Vitamin D Status and All-Cause Mortality in Patients With Chronic Kidney Disease: A Systematic Review and Dose-Response Meta-Analysis

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Context: The prevalence of vitamin D deficiency is high in patients with chronic kidney disease (CKD). Less attention has been paid to measurement and correction of a serum level of 25-hydroxyvitamin D [25(OH)D] in these patients.

Objective: We examined the association between different levels of serum 25(OH)D and risk of all-cause mortality in patients with CKD.

Data Sources: Systematic search was done using MEDLINE and EMBASE from inception to November 2016. Reference lists of all relevant articles and reviews also were searched.

Study Selection: Prospective or retrospective cohort studies that reported risk estimates of all-cause mortality for three or more categories of serum 25(OH)D in patients with CKD were selected. Studies that reported results as continuous also were included. Two independent investigators screened and selected the articles. Of 1281 identified studies, 13 prospective cohort studies, two retrospective cohort studies, and one nested case-control study with 17,053 patients and 7517 incident deaths were included.

Data Extraction: Two independent authors extracted data from included studies. Any discrepancies were resolved through consensus.

Data Synthesis: Reported risk estimates were combined using a random-effects model. Summary risk estimates of all-cause mortality were 1.63 [95% confidence interval (CI), 1.32 to 1.94] for severe deficiency ($<$10 ng/mL), 1.22 (95% CI, 1.09 to 1.35) for mild deficiency (10 to 20 ng/mL), and 1.12 (95% CI, 1.06 to 1.18) for insufficiency (20 to 30 ng/mL). Results were more evident in dialysis-dependent patients. A 10-ng/mL increment in serum 25(OH)D was associated with a 21% reduction in the risk of overall mortality (relative risk, 0.79; 95% CI, 0.70 to 0.87). Lower risk of all-cause mortality was observed at a serum 25(OH)D of $\sim$25 to 30 ng/mL. Dialysis treatment was one of the sources of variation between studies.

Conclusions: Higher levels of serum 25(OH)D were associated with a lower risk of all-cause mortality in patients with CKD, but we have no conclusive evidence regarding serum levels of $>$35 ng/mL. (***J Clin Endocrinol Metab*** **102: 2136–2145, 2017)**

Vitamin D, as a versatile and scarce nutrient, plays an important role in human health (1). Due to the low content of vitamin D in many dietary components, dietary intake lower than recommendations and, as a result, vitamin insufficiency or deficiency are common in different populations (2, 3). Like the general population, a large

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)D, 1,25-dihydroxyvitamin D; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; RR, relative risk.

number of patients with chronic kidney disease (CKD) have vitamin D deficiency (4). Poor nutritional status, lower dietary intake, more sun deprivation, and decreased ability of skin to convert the vitamin precursor are some factors that contribute to the development of vitamin D deficiency in patients with CKD (5, 6). In addition, lower conversion of vitamin D to the active form due to decreased renal function leads to secondary hyperparathyroidism and bone disorders (7). It has been suggested that, consistent with the general population (8–10), vitamin D deficiency in patients with CKD may be associated with adverse health outcomes, including more cardiovascular problems (11), faster progression to later stages of renal insufficiency (12), and greater risk of mortality (13). The effects of vitamin D in modulating the immune system mitigate the inflammatory status, and its cardioprotective and antitumorogenic activity may, in part, be responsible for adverse health outcomes (1, 14, 15). Thus, it is important to maintain the serum 25-hydroxyvitamin D [25(OH)D] concentration at about the optimal level to prevent such unfavorable outcomes (7). Results from interventional studies indicated that supplementation with vitamin D (as the active form) was significantly associated with a decrement in the risk of mortality in both the general population and patients with CKD (16, 17). However, there is no consensus on the optimal level of serum 25(OH)D (18–20). In patients with CKD, it is also not exactly clear what level of serum 25(OH)D achieves the best health outcomes. In addition, due to the use of different cut-points to categorize the serum level of 25(OH)D and to define the vitamin D deficiency in each study, we do not have a conclusive inference regarding the survival outcomes of different levels of vitamin D in patients with CKD. Differences in the degree of the association in dialysis-dependent patients and patients who are not on dialysis also have not been specified. Therefore, the aim of this study is to examine the association between vitamin D deficiency and insufficiency and risk of all-cause mortality in patients with CKD with and without the need for dialysis treatment. We also want to specify, using dose-response meta-analysis, the optimal level of serum 25(OH)D in patients with CKD with and without the need for dialysis treatment.

Materials and Methods

The Preferred Reporting Items for Systematic Review and Meta-analysis checklist was used to perform the meta-analysis and report the results (21).

