Metabolic alterations in dialysis patients

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CHAPTER

10

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

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Abstract

Objective: 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.
Design: Prospective cohort study of incident dialysis patients in the Netherlands (NECOSAD).

Methods: 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 follow-up) as well as long-term mortality (3 years follow-up). Associations of 25(OH)D levels with cardiovascular and non-cardiovascular mortality were also determined.

Results: Data from 762 patients (39% females, age 59±15yr, 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 1.9 (1.0-3.6) for short-term and 1.4 (1.0-1.9) for long-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 2.8 (1.1-6.7) and 1.6 (1.0-2.5) for early and long-term mortality, respectively. For non-cardiovascular mortality we observed no relevant association.

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.

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 recognised as an important health issue because it has been shown that (i) approximately 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]. 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 hormone [PTH], 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 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 hemodialysis

patients, low 25(OH)D levels were significantly associated with 90-day mortality in a nested case-control analysis [8]. Data on the association of 25(OH)D with long-term mortality in hemodialysis patients are unknown. The Vitamin D status and association with outcome is 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 as well as 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, analyzing data of a prospective multicenter cohort study of incident dialysis patients in the Netherlands.

Subjects and methods

Study Design

NECOSAD is an observational prospective follow-up study in which incident dialysis patients have been enrolled in 38 participating dialysis centers since 1997 in The Netherlands [11, 12]. Study visits took place at the start of dialysis, at 3 months, 6 months, and subsequently at 6 months intervals until the date of loss to follow-up (death, kidney transplantation, or transfer to a non-participating dialysis center) or the end of the follow-up at January 1, 2009. Baseline demographic and clinical data were obtained between four weeks prior to and two weeks after the start of long-term dialysis treatment. Blood and 24-hour 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 ESRD who were at least 18 years old and started long-term dialysis therapy for the first time were invited to participate in 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 centers 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 comorbidity. 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 comorbid conditions were reported by the patients nephrologists and used to calculate the comorbidity 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 autoanalyzer (DiaSorin, Saluggia/ Italy). This timepoint 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 centers. Height and weight were measured after dialysis sessions, and BMI was calculated as weight (kilograms) divided by height (meters) squared. Blood pressure was measured in the sitting position.

Definition of endpoints

Cardiovascular mortality was defined as death due to the following causes: myocardial ischemia and infarction; hyperkalemia; hypokalemia; cardiac arrest; (hypertensive) cardiac failure; fluid overload; cerebrovascular accident; haemorrhage from ruptured vascular aneurysm; mesenteric infarction; 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, 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.

We calculated Cox proportional hazard ratios (HR) with 95% confidence intervals (95% CI) for subsequent short-term (6 months) and long-term (3 years) periods, 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 to 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, use of vitamin supplements, levels of serum albumin, creatinine and hemoglobin. To account for the seasonal variation of vitamin D, we furthermore adjusted our analyses for the season of blood draw. We therefore used a binary variable reflecting the months October to March and April to 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. Finally, we tested potential interactions of Vitamin D with the use of vitamin supplements and with levels of alkaline phosphatase.

Cumulative mortality curves for CV mortality and non-CV mortality were made by competing risk analysis [13]. All p-values are reported two-sided, and considered significant at a level smaller than 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 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 Vitamin D. These patients were included in the present analyses. Of note, the included patients were not different from the remainder (excluded patients 1753-762=991). Both patient groups were very similar with regard to demographic and clinical characteristics including co-morbidity and levels of routine laboratory markers.

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 comorbidity. Patients on hemodialysis and males were less common in groups with lower 25(OH)D levels. Levels of alkaline phosphatase were higher in the patients with low 25(OH)D levels (for further baseline data see Table 1).

During the 3 years follow-up period, 213 patients died, of whom 118 patients died of cardiovascular causes, and 95 patients died of non-cardiovascular causes. 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.

