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Vitamin D status and clinical outcomes in incident dialysis patients: results from the NECOSAD study

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Abstract

Background. The majority of dialysis patients suffer from vitamin D deficiency, which might contribute to an adverse health outcome. We aimed to elucidate whether European dialysis patients with low 25-hydroxyvitamin D (25(OH)D) levels are at increased risk of mortality and specific fatal events.

Methods. This was a prospective cohort study of incident dialysis patients in the Netherlands (the NECOSAD). We selected all patients with measured 25(OH)D at 12 months after the start of dialysis, the baseline for our study. By Cox regression analyses, we assessed the impact of 25 (OH)D levels on short-term (6 months of follow-up) as well as longer-term mortality (3 years of follow-up). Associations of 25(OH)D levels with cardiovascular and non-cardiovascular mortality were also determined.

Results. The data from 762 patients (39% females, age 59 ± 15 years, 25(OH)D = 18 ± 11 ng/mL) were available. Fifty-one and 213 patients died during a follow-up of 6 months and 3 years, respectively. After adjustments for possible confounders, the hazard ratio (HR) (with 95% CI) for mortality was 2.0 (1.0–3.8) for short-term and 1.5 (1.0–2.1) for longer-term mortality when comparing patients with 25(OH)D levels ≤10 ng/mL with those presenting with 25(OH)D levels >10 ng/mL. Adjusted HRs for cardiovascular mortality were 2.7 (1.1–6.5) and 1.7 (1.1–2.7) for short- and longer-term mortality, respectively. For non-cardiovascular mortality, we observed no relevant association overall. The impact of 25(OH)D levels on clinical events was modified by parathyroid hormone (PTH) status, with low 25(OH)D levels meaningfully affecting outcomes only in patients with PTH levels above the median of 123 pmol/L.

Conclusions. Vitamin D deficiency in dialysis patients is associated with an adverse health outcome, in particular with short-term cardiovascular mortality. Intervention studies are urgently needed to evaluate whether vitamin D supplementation improves health outcomes of dialysis patients.

Keywords: cardiovascular; dialysis; epidemiology; mortality; vitamin D

Introduction

Accumulating evidence supports the hypothesis that vitamin D deficiency might contribute to the extraordinary high mortality risk among dialysis patients [1–8]. Most patients on maintenance dialysis suffer from vitamin D deficiency because ultraviolet-B (UV-B)-induced vitamin D production in the skin, the main source for vitamin D, is usually limited due to reduced sun exposure and impaired dermal vitamin D synthesis [1–8]. This high prevalence of vitamin D deficiency is increasingly recognized as an important health issue because it has been shown (i) that ~3% of the human genome is regulated by the vitamin D endocrine system and (ii) that the vitamin D receptor (VDR) is almost ubiquitously expressed [2,9]. The data from patients with and without chronic kidney disease (CKD) suggest that beyond its classic effects on bone and mineral metabolism, vitamin D may also protect against cardiovascular diseases, immune disorders or cancer [2,9,10].

The traditional view of vitamin D metabolism is that vitamin D is hydroxylated to 25-hydroxyvitamin D (25 (OH)D) in the liver. Then, 25(OH)D is further converted to the most active vitamin D metabolite 1,25-dihydroxyvitamin D (1,25(OH)2D) by the enzyme 1α-hydroxylase in the kidney. Serum levels of 1,25(OH)2D, which are mainly determined by renal production, are tightly regulated by parameters of mineral metabolism [i.e. parathyroid hor-

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mone (PTH) or fibroblast growth factor 23 (FGF-23)], decline with lower glomerular filtration rate (GFR), and are usually not closely associated with 25(OH)D levels [2,9,10]. The discovery that apart from the kidney many other organs are also able to produce 1,25(OH)2D on a local level revolutionized our understanding of vitamin D physiology [9,10]. Given that this extrarenal production of 1,25(OH)2D seems to be significantly dependent on substrate availability of 25(OH)D, the vitamin D status is classified according to circulating 25(OH)D levels [2,10].

Previous studies among patients with CKD largely indicate that low 25(OH)D levels are associated with increased mortality and in particular with cardiovascular events [1,4–8], but the data among dialysis patients are sparse [5,7,8]. Wolf *et al.* performed the largest study in this field and found that among 1000 incident haemodialysis patients, low 25(OH)D levels were significantly associated with 90-day mortality in a nested case–control analysis [8]. The data on the association of 25(OH)D with long-term mortality in haemodialysis patients are unknown. The vitamin D status and its association with outcome are furthermore of interest in other patient populations, which meaningfully differ in duration or modality of dialysis, primary kidney disease prevalences, and ethnic composition. There is also no previous study in CKD patients which addressed associations of vitamin D deficiency with both long-term and short-term outcome data for all-cause, cardiovascular and non-cardiovascular mortality. Hence, we aimed to assess the effect of 25(OH)D on morbidity and mortality in dialysis patients, analysing data of a prospective multicentre cohort study of incident dialysis patients in the Netherlands.

Materials and methods

Study design

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is an observational prospective follow-up study in which incident dialysis patients have been enrolled in 38 participating dialysis centres since 1997 in the Netherlands [11,12]. Study visits took place at the start of dialysis, at 3 months, at 6 months, and subsequently at 6-month intervals until the date of loss to follow-up (death, kidney transplantation or transfer to a non-participating dialysis centre) or the end of follow-up at 1 January 2009. Baseline demographic and clinical data were obtained between 4 weeks prior to and 2 weeks after the start of long-term dialysis treatment. Blood and 24-h urine samples were obtained at all visits. For the present analysis, baseline is defined as 12 months after the start of dialysis treatment, when the patients' fluid and metabolic conditions had stabilized and when adequate amounts of plasma material for laboratory measurements were available.

