Vitamin D Status and Cancer Prevalence of Hemodialysis Patients in Germany

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Abstract. *Aim: To describe Vitamin D (VitD) status and prevalence of cancer in a large cohort of ambulatory hemodialysis patients in Germany. Patients and Methods: In a registry study adult patients starting dialysis between 2006 and 2012 were analyzed for VitD blood levels and International classification of diseases (ICD)-10 cancer diagnoses. Results: Almost one third (32.7%) of patients initiating dialysis, had VitD levels <12.5 ng/ml and 79.7% had levels <30 ng/ml (n=8,377). Average VitD at dialysis initiation increased from 18.0 to 23.2 ng/ml between 2006 and 2012. Prevalence of cancer in this cohort was 22.1% with genital, renal and gastro-intestinal cancers being most common. Cancer frequencies were similar in patients with high and low vitamin D levels. Conclusion: Most chronic hemodialysis patients were vitamin D-deficient in spite of concurrent vitamin D supplementation. The burden of cancer was high in these patients. Future studies should address the role of vitamin D treatment on the course and progression of cancer in chronic kidney disease (CKD) patients.*

In chronic kidney disease (CKD), deficiency of 25-hydroxy vitamin D (25(OH)D; VitD) is common and associated with increased mortality (1-5). Causes of low VitD in CKD include disturbances in absorption, metabolism and function of vitamin D (6, 7), which exacerbate the wide spread prevalence of vitamin D deficiency in the general population (8). The 2009 KDIGO CKD-MBD guidelines (9), therefore, suggest measuring vitamin D levels and potentially correcting deficiencies.

Low levels of VitD can affect bone health and mineral metabolism and have also been associated with cardiovascular and autoimmune diseases, mood disorders and cancer (5, 10-14). Epidemiological and mechanistic studies provide evidence and plausible explanations for differential cancer development and progression between persons with normal *versus* low blood levels of VitD (13, 15, 16). The incidence of cancer in CKD and end-stage renal disease (ESRD) is low, possibly due to competing mortality risk of cardiovascular and infectious etiologies (17, 18). However, two recent studies (19, 20) indicate that renal and urothelial cancer risks are increased in patients with early-stage CKD, which may result in a cumulative increase in the prevalence of these cancers by the time patients reach CKD stage 5 and the need for renal replacement therapy. The prevalence and distribution of cancers in patients starting dialysis has not been well-described.

We, therefore, undertook an analysis of a large current cohort of incident ambulatory hemodialysis patients to assess the status of VitD blood levels, as well as the prevalence and distribution of cancer in this population.

Patients and Methods

Aim. To assess VitD status, cancer prevalence and their relationship in incident hemodialysis patients.

Study design. Retrospective cohort study.

Setting. Patients were eligible in one of 200 dialysis clinics (kidney centers) that are distributed throughout Germany and are run by the non-profit provider Curatorium for Dialysis and Kidney Transplantation (KfH) were eligible. Patients gave informed consent to participate in the prospective medical quality registry QiN (Quality

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Key Words: Vitamin D, chronic kidney disease, CKD, dialysis, ESRD, renal replacement therapy (RRT), cancer, epidemiology, CKD-MBD, mineral and bone disease.

in Nephrology). Data collection in QiN is based on the electronic health record system that is used throughout all KfH kidney centers. Approximately 20 – 25% of all dialysis patients in Germany are treated at KfH facilities and > 90% of KfH-patients participate in QiN.

Patients. Ambulatory hemodialysis patients between 2006 and 2012 who were at least 18 years old and who were enrolled into the QiN database within 6 months of their first dialysis.

Measurements. All patient data were obtained according to standards established by KfH for all kidney centers. Clinical chemistry values were drawn pre-dialysis after a long weekend interval unless otherwise stated. Measurements were performed at local certified laboratories and transferred electronically into the database. Clinical characteristics were recorded at the time of admission to the dialysis unit and at the time of any new diagnoses. Baseline laboratory parameters were determined by averaging all values measured during the first 90 days under observation.