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

	whole group	**Vit D categories**		
		1	**2**	**3**
		VitD <=10	10-30	>30
Numbers	n=762	n=193	n=469	n=100
Age (yrs)	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
Comorbidity				
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 per 1.73m²)	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				
Hemoglobin (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

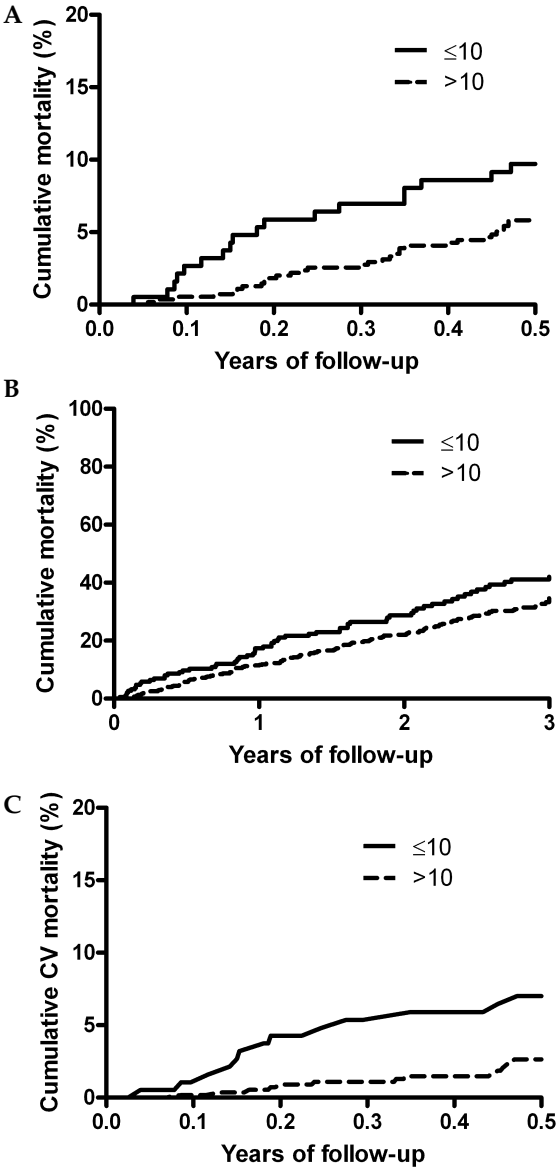
Vitamin D status and total mortality

We investigated short term and long 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 marginally significant associations when comparing patients with severe vitamin D deficiency with all other study participants (Table 2 and Figures 1A, 1B). In detail, the adjusted HRs for the 6 months and 3 years follow-up periods were 1.89 (0.99-3.62, p=0.06) and 1.35 (0.95-1.91, p=0.09), respectively. Additional adjustments for parameters of bone mineral metabolism decreased these HRs to 1.53 (0.78-2.99) for the 6 months follow-up and to 1.34 (0.95-1.90) for the 3 years follow-up analyses. 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. Using the three category approach for vitamin D status we observed a trend for an increased mortality in patients with severe vitamin D deficiency when compared to patients with vitamin D sufficiency (Table 3). Adjusted HRs for the group with severe vitamin D deficiency were 1.32 (95% CI: 0.48-3.61) for the 6 months follow-up and 1.16 (0.66-2.02) for the 3 years follow-up. These HRs remained materially unchanged after additional adjustments for parameters of bone mineral metabolism (data not shown).

Vitamin D status and cardiovascular mortality

Cardiovascular mortality was significantly increased in patients with severe vitamin D deficiency (Table 2 and Figures 1C, 1D). Compared to patients with 25(OH)D levels above 10 ng/ml the adjusted HRs were 2.75 (1.13-6.69, p=0.03) for the 6 months follow-up and 1.59 (1.00-2.54, p=0.05) for 3 the years follow-up (Table 2). After adjustments for parameters of bone mineral metabolism these HRs were 2.38 (0.93-6.13) and 1.60 (1.00-2.56) for the 6 months and the 3 years follow-up, respectively. Comparing patients with severe vitamin D deficiency with the vitamin D sufficient group the adjusted HRs were 2.50 (0.51-12.35) and 1.85

(0.79-4.33) for the 6 months and 3 years follow-up analyses, respectively. Further adjustments for parameters of bone mineral metabolism did not materially alter the results (data not shown).