Search strategy

We systematically searched the Medline and EMBASE databases from inception to November 2016 using the following keywords: "25(OH)D" or "25-hydroxyvitamin d" or "cholecalciferol" or "Vitamin D" or "calcitriol" and "dialysis" or "renal dialysis" or "hemodialysis" or "chronic kidney disease" or "chronic renal failure" or "CKD" or "renal failure" or "renal disease" or "renal insufficiency" or "chronic renal insufficiency" and "death" or "survival" or "mortality." Reference lists of retrieved articles and relevant reviews also were manually searched. The search was restricted to published English articles.

Eligibility and study selection

Studies with the following features met our criteria for inclusion in the meta-analysis: (1) studies with a cohort design (both prospective and retrospective) with any follow-up duration; (2) reported serum vitamin D status in at least three categories; (3) reported outcome of interest as all-cause mortality; (4) conducted in patients with CKD, including dialysis patients; and (5) reported risk estimates of all-cause mortality [relative risk (RR), hazard ratio, or odds ratio] and their corresponding 95% confidence interval (CI) for each category of serum 25(OH)D. Studies that reported the risk of all-cause mortality per unit increment in serum 25(OH)D also were considered eligible for our meta-analysis. For studies appearing in more than one publication, the later study was selected.

Data extraction

Two independent investigators (A.J., S.S.) extracted the following information from eligible studies: first author's name, publication year, study name, study design, follow-up duration, country, mean age, number of participants, number of all-cause deaths, sex, CKD stage, percentage of participants treated with dialysis, reported risk estimates either categorically or continuously, and covariates adjusted in the multivariate model. The models with the most covariate adjustment from each study were selected and used for the meta-analysis. Some of the information (especially number of deaths in each category) was obtained by correspondence. Any discrepancies were resolved through discussion.

Statistical analysis

Two different types of analysis were conducted for this meta-analysis. First, to examine the association between serum vitamin D status and risk of all-cause mortality, we standardized and categorized serum vitamin 25(OH)D into four categories: $<$10 ng/mL (severe deficiency), 10 to 20 ng/mL (mild deficiency), 20 to 30 ng/mL (insufficiency), and $\geq$30 ng/mL (normal range, as reference category). Then we assigned each RR from the original studies to its corresponding category. If more than one category of serum 25(OH)D from an original study fell into the same group in our meta-analysis, we combined risk estimates with inverse variance weights and used the pooled estimates for that group. Conversely, if one category of serum 25(OH)D from an original study covered more than one category in our meta-analysis, we assigned risk estimates of that category by its median. For studies in which the reference category was not the highest one, we recalculated risk estimates assuming the highest category as reference. Compared with the highest category, the pooled RRs and 95% CIs of all-cause mortality for all other categories of serum 25(OH)D were estimated using random-effects models. A DerSimonian and Laird random-effects model was used to combine risk estimates (22).

Second, we conducted a dose-response meta-analysis. A linear dose-response relation was estimated by using generalized least squares trend estimation, according to various methods (23–25). We used the two-stage generalized least-squares trend estimation method, first estimating study-specific slope lines and then combining these with studies in which the slopes were directly reported, to obtain an overall average slope (25). Study-specific results were combined using a random-effects model. The median point in each category of serum 25(OH)D was assigned. If medians were not reported, we estimated approximate medians by using the midpoint of the lower and upper bounds. If the upper boundary of the highest category or the lower boundary of the lowest category was not reported, we assumed that it had the same amplitude as the closest category. If the lowest category of serum 25(OH)D was not the reference category, we recalculated reported risk estimates assuming the lowest category as reference. Studies that reported risk estimates per any unit increment in serum 25(OH)D were also included. Potential nonlinear association was examined by modeling vitamin D level using restricted cubic splines with three knots at fixed percentiles (10%, 50%, and 90%) of the distribution (25). A P value for nonlinearity of the meta-analysis was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero (26). All analyses were conducted with Stata software, version 10.1 (StataCorp LP, College Station, TX). A P value <0.05 was considered significant.

Results

Literature search and study characteristics

Figure 1 shows the literature search and study selection process. The systematic search identified 1247 references following an electronic search and seven were identified by manual searching, of which 29 were duplicates and 1220 were not relevant and so were excluded at the initial screening of the title and abstract. By full-text review, another 16 studies were excluded: six studies were reviews, six studies were clinical trials, one study was a duplicate report from the same study, and three had only