Vitamin D status. Vitamin D status was determined using the first blood level of 25-hydroxyvitamin D (VitD) if it was drawn within 1 year of initial dialysis. Patients who had no VitD status were used as a comparison group. Patients with an active prescription for a vitamin D-containing medication at the time a VitD blood level was drawn were considered to be on vitamin D supplementation, while all other patients were classified as untreated with regard to vitamin D. Information on the dose of vitamin D supplementation and the type of medication given before beginning dialysis and entering the database was not available. No standards were in place regarding indications for or frequency of VitD blood level draws during the study period. In an exploratory analysis, VitD levels were grouped by month of sample collection and analyzed for differences between summer (May – October) and winter (November – April). Following Krause *et al*. (21) and Holick (8), measured VitD levels were divided into four categories: levels >30 ng/ml were considered replete, levels between 20-30 ng/ml were considered insufficient, 12.5-20 ng/ml deficient and <12.5 ng/ml severely deficient.

Cancer. Malignancy was defined by the following International classification of diseases (ICD)-10 codes (The International Statistical Classification of Diseases German Version 2014): C00.* – C97.*, D00.* – D09.*, D37.* – D48.*. This definition encompasses carcinoma in situ, low grade skin malignancies and neoplasms of unknown location or uncertain behavior except uncertain hematologic/lymphoid neoplasms. Malignancies were grouped as follows: gastro-intestinal (GI) malignancy, C00-C26 +D37; lung malignancy, C30-C39 +D38; skin malignancy, C43-C44 + D48.5; breast malignancy, C50 + D48.6; genital malignancy (male and female), C51-C63 + D39 + D40; urinary tract (UT) malignancy, C64-C68 + D41; renal malignancy, C64 + D41.0; and other malignancies, C40-C41 + C45-C49 + C69-C97 + D42 + D48.4 + D48.7 + D49.0. ICD-10 codes were recorded at the point of care to document clinically significant active or inactive disease for billing purposes.

Statistical methods. The Mann-Whitney *U*-test was used to test for differences in continuous variables. The Chi square test was used to test for differences in categorical variables. Reported outcomes are based on a 95% confidence interval and a two-sided $p<0.05$ was considered significant. Analyses were performed using IBM SPSS statistics, version 22.0.0.0 (http://www-01.ibm.com/software/analytics/spss/)

Results

Patients. Sixteen thousand four hundred and two incident hemodialysis patients were included in the analysis (Figure 1). Eleven patients with implausible VitD values were excluded from the analysis. Patients with and without VitD measurement differed in age, sex, average calcium and prevalence of diabetes at baseline (Table I). These differences were small and may be of limited clinical relevance. However, VitD levels were measured significantly more often in diabetic patients. Baseline values are provided in Table I.

Vitamin D status. VitD status was available for 8,377 patients (51.1%). The mean VitD blood level in all patients was 20.12 ng/ml (±12.36) but levels increased from 18.0 ng/ml (±12.27) for those who initiated dialysis in 2006 to 23.2 ng/ml (±13.89) for those who started in 2012 ($p<0.0001$; Figure 2). Most VitD levels were drawn in January and July with very few in the months between. Average levels in summer (May – October) were 21.36 ng/ml (±12.78) and 19.08 ng/ml (±12.31) in winter (November – Apr) ($p<0.001$).

At the start of dialysis, a large majority of patients (79.7%) were found to be VitD-deficient, with one third (32.7%) being severely deficient (<12.5 ng/ml; Table I). This finding is remarkable since most patients (5,136; 61.3%) were on vitamin D supplementation at that time. However, from 2006 to 2012, the fraction of patients with blood levels <30 ng/ml decreased from 82.2% to 71.5%, respectively ($p<0.0001$) (Figure 3). At the same time, use of supplementation was nearly constant around 61% suggesting that increasing doses were used for supplementation.