Patients

Patients with end-stage renal disease (ESRD) who were at least 18 years old and started long-term dialysis therapy for the first time were invited to participate in the NECOSAD. In the present analysis, all patients with available blood samples to perform measurements of 25(OH)D at 12 months after initiation of dialysis were included. The medical ethical committees of the participating centres approved the study, and all patients gave their written informed consent before inclusion.

Data collection

Demographic and clinical data included age, sex, ethnicity, smoking habits, primary kidney disease and co-morbidity. Primary kidney diseases and causes of death were classified according to the coding system of the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA). Diagnoses of co-morbid conditions were reported by the patient's nephrologists and used to calculate the co-morbidity score according to Khan. Plasma 25(OH)D levels were measured in samples taken at 12 months after the start of dialysis using a chemiluminescence immunoassay on the Liaison autoanalyser (DiaSorin, Saluggia, Italy). This time point was chosen because of the adequate availability of plasma material, and the measurements were performed centrally at the laboratory of the Department of Nephrology, University of Aachen, Germany. Plasma calcium, phosphorus, intact PTH, total alkaline phosphatase and albumin were measured by standard laboratory techniques in the different centres. Height and weight were measured after dialysis sessions, and BMI was calculated as weight (kilograms) divided by height (metres) squared. Blood pressure was measured in the sitting position.

Definition of end points

Cardiovascular mortality was defined as death due to the following causes: myocardial ischaemia and infarction, hyperkalaemia, hypokalaemia, cardiac arrest, (hypertensive) cardiac failure, fluid overload, cerebrovascular accident, haemorrhage from ruptured vascular aneurysm, mesenteric infarction, and cause of death uncertain/unknown. All other causes of death were designated as non-cardiovascular mortality.

Statistical analyses

Mean values with standard deviations (SD) were calculated for continuous variables, and median values with interquartile range (IQR) as appropriate. Categorical variables were expressed as proportions.

In line with widely used cut-off values, the patients were categorized into severely vitamin D deficient (≤10.0 ng/mL), moderately vitamin D deficient (>10–≤30 ng/mL) and vitamin D sufficient (>30 ng/mL). Due to the relatively low numbers of fatal events and due to results from previous studies suggesting that 10 ng/mL is an appropriate threshold to identify patients at high mortality risk, we mainly performed a categorization into only two groups: patients with 25(OH)D levels ≤10 ng/mL and patients with 25(OH)D levels >10 ng/mL. These two groups were mainly used to assess the associations of 25(OH)D levels with all-cause mortality and death from cardiovascular and non-cardiovascular causes.

Cumulative mortality curves were calculated using Kaplan–Meier analysis for all-cause mortality. This method has been known to overestimate profoundly the cumulative mortality when analysing competing end points [13]. Separate analysis of cardiovascular (CV) mortality and non-CV mortality is a clear example of competing end points. For that reason, we calculated the cumulative mortality curves for CV mortality and non-CV mortality using competing risk analysis, taking into account that patients dying of CV causes are no longer at risk to die of non-CV causes, and vice versa [13,14].

We calculated Cox proportional hazard ratios (HR) with 95% confidence intervals (95% CI) for subsequent short-term (6 months) and longer-term (3 years) periods (including the first 6 months), according to 25(OH)D levels at baseline. In addition, we investigated conditional risks, i.e. the risks to die within 3 years, conditional on having survived the first half year. HRs were calculated for patients with 25(OH)D levels ≤10 ng/mL compared with those with higher 25(OH)D levels as well as for comparisons between the groups with severe vitamin D deficiency, moderate vitamin D deficiency and vitamin D sufficiency. The highest category of 25(OH)D was used as the reference group. We calculated a crude model and a model adjusted for potential confounders including age, sex, ethnicity, dialysis modality, primary kidney disease, diabetes mellitus, cardiovascular disease, blood pressure, body mass index, smoking status, use of vitamin supplements, levels of cholesterol, serum albumin, creatinine and haemoglobin. To account for the seasonal variation of vitamin D, we further adjusted our analyses for the season of blood draw. We therefore used a binary variable reflecting the months October–March and April–September, respectively. In order to explore possible pathways, we performed further analyses with additional inclusion of parameters of bone mineral metabolism including levels of calcium, PTH, phosphate and alkaline phosphatase. As the parameters of physical performance and dialysis access were available in subsets of patients only, we performed sensitivity analyses with further adjustments for these variables. In addition, we tested potential interactions of vitamin D with the use of vitamin supplements and with levels of alkaline phosphatase. Finally, we analysed the association of

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25(OH)D status with adverse outcomes in subgroups of patients according to their PTH level (below and above the median).

All P-values are reported two-sided and considered significant at a level <0.05. Analyses were performed using SPSS version 16.0.

Results

Patients

A total of 1753 patients with ESRD who started long-term dialysis and were included still participated in the NECOSAD at 12 months after the initiation of dialysis therapy (baseline). Of those, vitamin D was measured in 762 patients, in whom the amount of collected blood was sufficient for the measurement of 25(OH)D. These patients were included in the present analyses. Of note, the included patients were not different from the remaining study cohort (n = 991). Both patient groups were similar with regard to demographic and clinical characteristics including co-morbidities and levels of routine laboratory markers (data not shown).

In the study population (n = 762), the mean (standard deviation) age was 59 (15)years, and 61% of the patients were male. In general, the mean (standard deviation) level of 25(OH)D at baseline was 18.2 (11.0)ng/mL. As expected, we observed a seasonal variation of 25(OH)D in our patients, with the lowest concentrations in March [14.1 (6.9)ng/mL] and the highest concentrations in August [25.0 (13.0)ng/mL].