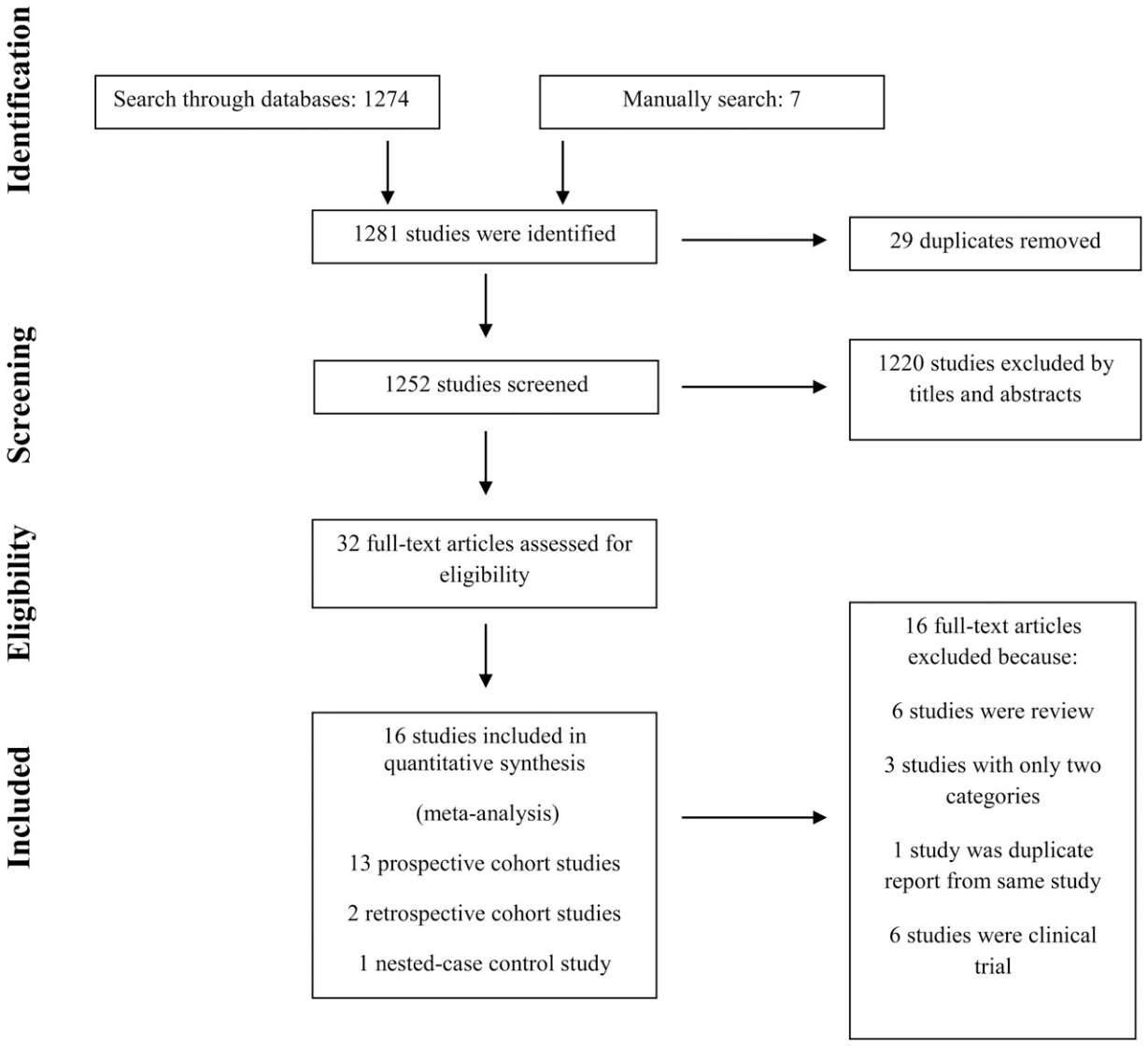

Figure 1. Literature search and study selection process for inclusion in a meta-analysis of vitamin D status and all-cause mortality in patients with CKD.

two categories of serum 25(OH)D. Ultimately, 16 studies with 17,053 patients and 7517 incident deaths were eligible for our meta-analysis (Table 1) (27–42). Thirteen studies were prospective cohorts (27–30, 32–40), two studies were cohorts with a retrospective design (31, 41), and one study was a nested case-control study (42). Eight studies included only dialysis patients (28, 30, 31, 33, 37–39, 42), and seven studies were conducted in patients with CKD stages 2 to 5 without dialysis treatment (27, 29, 32, 34, 35, 40, 41). Four studies were prospective evaluations of randomized controlled trial studies (28, 30, 33, 40), and one study reported risk estimates only as a univariate model (37). One study reported risk estimates for only cardiovascular mortality (35), but we decided to include this study because cardiovascular mortality is the main cause of death in patients with CKD (43). Mean 25(OH)D concentrations were from 15.6 to 23 ng/mL, and participants with a serum 25(OH)D <30 ng/mL ranged from 72% to 92%. In most included studies, participants with a vitamin D deficiency tended to have the following features: older age, female sex, greater history of diabetes and cardiovascular disease (CVD), higher cardiovascular

Table 1. Baseline Characteristics of Included Studies in the Meta-analysis on the Association Between Serum 25(OH)D Levels and Risk of All-Cause Mortality in Patients With CKD