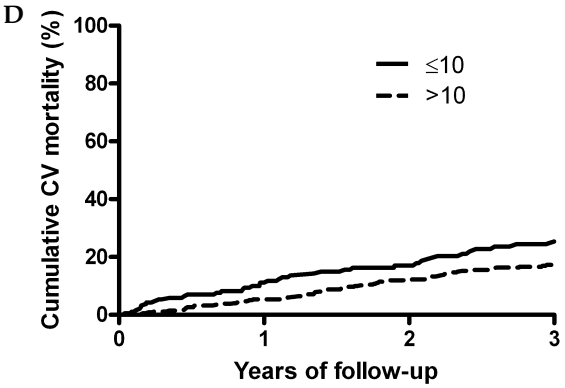


Figure 1 A-D: Cumulative mortality curves for A) all-cause mortality within 6 months, B) all-cause mortality within 3 years, C) cardiovascular mortality within 6 months and D) and cardiovascular mortality within 3 years according to Vitamin D status at baseline

Vitamin D status and non-cardiovascular mortality

There was no meaningful association of vitamin D status with non-cardiovascular mortality in any of our Cox regression analyses (Table 2 and Table 3). Compared to patients with 25(OH)D levels above 10 ng/ml, the risk of non-cardiovascular mortality was tentatively higher in patients with severe vitamin D deficiency with adjusted HRs of 1.23 (0.44-3.40, p=0.73) for the 6 months follow-up and 1.12 (0.67-1.87, p=0.67) for the 3 years follow-up (Table 2). Furthermore, no association was seen in the analyses comparing three categories of vitamin D status (Table 3). Additional adjustments for parameters of bone mineral metabolism did not materially change these results for the associations of 25(OH)D levels and non-cardiovascular mortality (data not shown).

Table 2. Hazard ratios with 95% confidence intervals for all-cause mortality, cardiovascular and non-cardiovascular mortality according to Vitamin D status: severely defieient vs non-severely deficient or sufficient

All-cause mortality				
		6 months	**3 years**	**conditional: between 6 months and 3 years**
crude	≤ 10	1.74 (0.98-3.11)	1.34 (1.00-1.80)	1.23 (0.88-1.73)
	>10	1	1	1
adjusted	≤ 10	1.89 (0.99-3.62)	1.35 (0.95-1.91)	1.29 (0.86-1.93)
	>10	1	1	1
Cardiovascular mortality				
		6 months	**3 years**	**conditional: between 6 months and 3 years**
crude	≤ 10	2.79 (1.31-5.93)	1.55 (1.06-2.28)	1.27 (0.81-2.01)
	>10	1	1	1
adjusted	≤ 10	2.75 (1.13-6.69)	1.59 (1.00-2.54)	1.42 (0.81-2.47)
	>10	1	1	1
Non-cardiovascular mortality				
		6 months	**3 years**	**conditional: between 6 months and 3 years**
crude	≤ 10	0.88 (0.33-2.39)	1.11 (0.70-1.75)	1.18 (0.71-1.98)
	>10	1	1	1
adjusted	≤ 10	1.23 (0.44-3.40)	1.12 (0.67-1.87)	1.17 (0.65-2.10)
	>10	1	1	1

* adjusted for age, sex, dialysis modality, ethnicity, primary kidney disease, diabetes mellitus, cardiovascular disease, body mass index, systolic blood pressure, use of vitamin supplements, levels of albumin, hemoglobin and creatinine, and for the seasonal variation of vitamin D

Table 3. Hazard ratios with 95% confidence intervals for all-cause mortality, cardiovascular and non-cardiovascular mortality according to levels of 25-hydroxyitamin D at baseline (severely vitamin D deficient, vitamin D deficient, vitamin D sufficient)

