HR 1.02 (0.87, 1.20)
2019	Manson (VITAL)	men ≥50, women≥55 years (US)	25871	2000 IU D3 or placebo	MACE (MI, stroke, CV death)	5.3 years	HR 0.97 (0.85, 1.12)

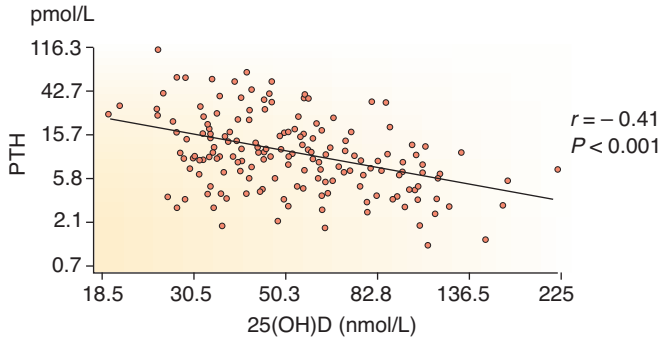
2022	Virtanen (Finnish Vitamin D Trial)	men ≥60, women≥65 years (Finland)	2495	1600 IU D3 or 3200 IU D3 (three arms) or placebo	Major CVD events	5 years	HR 0.97 (0.63, 1.49); 0.84 (0.54, 1.31)	
Cancer								
2006	Wende (WHI)	postmenopausal women (US)	36282	1000 mg Ca plus 400 IU D3 or placebo	Colorectal cancer	7 years	HR 1.08 (0.86, 1.34)	
2017	Lappe	postmenopausal women (31 rural countries)	2303	1500 mg CA plus 2000 IU D3 daily or placebo	Incident cancer	4 years	Difference 1.69% (-0.06,3.46%)	
2019	Manson (VITAL)	men ≥50, women≥55 years (US)	25871	2000 IU D3 or placebo	invasive cancer	5.3 years	HR 0.96 (0.88, 1.06)	
2022	Virtanen (Finnish Vitamin D Trial)	men ≥60, women≥65 years (Finland)	2495	1600 IU D3 or 3200 IU D3 (three arms) or placebo	invasive cancer	5 years	HR 1.14 (0.75, 1.72); 0.95 (0.61, 1.47)	
Mortality								
2019	Brower (PETAL)	critically ill adults with 25OHD <20 ng/mL	1078	540000 IU D3 once or placebo	All-cause mortality	90 days	Difference 2.9% (-2.1, 7.9%)	
2022	Neale (D-Health)	Australians 60 years or older	21315	60000 IU D3 monthly or placebo	All-cause mortality	5.7 years	HR 1.04 (0.93, 1.18)	