Published Study	Study	Country	Design	Duration	Participants/ Death, No.	Sex	Mean/ Median Age, y	CKD Stage	Dialysis, %
Pilz, 2011 (27)	Ludwigshafen Risk and Cardiovascular Health Study	Germany	Prospective cohort	9.4 y	444/227	Both	70	3–5	0
Jean, 2011 (28)	ARNOS French cohort	France	Prospective cohort	3.5 y	648/247	Both	67	ESRD	100
Kramer, 2012 (29)	NHANES III	United States	Prospective cohort	18 y	1097/902	Both	72	3–5	0
Chonchol, 2016 (30)	HEMO study	United States	Prospective cohort	3 y	1340/582	Both	57	ESRD	100
Krause, 2012 (31)	German Renal Registry	Germany	Retrospective cohort	Retrospective evaluation of a subcohort of hemodialysis patients from the incidence cohorts, 1997– 2006	6518/3010	Both	71	ESRD	100
Molina, 2016 (32)	OSERCE-2 study	Spain	Prospective cohort	3 y	470/46	Both	66	3–5	0
Drechsler, 2010 (33)	German Diabetes and Dialysis Study	Germany	Prospective cohort	4 y	1108/545	Both	66	ESRD	100
Ravani, 2009 (34)	Cremona Hospital	Italy	Prospective cohort	4 y	168/78	Both	70	2–5	0
Jassal, 2010 (35)	Rancho Bernardo Study	United States	Prospective cohort	6.8 y	233/40	Both	80	3–4	0
Barreto, 2009 (36)	Amiens University Hospital	France	Prospective cohort	1.7 y	140/25	Both	67	2–5	33
Wang, 2008 (37)	A prospective cohort study	Hong Kong	Prospective cohort	3 y	230/70	Both	55	ESRD	100
Drechsler, 2011 (38)	NECOSAD	Netherlands	Prospective cohort	3 y	762/213	Both	59	ESRD	100
Schiller, 2015 (39)	South-Eastern European Dialysis Cohort	Romania	Prospective cohort	1.2 y	570/68	Both	55	ESRD	100
Kendrick, 2012 (40)	The Homocysteine Study	United States	Prospective cohort	2.9 y	1099/453	Both	69	4–5	0
Navaneethan, 2011 (41)	Electronic health record–based CKD registry	United States	Retrospective cohort	1.2 y	12,427/767	Both	71.5	3–4	0
Wolf, 2007 (42)	ArMORR	United States	Nested case-control	90 d	984/244	Both	63	ESRD	100

Abbreviations: ArMORR, Accelerated Mortality on Renal Replacement; ARNOS, Association Régionale des Néphrologues Ostéodystrophie; ESRD, end-stage renal disease; HEMO, Hemodialysis study; NECOSAD, The Netherlands Cooperative Study on the Adequacy of Dialysis; NHANES, National Health and Nutrition Examination Survey; OSERCE, Spanish acronym for "Epidemiological Study of Bone Disease in Chronic Kidney Disease in Spain."

risk profile, and worse inflammatory status. Baseline characteristics of included studies are shown in Table 1, and reported risk estimates of all-cause mortality for multiple categories of serum 25(OH)D are presented in Supplemental Table 1.

Vitamin D status and all-cause mortality

We could standardize and categorize data from 12 studies (28–33, 36, 38–42), and results showed that in comparison with patients with a serum vitamin D >30 ng/mL, severely deficient patients (<10 ng/mL) had a 63% higher risk of all-cause mortality (pooled RR, 1.63; 95% CI, 1.32 to 1.94; $I^2 = 73$, $P < 0.0001$), with a lower risk of mortality in patients without a need for dialysis treatment (Supplemental Fig. 1). After exclusion of two retrospective cohort studies (31, 41), the heterogeneity disappeared and results altered to 1.50 (95% CI, 1.33 to 1.68).

For mild deficiency (10 to 20 ng/mL), the summary risk estimate of all-cause mortality was 1.22 (95% CI, 1.09 to 1.35) without evidence of heterogeneity. Similar to severe deficiency, the associations were statistically significant in both dependent and nondependent dialysis patients, with greater risk for dialysis patients (Supplemental Fig. 2). In a sensitivity analysis after exclusion of Kramer *et al.* (29), a large cohort study in the United States, the result for total patients did not alter substantially, but for nondependent dialysis patients, a significant association was no longer observed (results not shown).

We also observed that patients with vitamin D insufficiency (20 to 30 ng/mL) had a 12% higher risk of overall mortality, in comparison to patients with normal serum vitamin D (pooled RR, 1.12; 95% CI, 1.06 to 1.18), with no evidence of heterogeneity (Supplemental Fig. 3). Exclusion of studies with a retrospective design did not change the results, but with exclusion of Kramer *et al.* (29), we did not observe a significant association in dependent or nondependent dialysis patients. Egger's regression test did not show any evidence of publication bias ($P = 0.3$).