The patient characteristics are shown in Table 1. Significant findings at baseline were that with lower 25(OH)D levels, more patients had diabetes mellitus either as the primary kidney disease or as co-morbidity. Male patients and those on haemodialysis were less common in groups with lower 25(OH)D levels. Levels of alkaline phosphatase were higher in patients with low 25(OH)D levels (for further baseline data see Table 1).

During the 3-year follow-up period, 213 patients died, of whom 118 patients died of cardiovascular causes, and 95 patients died of non-cardiovascular causes. In detail, the 118 cardiovascular deaths included 21 deaths due to myocardial ischaemia and infarction, 1 death due to hyperkalaemia, 15 deaths due to cardiac failure, 27 sudden cardiac deaths, 1 death due to fluid overload/pulmonary oedema, 10 cerebrovascular deaths, 3 deaths due to mesenteric infarction, and 40 deaths in which the specific cause was un-

Table 1. Baseline characteristics of the study population, and according to 25(OH)D status

		Vitamin D categories		
	Whole group	Severely vitamin D deficient ≤10.0 ng/mL	Moderately vitamin D deficient >10–≤30 ng/mL	Vitamin D sufficient >30 ng/mL
Numbers	n = 762	n = 193	n = 469	n = 100
Age (years)	59 ± 15	57 ± 15	60 ± 15	57 ± 15
Male (%)	61	50	63	78
Dialysis modality (% HD)	64	55	68	76
Primary kidney disease				
Diabetes mellitus (%)	15	23	14	6
Glomerulonephritis (%)	15	12	15	21
Renal vascular disease (%)	17	16	17	15
Other (%)	53	49	54	58
Body mass index (kg/m²)	24.9 ± 4.1	25.0 ± 4.6	25.0 ± 3.8	24.6 ± 4.2
Blood pressure (mmHg)				
Systolic	149 ± 23	149 ± 24	150 ± 23	146 ± 22
Diastolic	83 ± 13	82 ± 13	83 ± 13	83 ± 13
Active smokers (%)	22	27	20	18
Vitamin supplementation (%)	94	92	94	94
Co-morbidity				
Diabetes mellitus (%)	20	31	18	8
Cardiovascular disease (%)	32	27	35	25
Khan score				
Low (%)	38	35	37	53
Intermediate (%)	34	42	34	20
High (%)	28	24	29	28
GFR (mL/min/1.73 m²)	2.0 (0.7–3.9)	1.9 (0.7–4.2)	2.1 (0.7–4.0)	1.7 (0.5–3.3)
Laboratory values				
Haemoglobin (g/dL)	11.4 ± 1.4	11.2 ± 1.4	11.5 ± 1.4	11.4 ± 1.2
Albumin (g/L)	36 ± 6	35 ± 6	36 ± 6	36 ± 5
25-hydroxyvitamin D (ng/mL)	18 ± 11	8 ± 2	18 ± 5	40 ± 10
Alkaline phosphatase	78 ± 53	90 ± 72	75 ± 46	72 ± 38
Serum calcium (mmol/L)	2.4 ± 0.2	2.4 ± 0.3	2.4 ± 0.2	2.4 ± 0.2
Serum phosphate (mmol/L)	1.8 ± 0.5	1.8 ± 0.6	1.8 ± 0.5	1.9 ± 0.5
PTH (pmol/L)	13.0 (5.0–27.0)	14.0 (4.8–26.8)	12.2 (4.8–29.3)	13.1 (5.6–25.5)
Cholesterol (mmol/L)	4.85 ± 1.31	5.0 ± 1.5	4.9 ± 1.3	4.6 ± 1.2

Continuous data are expressed as means ± standard deviation and as medians with interquartile range, and categorical data are shown as percentages. GFR, glomerular filtration rate.

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Table 2. Hazard ratios (95% CI) for all-cause mortality in the presence of severe vitamin D deficiency

		6 months	3 years	Conditional: between 6 months and 3 years
All-cause mortality				
25(OH)D level (ng/mL)				
Crude	≤10	1.74 (0.98–3.11) P = 0.061	1.34 (1.00–1.80) P = 0.05	1.23 (0.88–1.73) P = 0.233
	>10	1	1	1
Adjusted 1	≤10	1.77 (0.94–3.33) P = 0.079	1.46 (1.04–2.05) P = 0.03	1.41 (0.95–2.09) P = 0.093
	>10	1	1	1
Adjusted 2	≤10	1.45 (0.74–2.81) P = 0.277	1.37 (0.97–1.94) P = 0.075	1.30 (0.87–1.95) P = 0.204
	>10	1	1	1
Stratified by PTH				
Below the median (<123 pmol/L)				
Crude	≤10	1.14 (0.45–2.88) P = 0.779	0.95 (0.61–1.49) P = 0.139	0.90 (0.54–1.50) P = 0.694
	>10	1	1	1
Adjusted 1	≤10	1.19 (0.42–3.35) P = 0.749	0.86 (0.50–1.46) P = 0.572	0.83 (0.45–1.53) P = 0.832
	>10	1	1	1
Above the median (>123 pmol/L)				
Crude	≤10	2.48 (1.09–5.62) P = 0.03	1.78 (1.17–2.70) P = 0.007	1.58 (0.97–2.59) P = 0.067
	>10	1	1	1
Adjusted 1	≤10	3.13 (1.31–7.50) P = 0.055	2.59 (1.56–4.30) P < 0.001	2.62 (1.44–4.79) P = 0.002
	>10	1	1	1

1, adjusted for age, sex, dialysis modality, ethnicity, primary kidney disease, diabetes mellitus, cardiovascular disease, body mass index, systolic blood pressure, smoking, cholesterol, use of vitamin supplements, levels of albumin, haemoglobin and creatinine, and for the seasonal variation of vitamin D; 2, further adjusted for levels of PTH, calcium, phosphate and alkaline phosphatase.

certain. Of all deaths, 51 occurred in the short-term, i.e. within 6 months after baseline. These included 29 cardiovascular and 22 non-cardiovascular deaths.