In those patients who were initially not on any vitamin D supplementation (n=3,241), mean VitD levels were 19.31 ng/ml (±12.51) and 35.7% were severely VitD deficient, whereas 25.2% and 20.8% had low (12.5-20 ng/ml) and intermediately low (20-30 ng/ml) VitD levels, respectively. Almost one-fifth (18.3%) of patients not receiving supplementation had replete levels. In contrast, in those who received VitD supplementation (n=5,136), the average VitD level was 20.63 ng/ml (±12.59) and 21.5 % had replete VitD levels. VitD levels for the remaining patients receiving VitD supplementation were severely deficient (30.8 % of patients), deficient (23.0% of patients) and insufficient (24.7% of patients).

Cancer prevalence in incident hemodialysis patients. Three thousand six hundred and thirty-one patients (22.1% of all patients) had a diagnosis of cancer when they started ambulatory dialysis. The most common types were cancer of male and female genital organs (11.5%), renal cancer (11.2%), gastrointestinal cancer (10.9%), cancer of the urinary tract (7.5%) and skin cancer (5.8%) (Table II).

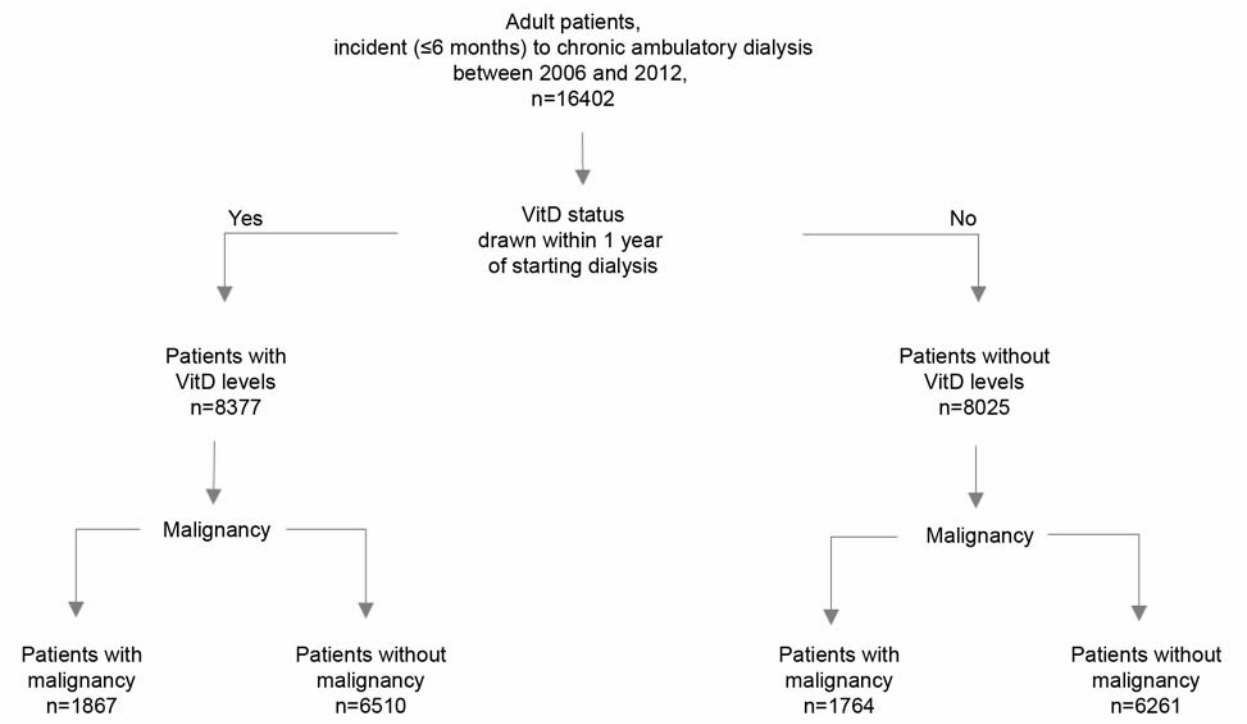

Figure 1. *Selection of patients for analysis*.