All-cause mortality				
		6 months	**3 years**	**conditional: between 6 months and 3 years**
crude	≤ 10	1.50 (0.60-3.78)	1.38 (0.86-2.23)	1.34 (0.77-2.34)
	10-30	0.83 (0.34-2.03)	1.04 (0.67-1.62)	1.11 (0.66-1.85)
	>30	1	1	1
adjusted	≤ 10	1.32 (0.48-3.61)	1.16 (0.66-2.02)	1.21 (0.62-2.34)
	10-30	0.66 (0.26-1.66)	0.85 (0.52-1.38)	0.93 (0.53-1.65)
	>30	1	1	1
Cardiovascular mortality				
		6 months	**3 years**	**conditional: between 6 months and 3 years**
crude	≤ 10	3.25 (0.73-14.40)	1.89 (0.87-4.12)	2.15 (0.88-5.21)
	10-30	1.20 (0.27-5.36)	1.53 (0.73-3.19)	1.82 (0.78-4.21)
	>30	1	1	1
adjusted	≤10	2.50 (0.51-12.35)	1.85 (0.79-4.33)	1.84 (0.68-5.02)
	10-30	0.97 (0.21-4.45)	1.18 (0.55-2.52)	1.32 (0.55-3.17)
	>30	1	1	1
Non-cardiovascular mortality				
		6 months	**3 years**	**conditional: between 6 months and 3 years**
crude	≤ 10	0.63 (0.17-2.33)	0.83 (0.44-1.57)	0.90 (0.43-1.89)
	10-30	0.65 (0.21-2.00)	0.70 (0.40-1.24)	0.72 (0.37-1.40)
	>30	1	1	1
adjusted	≤ 10	0.72 (0.18-2.87)	0.75 (0.35-1.60)	0.82 (0.34-2.00)
	10-30	0.53 (0.16-1.70)	0.64 (0.34-1.21)	0.67 (0.31-1.44)
	>30	1	1	1

* adjusted for age, sex, dialysis modality, ethnicity, primary kidney disease, diabetes mellitus, cardiovascular disease, body mass index, systolic blood pressure, use of vitamin supplements, levels of albumin, hemoglobin and creatinine, and for the seasonal variation of vitamin D

Discussion

Our data from incident dialysis patients show an increased mortality in patients with severe vitamin D deficiency compared to 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.

Our findings are of particular interest because the majority of dialysis patients is 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 [14, 15], cancer [16], infections [17] and autoimmune diseases [18] 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 [19, 20]. 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 [21, 22]. Natural vitamin D supplementation, 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 novel data, in particular because it is the first study among both chronic hemodialysis as well as peritoneal dialysis patients that addresses the association

of vitamin D status with short-term as well as long-term mortality. Our data showed that 25(OH)D were associated with overall survival, the effect sizes however being smaller compared to two previous studies investigating vitamin D deficiency in hemodialysis 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 hemodialysis patients Wolf et al reported about an association of low 25(OH)D levels with increased mortality within 90 days after initiating hemodialysis 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 hemodialysis 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 long-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 any more, once they had survived the first 6 months after Vitamin D assessment. Considering that Vitamin D levels were determined only once in single measurements, potential changes in Vitamin D status over time may contribute to explain the time-differentiating effects, which remains 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, 23]. 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 [24-26]. Concerning classic cardiovascular risk factors there exists evidence that vitamin D has anti-diabetic [27], anti-hypertensive [28] and anti-inflammatory properties [2, 9, 10, 19]. In addition, vitamin D effects seem to be important for the maintenance of normal myocardial structure and function [29]. In this context vitamin D deficiency has been associated with sudden cardiac death and heart failure [29, 30], in particular with diastolic dysfunction [31, 32]. 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.

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 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 to 60 ng/mL (75 to 150 nmol/L) are considered absolutely safe when using the rule of thumb that 1,000 IU vitamin D increase 25(OH)D levels by 10 ng/mL (25 nmol/L) [33]. It should also be considered that vitamin D has been shown to exert multiple health benefits including a 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, 34].

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 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 apart from 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 1,25(OH)2D and fibroblast growth factor-23 (FGF-23), which suppresses 1α-hydroxylase activity [35].

In conclusion we found an increased mortality risk in severe vitamin D deficient incident dialysis patients. 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 short-term when compared to long-term follow-up analyses. RCTs are urgently needed to elucidate whether vitamin D supplementation reduces mortality and cardiovascular events in dialysis patients.

Funding:

C. Drechsler is grateful to the European Renal Association – European Dialysis and Transplant Association and the Deutsche Forschungsgemeinschaft (DR 804/1-1) for the support with a research fellowship.

Acknowledgements

We thank the investigators and study nurses of the participating dialysis centres, and the data managers of the NECOSAD study for collection and management of the data.

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