Vitamin D status and total mortality

We investigated short-term and longer-term mortality according to vitamin D status. The respective follow-up intervals were 6 months and 3 years following the measurements of 25(OH)D. We observed significant associations when comparing patients with severe vitamin D deficiency with all other study participants (Table 2 and Figure 1A and B). In detail, the adjusted HRs for the 6-month and 3-year follow-up periods were 1.98 (1.03–3.79, P = 0.04) and 1.46 (1.04–2.05, P = 0.03), respectively. Additional adjustments for parameters of bone mineral metabolism decreased these HRs to 1.87 (0.84–3.71) for the 6-month follow-up and to 1.37 (0.97–1.94) for the 3-year follow-up analyses. The results largely persisted when further adjustments were made for daily walking ability and dialysis access in sensitivity analyses (data not shown). Conditional on having survived the first 6 months after assessment of the vitamin D status, there was no meaningful increase in deaths for the severely deficient patients any more (conditional analyses, Table 2). Of note, there was no interaction observed between vitamin D status and the use of vitamin supplements, nor with levels of alkaline phosphatase in the association with mortality. Further analyses in the strata of PTH (below and above the median of 123 pmol/L) showed that the effects of low 25(OH)D levels on mortality were more pronounced in patients with high PTH levels (Table 2). Using the three-category approach for vitamin D status, we did not find significant associations when comparing patients with severe vitamin D deficiency with patients with vitamin D sufficiency, being aware of the low number of patients and events in the latter group (Table 3). Adjusted HRs for the group with severe vitamin D deficiency were 1.28 (95% CI 0.47–3.46, P = 0.63) for the 6-month follow-up and 1.25 (95% CI 0.71–2.18; P = 0.43) for the 3-year follow-up.

Vitamin D status and cardiovascular mortality

Cardiovascular mortality was significantly increased in patients with severe vitamin D deficiency (Table 4 and Figure 1C and D). Compared with patients with 25(OH)D levels >10 ng/mL, the adjusted HRs were 2.67 (1.11–6.47, P = 0.03) for the 6-month follow-up and 1.73 (1.10–2.72, P = 0.05) for the 3-year follow-up (Table 4). After adjustments for parameters of bone mineral metabolism, these HRs were 2.72 (1.05–7.05, P = 0.04) and 1.61 (1.00–2.57, P = 0.048) for the 6-month and 3-year follow-up, respectively. Additional analyses in the strata of PTH showed that patients with high PTH levels (above the median) experienced particularly high risks of cardiovascular death with poor 25(OH)D status [HR 3.37 (1.64–6.91), P = 0.001] (Table 4). Comparing patients with severe vitamin D deficiency with the vitamin D-sufficient group, the adjusted HRs were 3.01 (0.60–15.10, P = 0.18)

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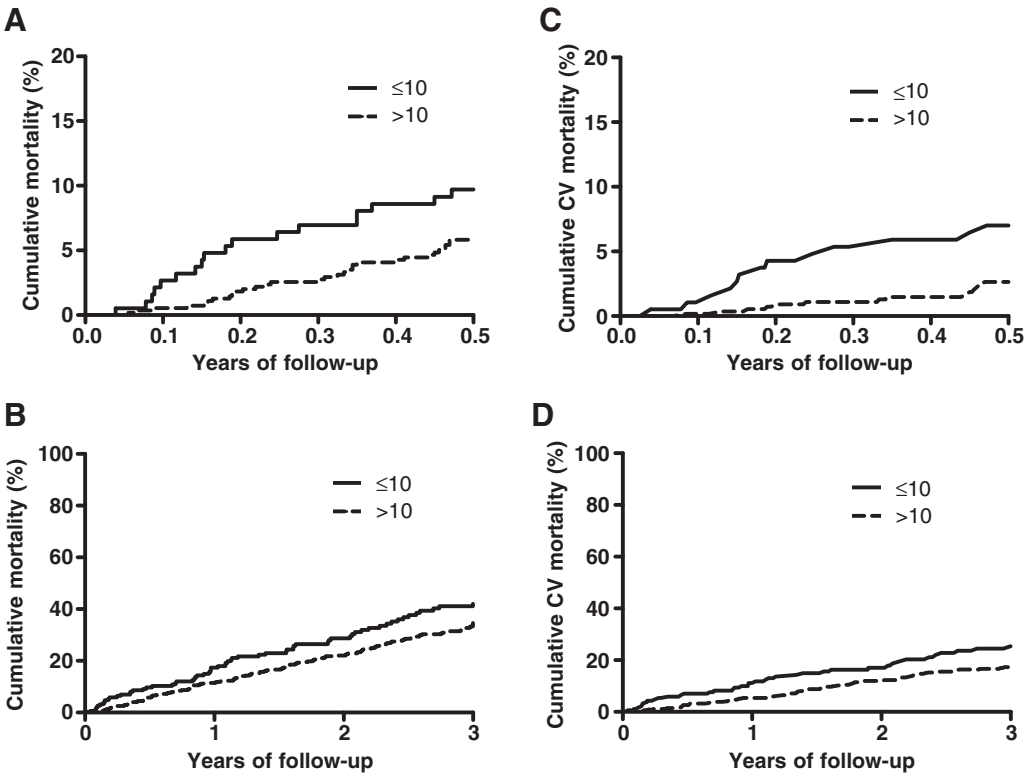

Fig. 1. (**A**–**D**) Cumulative mortality curves for (A) all-cause mortality within 6 months, (B) all-cause mortality within 3 years, (C) cardiovascular mortality within 6 months and (D) cardiovascular mortality within 3 years according to vitamin D status at baseline.

and 2.11 (0.90–4.93, P = 0.08) for the 6-month and 3-year follow-up analyses, respectively.