Dose-response meta-analysis

To examine the linear trend between serum 25(OH)D and all-cause mortality, we included 11 studies (27–37), and summary results indicated that a 10-ng/mL increment in serum 25(OH)D was associated with a 21% reduction in the risk of overall mortality [pooled RR, 0.79; 95% CI, 0.70 to 0.87 (Supplemental Fig. 4)], with substantial evidence of heterogeneity ($P < 0.0001$). Influence analysis by removing one study at a time showed that the summary results changed from 0.77 (95% CI, 0.68 to 0.77; $P_{\text{Heterogeneity}} < 0.0001$) after exclusion of Chonchol *et al.* (30) to 0.82 (95% CI, 0.77 to 0.88; $P_{\text{Heterogeneity}} = 0.005$) after exclusion of Krause *et al.* (31) (Supplemental Fig. 5).

We also observed that an increase in serum 25(OH)D was associated with better survival in patients with CKD without a need for dialysis (pooled RR, 0.75; 95% CI, 0.61 to 0.89; $P_{\text{Heterogeneity}} = 0.001$), in comparison with dialysis-dependent patients (pooled RR, 0.83; 95% CI, 0.73 to 0.94; $P_{\text{Heterogeneity}} < 0.0001$).

Seven studies (27–33) reported sufficient information for inclusion in a nonlinear dose-response meta-analysis, and we could observe a significant curvilinear association between serum 25(OH)D and risk of overall mortality (P for nonlinearity = 0.002). By nonlinear dose-response meta-analysis, the lower risk of all-cause mortality was seen at a serum 25(OH)D of ~25 ng/mL (Fig. 2). From seven included studies in a nonlinear dose-response meta-analysis, only a large cohort study in the United States (29) reported risk estimates of all-cause mortality for serum 25(OH)D levels >40 ng/mL, so we repeated the analysis after exclusion of this study, and sensitivity analysis showed that the risk of all-cause mortality decreased continuously with increasing serum levels of 25(OH)D from 5 ng/mL to 30 ng/mL and then reached a plateau (P for nonlinearity = 0.004; Fig. 3).

Our results (from the first type of analysis) also showed that vitamin D deficiency and insufficiency were accompanied with worse prognosis in dialysis-dependent patients. However, to more accurately test the shape of the nonlinear association between serum 25(OH)D and risk of all-cause mortality, we separately examined dose-response associations in dependent and nondependent dialysis patients. We observed that in dialysis-dependent patients (28, 30, 31, 33), the risk decreased continuously with increasing serum 25(OH)D levels from 5 ng/mL to ~40 ng/mL (P for nonlinearity = 0.11; Supplemental Fig. 6), and in nondependent dialysis patients (27, 29, 32), no further risk reduction was seen at 25(OH)D levels greater than ~25 ng/mL (P for nonlinearity = 0.005; Supplemental Fig. 7).

Discussion

The present meta-analysis confirms previous findings and indicates that better vitamin D status in patients with CKD is associated with better outcomes. We observed that severe vitamin D deficiency, mild deficiency, and vitamin D insufficiency were associated with a 63%, 22%, and 12% higher risk of all-cause mortality, respectively. We also found that every 10-ng/mL increment in serum 25(OH)D was associated with a 21% reduction in the risk of overall mortality, compared with 14% in a meta-analysis conducted by Pilz *et al.* (13). We found that results were not equal in patients with and without