Overview of vitamin D metabolism

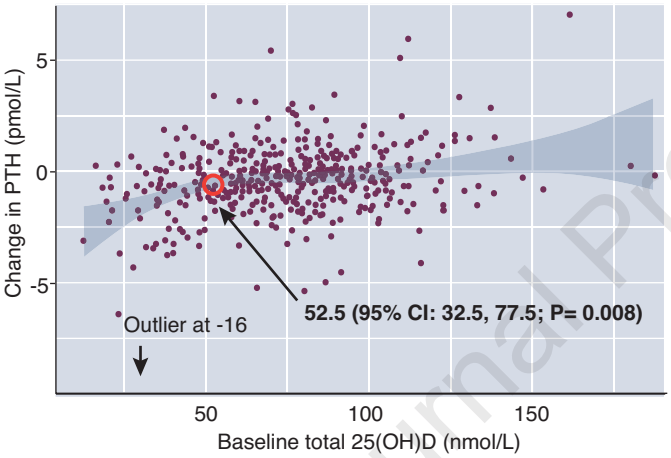


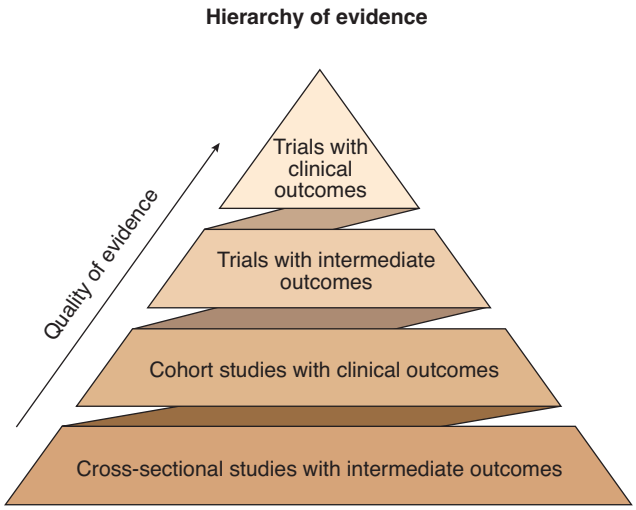
The relationship between 25(OH)D and PTH in people with CKD and the general population.

a **CKD population**



b **General population**





Contrasting effects of observational and trial data of vitamin D on mortality

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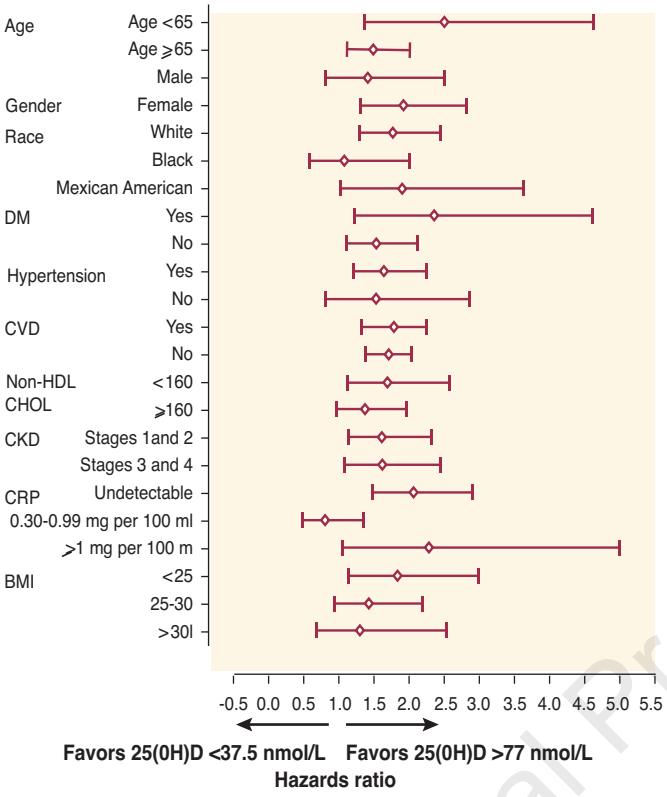

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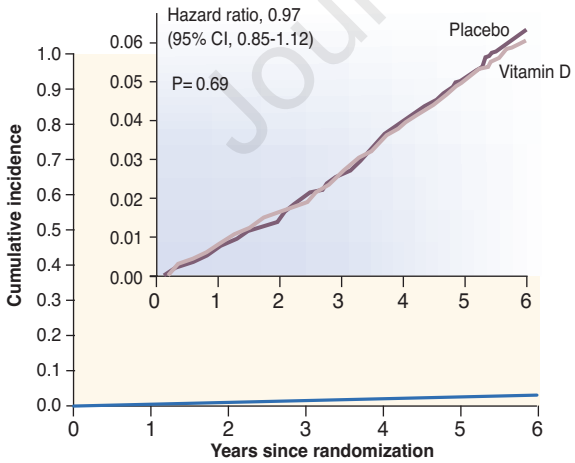

No. at risk

Placebo	12.944	12.862	12.747	12.593	12.289	9841	766
Vitamin D	12,927	12,842	12,723	12,593	12,314	9862	774