Vitamin D status and non-cardiovascular mortality

There was no meaningful association of vitamin D status with non-cardiovascular mortality in our main Cox regression analyses (Tables 3 and 5). Compared to patients with 25(OH)D levels >10 ng/mL, the risk of non-cardiovascular mortality was tentatively higher in patients with severe vitamin D deficiency with adjusted HRs of 1.22 (0.44–3.40, P = 0.70) for the 6-month follow-up and 1.20 (0.71–2.01, P = 0.49) for the 3-year follow-up (Table 5). Additional adjustments for parameters of bone mineral metabolism did not materially change these results. Of note, the risk of non-cardiovascular death was more than 2-fold increased in patients presenting with high PTH levels above the median; the adjusted HR was 2.32 (1.09–4.94, P = 0.029) during the 3-year follow-up. Results of the analyses comparing the three categories of vitamin D status are shown in Table 3.

Discussion

Our data from incident dialysis patients show an increased mortality in patients with severe vitamin D deficiency compared with those without severe vitamin D deficiency. In analyses of specific fatal events, we found a strong association of severe vitamin D deficiency with cardiovascular mortality, in particular for short-term follow-up analyses. For non-cardiovascular mortality, we observed no significant association with vitamin D status, but these latter data should be interpreted with caution when considering the relatively low numbers of events. Analyses in the strata of PTH showed that the impact of 25(OH)D levels on clinical events was modified by PTH status, with low 25(OH)D levels meaningfully affecting outcomes only in patients with PTH levels above the median.

Our findings are of particular interest because the majority of dialysis patients are vitamin D deficient, and it has been shown that the vitamin D endocrine system is involved in various pathophysiological processes beyond the classic vitamin D effects on bone health and mineral metabolism [2,9,10]. Vitamin D deficiency has been associated with cardiovascular diseases [15,16], cancer [17], infections [18] and autoimmune diseases [19], but these data were largely derived from patients without end-stage renal disease. There is also increasing evidence that a sufficient vitamin D status might be renoprotective by inhibition of the renin–angiotensin–aldosterone system, decreasing proteinuria or anti-inflammatory properties [20,21]. In dialysis patients, 1,25(OH)D or its analogues are frequently used, and this therapy is associated with improved survival, although it should be mentioned that further studies are still needed to establish the benefit of this active vitamin D treatment [22,23]. Natural vitamin D sup-

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Table 3. Hazard ratios (95% CI) for all-cause, cardiovascular and non-cardiovascular mortality according to levels of 25(OH)D

		6 months	3 years	Conditional: between 6 months and 3 years
All-cause mortality				
25(OH)D level (ng/mL)				
Crude	≤10	1.50 (0.60–3.78) P = 0.389	1.38 (0.86–2.23) P = 0.183	1.34 (0.77–2.34) P = 0.301
	10–30	0.83 (0.34–2.03) P = 0.689	1.04 (0.67–1.62) P = 0.872	1.11 (0.66–1.85) P = 0.699
	>30	1	1	1
Adjusted[a]	≤10	1.28 (0.47–3.46) P = 0.633	1.25 (0.71–2.18) P = 0.438	1.19 (0.61–2.32) P = 0.604
	10–30	0.66 (0.27–1.64) P = 0.373	0.84 (0.52–1.38) P = 0.493	0.84 (0.47–1.50) P = 0.548
	>30	1	1	1
Cardiovascular mortality				
Crude	≤10	3.25 (0.73–14.40) P = 0.121	2.42 (1.13–5.18) P = 0.023	2.15 (0.88–5.21) P = 0.092
	10–30	1.20 (0.27–5.36) P = 0.812	1.67 (0.80–3.47) P = 0.171	1.82 (0.78–4.21) P = 0.164
	>30	1	1	1
Adjusted[a]	≤10	3.01 (0.60–15.10) P = 0.181	2.11 (0.90–4.93) P = 0.084	1.94 (0.71–5.31) P = 0.196
	10–30	1.15 (0.25–5.32) P = 0.862	1.24 (0.58–2.66) P = 0.585	1.25 (0.51–3.03) P = 0.630
	>30	1	1	1
Non-cardiovascular mortality				
Crude	≤10	0.63 (0.17–2.33) P = 0.485	0.83 (0.44–1.57) P = 0.566	0.90 (0.43–1.89) P = 0.785
	10–30	0.65 (0.21–2.00) P = 0.453	0.70 (0.40–1.24) P = 0.223	0.72 (0.37–1.40) P = 0.331
	>30	1	1	1
Adjusted[a]	≤10	0.68 (0.17–2.76) P = 0.590	0.76 (0.35–1.63) P = 0.480	0.75 (0.30–1.86) P = 0.534
	10–30	0.51 (0.16–1.61) P = 0.249	0.60 (0.31–1.14) P = 0.118	0.57 (0.26–1.25) P = 0.161
	>30	1	1	1

[a]Adjusted for age, sex, dialysis modality, ethnicity, primary kidney disease, diabetes mellitus, cardiovascular disease, body mass index, systolic blood pressure, smoking, cholesterol, use of vitamin supplements, levels of albumin, haemoglobin and creatinine, and for the seasonal variation of vitamin D.

plementation, which increases 25(OH)D levels, is currently not an integral part of the treatment of dialysis patients, although most of them are vitamin D deficient [1,3–8]. However, even patients receiving active vitamin D treatment might benefit from natural vitamin D intake because in organs expressing 1α-hydroxylase, tissue levels of 1,25 (OH)2D are mainly determined by local conversion of 25 (OH)D to 1,25(OH)2D and not by circulating 1,25(OH)2D levels [10].