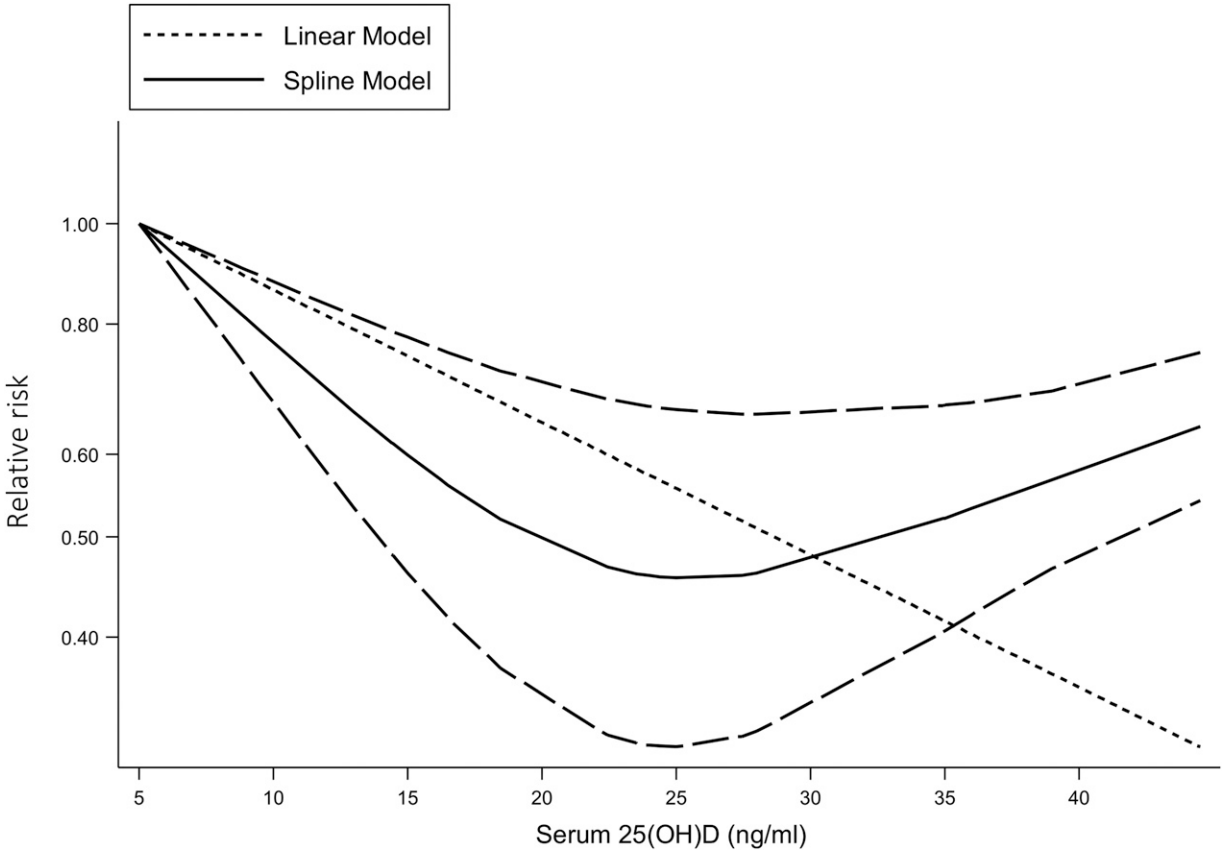

Figure 2. Dose-response association between serum 25(OH)D and risk of all-cause mortality in patients with CKD (from seven studies). The *P* value for nonlinearity was 0.002.

dialysis treatment, and vitamin D deficiency was associated with a greater risk of mortality in dialysis patients.

Many explanations can justify this relationship. It has been reported that CVD is the leading cause of death in patients with CKD (43, 44). The association found between vitamin D deficiency and higher risk of hypertension (45, 46), coronary artery calcification (47), left ventricular hypertrophy (48), and cardiovascular risk markers (49) can explain the role of vitamin D deficiency in the development of CVD in patients with CKD. Vitamin D also plays a key role in modulation of the immune system (1), and it has been shown that its deficiency was independently associated with a higher risk of infectious disease, in both the general population and patients with CKD (30, 31, 50). Regulating the production of inflammatory cytokines and inhibiting the proliferation of proinflammatory cells are other functions of vitamin D that can participate in the prevention of adverse health outcomes (51).

Considering the decreased ability of kidneys to produce the active form of vitamin D in patients with CKD, less attention has been paid to measurement and correction of serum level of 25(OH)D in these patients, especially in dialysis-dependent individuals. Today, measurement of 25(OH)D is not common in patients with CKD, although some guidelines suggest that measurement and correction of the serum level of 25(OH)D can be considered part of their therapy (52). It has been shown that supplementation with the active form of vitamin D was associated with a lower risk of all-cause and cardiovascular mortality, in both dependent and nondependent dialysis patients (17). However, concerning 25(OH)D, there is no such evidence.

Despite the strong inverse association between the serum level of 25(OH)D and mortality in our meta-analysis, we did not find any clinical trials to examine the association between 25(OH)D supplementation and survival in patients with CKD. A meta-analysis conducted by Kandula *et al.* (53), including 17 observational and 5 clinical trials, indicated that vitamin D supplementation (ergocalciferol or cholecalciferol) in both dependent and nondependent dialysis patients is associated with a significant decrease in serum parathyroid hormone, which, when elevated, is highly associated with mortality in patients with CKD (54, 55).

Notwithstanding the reduced renal function, extrarenal production of 1,25-dihydroxyvitamin D_3 also implies the importance of the serum level of 25(OH)D (5, 56, 57), especially because extrarenal 1α-hydroxylase