Whether natural vitamin D supplementation in dialysis patients reduces mortality and cardiovascular events is now the burning question. Current knowledge on this topic is based on only a few observational studies [5,7,8]. The NECOSAD study provides important data because it includes both chronic haemodialysis and peritoneal dialysis patients and addresses the association of vitamin D status with short-term as well as longer-term mortality. Our data showed that 25(OH)D levels were associated with overall survival, the effect sizes however being smaller compared with two previous studies investigating vitamin D deficiency in haemodialysis patients [5,8]. Apart from a possible publication bias, we believe that underlying differences in the study populations (i.e. duration and mode of dialysis, primary kidney disease, or follow-up time) might be a reasonable explanation for these partly differing results. Among 1000 haemodialysis patients, Wolf *et al.* reported an association of low 25(OH)D levels with increased mortality within 90 days after initiating haemodialysis therapy, whereas the baseline examination for our present analysis was performed after 12 months of dialysis therapy [8]. In another obviously heterogeneous cohort of 102 haemodialysis patients, low 25(OH)D levels were also significantly associated with early mortality [5]. Consistent with our results, there was no significant association of 25(OH)D and mortality in a 3-year follow-up study of 230 Chinese patients with a median peritoneal dialysis duration of 26 months [7]. Taken together, the currently available literature suggests that vitamin D deficiency is a better predictor of short-term mortality than longer-term mortality. This is supported by our results of the conditional analyses, showing no meaningful increase in deaths for the severely vitamin D-deficient patients, once they have survived the first 6 months after vitamin D assessment. Considering that 25(OH)D levels were determined only once in

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Table 4. Hazard ratios (95% CI) for cardiovascular mortality in the presence of severe vitamin D deficiency

		6 months	3 years	Conditional: between 6 months and 3 years
Cardiovascular mortality				
25(OH)D level (ng/mL)				
Crude	≤10	2.79 (1.31–5.93) P = 0.008	1.55 (1.06–2.28) P = 0.026	1.27 (0.81–2.01) P = 0.302
	>10	1	1	1
Adjusted 1	≤10	2.67 (1.11–6.47) P = 0.029	1.73 (1.10–2.72) P = 0.018	1.58 (0.92–2.71) P = 0.098
	>10	1	1	1
Adjusted 2	≤10	2.72 (1.05–7.05) P = 0.040	1.61 (1.00–2.57) P = 0.048	1.40 (0.80–2.44) P = 0.244
	>10	1	1	1
Stratified by PTH				
Below the median (<123 pmol/L)				
Crude	≤10	n.a.	1.12 (0.62–2.02) P = 0.697	0.86 (0.43–1.73) P = 0.670
	>10	n.a.	1	1
Adjusted 1	≤10	n.a.	0.90 (0.43–1.88) P = 0.779	0.82 (0.35–1.93) P = 0.652
	>10	n.a.	1	1
Above the median (>123 pmol/L)				
Crude	≤10	n.a.	1.84 (1.05–3.21) P = 0.032	1.58 (0.81–3.08) P = 0.180
	>10	n.a.	1	1
Adjusted 1	≤10	n.a.	3.37 (1.64–6.91) P = 0.001	3.66 (1.51–8.87) P = 0.004
	>10	n.a.	1	1

1, adjusted for age, sex, dialysis modality, ethnicity, primary kidney disease, diabetes mellitus, cardiovascular disease, body mass index, systolic blood pressure, smoking, cholesterol, use of vitamin supplements, levels of albumin, haemoglobin and creatinine, and for the seasonal variation of vitamin D; 2, further adjusted for levels of PTH, calcium, phosphate and alkaline phosphatase; n.a., stratification not possible due to the low numbers of events.

single measurements, potential changes in vitamin D status over time may contribute to explain the time-differentiating effects, which remain to be investigated in future studies.

Interestingly, there was a significant association of vitamin D deficiency with increased risk of cardiovascular events in peritoneal dialysis patients [7], which is in line with our data and the findings by Wolf *et al.* [8]. Hence, these data suggest a possible relationship between vitamin D deficiency and cardiovascular events. It is difficult to draw conclusions regarding causality from the observational NECOSAD study, but accumulating evidence suggests that vitamin D supplementation might decrease cardiovascular risk [2,9,10,24]. Beneficial vitamin D effects on CKD–mineral and bone disorders (CKD–MBD) (i.e. secondary hyperparathyroidism) might protect the cardiovascular system when considering the observed associations of CKD–MBD and increased cardiovascular risk [25–27]. Concerning classic cardiovascular risk factors, there is evidence that vitamin D has anti-diabetic [28], anti-hypertensive [29] and anti-inflammatory properties [2,9,10,20]. In addition, the effects of vitamin D seem to be important for the maintenance of normal myocardial structure and function [30]. In this context, vitamin D deficiency has been associated with sudden cardiac death and heart failure [30,31], in particular with diastolic dysfunction [32,33]. Furthermore, there is evidence suggesting that vitamin D is beneficial in the prevention of strokes [34]. However, when discussing a possible role of vitamin D in cardiovascular diseases, it should also be underlined that despite careful adjustments of our analyses for various cardiovascular risk factors and parameters of bone mineral metabolism, 25(OH)D levels may simply be an indicator of a poor health status which is associated with malnutrition and reduced outdoor exposure leading to vitamin D deficiency.