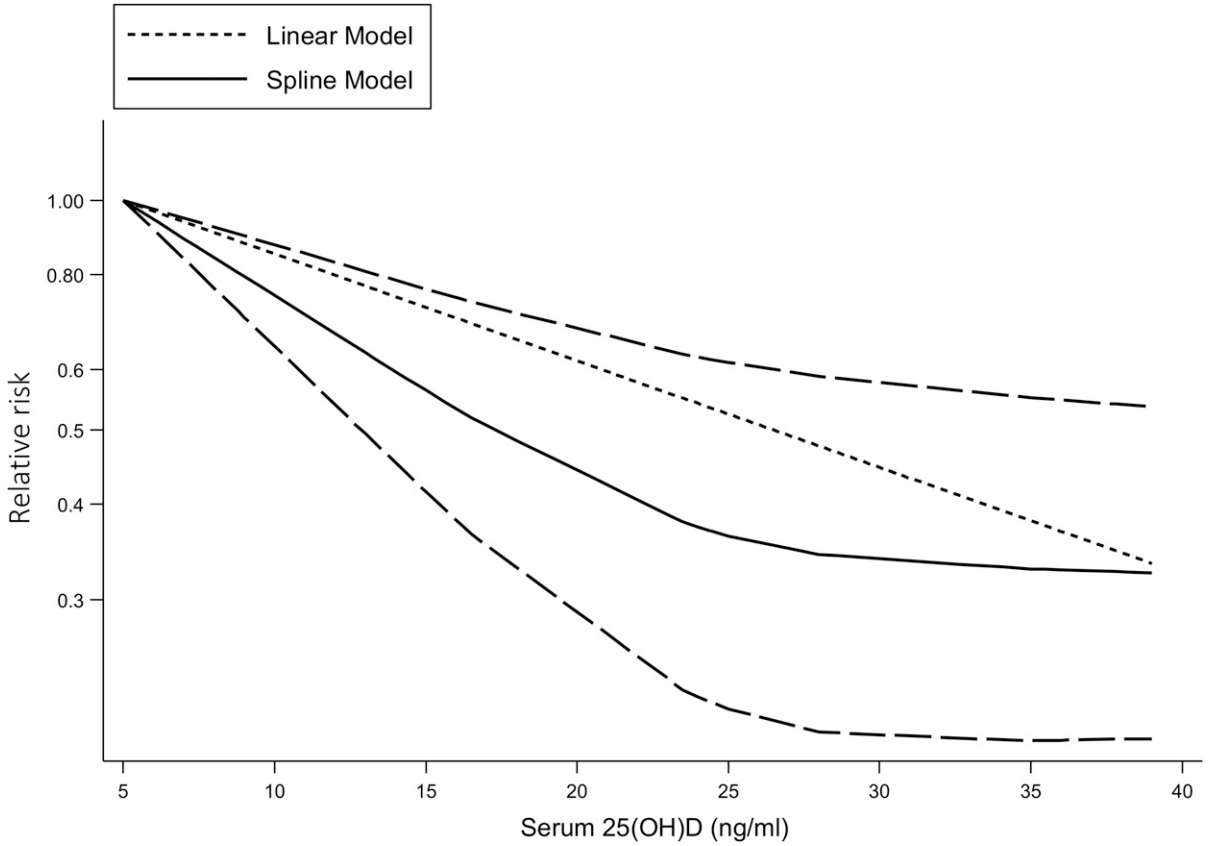

Figure 3. Dose-response association between serum 25(OH)D and risk of all-cause mortality in patients with CKD [after exclusion of a study with the highest category as >40 ng/mL (34)]. The *P* value for nonlinearity was 0.004.

activity may have a role in regulating the immune system and inflammatory response (58). Although it now is assumed that local production of calcitriol does not contribute to the serum level of 1,25-dihydroxyvitamin D [1,25(OH)D] (56), two clinical trials indicated that supplementation with cholecalciferol led to a significant increase in the serum level of 1,25-dihydroxyvitamin D_3 in hemodialysis patients (59, 60). In addition, some evidence suggested that 25(OH)D may have a direct effect on the vitamin D receptor (61). These facts, taking the reduced renal production of calcitriol into account, may partially explain the worse prognosis of 25(OH)D deficiency in dialysis-dependent patients. In particular, glucocorticoids, which are widely used in dialysis-dependent patients as potent inhibitors of inflammatory processes, may be another cause of less serum vitamin D in these patients compared with patients who are not dependent on dialysis.

We observed that the association between vitamin D deficiency and mortality also was more evident in dialysis-dependent patients, who generally were treated with the active form of vitamin D. Regarding the absence of renal production of calcitriol in dialysis patients, this result may imply the importance of maintaining the optimal level of 25(OH)D and its crucial role in patients with CKD, independent of calcitriol. It should be noted, however, that of the eight studies that were conducted in dialysis-dependent patients, only five studies reported sufficient information regarding supplementation with the active form of vitamin D (28, 30, 33, 36, 37), in which the proportion of supplementation included one patient in Barreto *et al.* (this study included both dependent and nondependent dialysis patients) (36), 18.3% in Drechsler *et al.* (33), 37.4% in Wang *et al.* (37), 46.6% in Jean *et al.* (28), and 53.7% in Chonchol *et al.* (30). Therefore, we do not have sufficient information regarding supplementation with the active form of vitamin D and, as a result, we could not specify clearly how supplementation with the active form potentially affects the survival outcomes of 25(OH)D deficiency or insufficiency in these patients. In addition, from all 15 included studies, only 5 studies reported information regarding medication regimens in their participants (27, 32, 33, 35, 40), taking into account that some types of medications, including statin therapy, may be accompanied with better outcomes in patients with CKD (62–6464). By nonlinear dose-response meta-analysis, we also found the lower risk of all-cause mortality at a serum level of 25(OH)D of ~25 ng/mL, compared with >30 ng/mL in the general population (65). By contrast, in the general population,