Effect modification by PTH status for the association of 25(OH)D levels and adverse outcomes is an interesting finding which has not been specifically reported in previous studies among dialysis patients. Underlying mechanisms for this interaction remain speculative, but it would make sense that in more advanced stages of CKD–MBD, evidenced by high PTH levels, patients might be more sensitive to additional impairments of mineral metabolism such as vitamin D deficiency. We can, however, not rule out that the strong association of vitamin D status and mortality in groups with high PTH levels is driven by otherwise specific patient characteristics or subsequent treatment modalities of those patients.

Randomized controlled trials (RCTs) are therefore urgently needed to elucidate whether vitamin D supplementation in dialysis patients reduces cardiovascular risk or mortality. Waiting for the results of these RCTs, we remain with the unanswered question of whether we should prescribe natural vitamin D to our dialysis patients. Without raising a general recommendation, we want to stress that natural vitamin D doses to reach proposed target levels of 25(OH)D of 30–60 ng/mL (75–150 nmol/L) are considered absolutely safe when using the rule of thumb that 1000 IU of vitamin D increases 25(OH)D levels by 10 ng/mL (25 nmol/L) [35]. It should also be considered

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Table 5. Hazard ratios (95% CI) for non-cardiovascular mortality in the presence of severe vitamin D deficiency

		6 months	3 years	Conditional: between 6 months and 3 years
Non-cardiovascular mortality				
25(OH)D level (ng/mL)				
Crude	≤10	0.88 (0.33–2.39) P = 0.805	1.11 (0.70–1.75) P = 0.662	1.18 (0.71–1.98) P = 0.525
	>10	1	1	1
Adjusted 1	≤10	1.22 (0.44–3.40) P = 0.704	1.20 (0.71–2.01) P = 0.492	1.24 (0.68–2.24) P = 0.484
	>10	1	1	1
Adjusted 2	≤10	1.20 (0.43–3.33) P = 0.732	1.14 (0.68–1.92) P = 0.622	1.16 (0.64–2.13) P = 0.620
	>10	1	1	1
Stratified by PTH				
Below the median (<123 pmol/L)				
Crude	≤10	n.a.	0.77 (0.39–1.54) P = 0.465	0.96 (0.45–2.02) P = 0.908
	>10	n.a.	1	1
Adjusted 1	≤10	n.a.	0.82 (0.37–1.81) P = 0.624	0.87 (0.35–2.15) P = 0.763
	>10	n.a.	1	1
Above the median (>123 pmol/L)				
Crude	≤10	n.a.	1.70 (0.91–3.21) P = 0.099	1.59 (0.77–3.28) P = 0.211
	>10	n.a.	1	1
Adjusted 1	≤10	n.a.	2.32 (1.09–4.94) P = 0.029	2.31 (0.96–5.59) P = 0.063
	>10	n.a.	1	1

1, adjusted for age, sex, dialysis modality, ethnicity, primary kidney disease, diabetes mellitus, cardiovascular disease, body mass index, systolic blood pressure, smoking, cholesterol, use of vitamin supplements, levels of albumin, haemoglobin and creatinine, and for the seasonal variation of vitamin D; 2, further adjusted for levels of PTH, calcium, phosphate and alkaline phosphatase; n.a., stratification not possible due to the low numbers of events.

that vitamin D has been shown to exert multiple health benefits including significant reduction in total mortality in a meta-analysis of RCTs, although we have to acknowledge that most of these data were derived from study cohorts without significant CKD [2,9,10,16–18,27–29,36].

Our results are limited because it is difficult to draw conclusions regarding causality from an observational study. Furthermore, we have relatively wide confidence intervals for the results of our Cox regression analyses. Existence of residual confounding factors cannot be excluded despite careful adjustments of our statistical analyses. On the other hand, it can be hypothesized that several covariates of our Cox regression models may partially lie in the causal pathway of adverse effects of vitamin D deficiency. The data on vitamin supplementation also include further vitamins other than vitamin D, so that the exact percentage of vitamin D supplementation is expected to be lower. Other limitations of our study are missing data on sunlight exposure or physical activity and lack of measurements of 1,25(OH)2D and FGF-23, which suppresses 1α-hydroxylase activity and thereby down-regulates 1,25(OH)2D levels [37].

In conclusion, we found an increased mortality risk in severe vitamin D-deficient incident dialysis patients. The risk of cardiovascular mortality was strongly increased in patients with severe vitamin D deficiency, whereas there was no significant association with non-cardiovascular mortality. Associations of vitamin D status with adverse outcomes were more pronounced in the short-term when compared with longer-term follow-up analyses. Furthermore, the impact of 25(OH)D levels on clinical events was modified by PTH status, with severe 25(OH)D deficiency being associated with particularly high risks of adverse outcomes in patients with PTH levels above the median. RCTs are urgently needed to elucidate whether vitamin D supplementation reduces mortality and cardiovascular events in dialysis patients.

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Conflict of interest statement. None declared.

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References

1. Barreto DV, Baretto FC, Liabeuf S *et al*. Vitamin D affects survival independently of vascular calcification in chronic kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 1128–1135
2. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357: 266–281
3. Jacob AI, Sallman A, Santz Z *et al*. Defective photoproduction of cholecalciferol in normal and uremic humans. *J Nutr* 1984; 114: 1313–1319