we observed that a serum level of 25(OH)D of >25 to 28 ng/mL was associated with a higher risk of mortality in patients with CKD. It should be noted that of seven included studies in the nonlinear dose-response meta-analysis, only one study reported risk estimates for serum 25(OH)D levels >40 ng/mL, with a range of 24 to 30 ng/mL as the reference category (29). The range of the highest category was >30 ng/mL in four studies (27, 31–33), >32 ng/mL in one study (28), and >26 ng/mL in another study (30). Some studies showed a U-shaped relationship between 25(OH)D and health outcomes (65). The results of Wang *et al.* (65) showed that there was no additional reduction in risk for CVD at levels >75 nmol/L 25(OH)D and that the dose-response relationship may be U-shaped at >75 nmol/L. However, these results should be interpreted with caution. Garland *et al.* (66), using 30 prospective cohort and 2 nested case-control studies, indicated that the risk of all-cause mortality in the general population decreased substantially with increasing serum levels of 25(OH)D to ~40 ng/mL, without further risk reduction at higher levels up to 70 ng/mL. However, concerning patients with CKD, it is not conclusively clear how the risk of all-cause mortality will change at serum 25(OH)D levels of >35 ng/mL. The better description for our findings may be that risk of mortality decreases with increasing 25(OH)D, but the benefit levels off at ~30 ng/mL. In the case of patients with CKD stages 3 and 4, the Kidney Disease Outcomes Quality Initiative guideline defined vitamin D deficiency and insufficiency as <30 ng/mL and <15 ng/mL, respectively (67), but it seems necessary to examine health outcomes of higher levels of 25(OH)D in future studies to specify the optimal level of 25(OH)D in these patients. Moreover, regarding many modifiers of 25(OH)D concentration, future research should take into account the health status and life stage of study participants, time of exposure assessment, and the effects of adiposity, estrogen exposure, different medications, and nutritional status.

The present meta-analysis has some strengths. First, we could standardize serum vitamin D categories in studies with different cut-points to define vitamin D deficiency and insufficiency, which enabled us to better extrapolate the results. Second, we could test the shape of the association between serum 25(OH)D and all-cause mortality using a nonlinear dose-response meta-analysis for all participants and also separately for dependent and nondependent dialysis patients, which conferred more exact details. Third, our meta-analysis indicated that severe and mild vitamin D deficiency was accompanied with worse outcomes in dialysis-dependent patients. Considering treatment of dialysis-dependent patients with the active form of vitamin D, this stronger association should be considered and may imply the high importance of extrarenal production of 1,25(OH)D in dialysis patients with lower kidney function.

We also have some considerable limitations. In many of the included studies, vitamin D deficiency was associated with other risk factors, including older age, higher prevalence of diabetes, more history of CVD, and more CVD risk factors (27–33, 36, 38, 39, 41, 42), which indicated that a lower level of 25(OH)D may be a consequence of a worse health condition and not a risk factor for mortality. Our results also were accompanied by considerable heterogeneity that could be due to seasonal variations in the time of sampling, different cut-points used for categorization, different methods to assay serum levels of 25(OH)D, different stages of CKD in study participants, different prevalence of comorbidities, and different proportion of supplementation with both 25(OH)D and 1,25(OH)D in study participants. Concerning seasonal variation in serum levels of 25(OH)D, only five studies addressed this issue (27, 29, 33, 39, 41), in which all samples were collected during one season in only one study (39), making it impossible for us to assess the potential confounding effects of seasonal variation on the association between 25(OH)D deficiency and clinical outcomes in that study. The low number of studies in our meta-analysis, especially for nonlinear meta-analysis, was another limitation that did not allow us to perform a powerful statistical analysis. Moreover, we could show a dose-dependent association for serum 25(OH)D levels only between 5 and 35 ng/mL; concerning health outcomes at higher levels, we have no conclusive evidence.

Conclusion

The current meta-analysis showed that the vitamin D deficiency and insufficiency are highly associated with the risk of all-cause mortality, with worse prognosis for dialysis-dependent patients. Our findings put an emphasis on the importance of measurement and correction of serum 25(OH)D in patients with CKD. However, it seems necessary to conduct well-designed, placebo-controlled clinical trials to examine the survival effects of 25(OH)D supplementation. In addition, concerning health outcomes of serum 25(OH)D levels >35 ng/mL in patients with CKD, we have no clear evidence.

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