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4. Mehrotra R, Kermah DA, Salusky IB *et al*. Chronic kidney disease, hypovitaminosis D, and mortality in the United States. *Kidney Int* 2009; 76: 931–933
5. Pecovnik-Balon B, Jakopin E, Bevc S *et al*. Vitamin D and mortality as a novel nontraditional risk factor for mortality in hemodialysis patients. *Ther Apher Dial* 2009; 13: 268–272
6. Ravani P, Malberti F, Tripepi G *et al*. Vitamin D levels and patient outcome in chronic kidney disease. *Kidney Int* 2009; 75: 88–95
7. Wang AY, Lam CW, Sanderson JE *et al*. Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: a 3-y prospective cohort study. *Am J Clin Nutr* 2008; 87: 1631–1638
8. Wolf M, Shah A, Gutierrez O *et al*. Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 2007; 72: 1004–1013
9. Bouillon R, Carmeliet G, Verlinden L *et al*. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev* 2008; 29: 726–776
10. Peterlik M, Cross HS. Vitamin D and calcium deficits predispose for multiple chronic diseases. *Eur J Clin Invest* 2005; 35: 290–304
11. Merkus MP, Jager KJ, Dekker FW *et al*. Quality of life in patients on chronic dialysis: self-assessment 3 months after the start of treatment. The Necosad Study Group. *Am J Kidney Dis* 1997; 29: 584–592
12. Noordzij M, Korevaar JC, Bos WJ *et al*. Mineral metabolism and cardiovascular morbidity and mortality risk: peritoneal dialysis patients compared with haemodialysis patients. *Nephrol Dial Transplant* 2006; 21: 2513–2520
13. Southern DA, Faris PD, Brant R. Kaplan-Meier methods yielded misleading results in competing risk scenarios. *J Clin Epidemiol* 2006; 59: 1110–1114
14. Satagopan JM, Ben-Porat L, Berwick M *et al*. A note on competing risks in survival data analysis. *Br J Cancer* 2004; 91: 1229–1235
15. Chonchol M, Cigolini M, Targher G. Association between 25-hydroxyvitamin D deficiency and cardiovascular disease in type 2 diabetic patients with mild kidney dysfunction. *Nephrol Dial Transplant* 2008; 23: 269–274
16. Matias PJ, Ferreira C, Jorge C *et al*. 25-Hydroxyvitamin D3, arterial calcifications and cardiovascular risk markers in haemodialysis patients. *Nephrol Dial Transplant* 2009; 24: 611–618
17. Pilz S, Tomaschitz A, Obermayer-Pietsch B *et al*. Epidemiology of vitamin D insufficiency and cancer mortality. *Anticancer Res* 2009; 29: 3699–3704
18. Yamshchikov AV, Desai NS, Blumberg H *et al*. Vitamin D for treatment and prevention of infectious diseases: a systematic review of randomized controlled trials. *Endocr Pract* 2009; 15: 438–449
19. Adorini L, Penna G. Control of autoimmune diseases by the vitamin D endocrine system. *Nat Clin Pract Rheumatol* 2008; 4: 404–412
20. Doorenbos CR, van den Born J, Navis G *et al*. Possible renoprotection by vitamin D in chronic renal disease: beyond mineral metabolism. *Nat Rev Nephrol* 2009; 5: 691–700
21. Melamed ML, Astor B, Michos ED *et al*. 25-hydroxyvitamin D levels, race, and the progression of kidney disease. *J Am Soc Nephrol* 2009; 20: 2631–2639
22. Kalantar-Zadeh K, Kovesdy CP. Clinical outcomes with active versus nutritional vitamin D compounds in chronic kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 1529–1539
23. Tentori F, Albert JM, Young EW *et al*. The survival advantage for haemodialysis patients taking vitamin D is questioned: findings from the Dialysis Outcomes and Practice Patterns Study. *Nephrol Dial Transplant* 2009; 24: 963–972
24. Kaisar MD, Isbel NM, Johnson DW. Recent clinical trials of pharmacologic cardiovascular interventions in patients with chronic kidney disease. *Rev Recent Clin Trials* 2008; 3: 79–88
25. Jean G, Terrat JC, Vanel T *et al*. Daily oral 25-hydroxycholecalciferol supplementation for vitamin D deficiency in haemodialysis patients: effects on mineral metabolism and bone markers. *Nephrol Dial Transplant* 2008; 23: 3670–3676
26. Jean G, Souberbielle JC, Chazot C. Monthly cholecalciferol administration in haemodialysis patients: a simple and efficient strategy for vitamin D supplementation. *Nephrol Dial Transplant* 2009; 24: 3799–3805
27. Mehrotra R, Kermah D, Budoff M *et al*. Hypovitaminosis in chronic kidney disease. *Clin J Am Soc Nephrol* 2008; 3: 1144–1151
28. Pittas AG, Lau J, Hu FB *et al*. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2007; 92: 2017–2029
29. Pilz S, Tomaschitz A, Ritz E *et al*. Vitamin D status and arterial hypertension: a systematic review. *Nat Rev Cardiol* 2009; 6: 621–630
30. Zittermann A, Schleithoff SS, Koerfer R. Vitamin D insufficiency in congestive heart failure: why and what to do about it? *Heart Fail Rev* 2006; 11: 25–33
31. Pilz S, März W, Wellnitz B *et al*. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cohort of patients referred for coronary angiography. *J Clin Endocrinol Metab* 2008; 93: 3927–3935
32. Bodyak N, Ayus JC, Achinger S *et al*. Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. *Proc Natl Acad Sci USA* 2007; 104: 16810–16815
33. Tishkoff DX, Nibbelink KA, Holmberg KH *et al*. Functional vitamin D receptor (VDR) in the t-tubules of cardiac myocytes: VDR knockout cardiomyocyte contractility. *Endocrinology* 2008; 149: 558–564
34. Pilz S, Tomaschitz A, Drechsler C *et al*. Vitamin D supplementation: a promising approach for the prevention and treatment of strokes. *Curr Drug Targets* 2010 Aug 27. Epub ahead of print
35. Hathcock JN, Shao A, Vieth R *et al*. Risk assessment for vitamin D. *Am J Clin Nutr* 2007; 85: 6–18
36. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; 167: 1730–1737
37. Gutierrez OM, Mannstadt M, Isakov T *et al*. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008; 359: 584–592

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