Table I. *Baseline characteristics of patients analyzed for vitamin D status and cancer prevalence*.

Baseline characteristics		with VitD levels	without VitD levels	*p*-Value
Patients [n]	16,402	8,377	8,025	
Age [years] (SD)	71.5 (13.9)	71.1 (13.8)	72.0 (13.9)	<0.001
Male [%]	62.3	61.4	63.2	0.023
Diabetes (DM) [%]	41.4	45.1	37.5	<0.001
Laboratory values (means)				
25(OH)VitD3 [ng/ml] (SD)		20.12 (12.58)		
Phosphate [mmol/l] (SD)	1.68 (0.46)	1.68 (0.44)	1.67 (0.47)	0.091
Calcium [mmol/l] (SD)	2.21 (0.18)	2.22 (0.17)	2.20 (0.18)	<0.001
PTH [pg/ml] (SD)	191.55 (124.18)	192.89 (123.58)	189.83 (124.92)	0.061
Vitamin D status				
Severely deficient (<12.5 ng/ml) [%]		32.7		
Deficient (12.5-<20 ng/ml) [%]		23.8		
Insufficient (20-<30 ng/ml) [%]		23.2		
Replete (30-150 ng/ml) [%]		20.3		

Vitamin D status was determined using the first VitD level that was drawn within 1 year after first dialysis. **p* for comparison of patients who did or did not have a VitD level drawn, respectively. SD, Standard deviation; DM, diabetes mellitus; PTH, parathyroid hormone.

VitD status and cancer prevalence. VitD status was available in 1,867 patients. The overall cancer prevalence or the frequency of types of cancer were not different in patients without VitD status (data not shown). The overall cancer prevalence did not differ substantially between patients with replete or deficient VitD status, although there was a non-significant increase of cancer in severely VitD deficient patients compared to patients with a replete VitD status

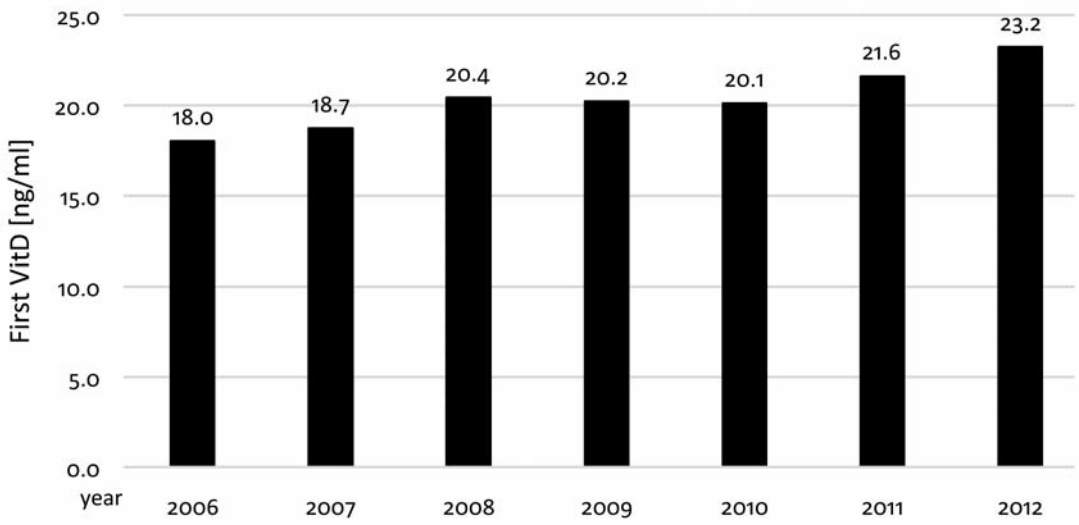

Figure 2. *First 25 (OH) vitamin D blood levels in patients who initiated hemodialysis in the years from 2006 to 2012.*

(23.3% *vs*. 17.4%; p=0.312). Also, there was a statistically significant difference in distribution of cancer types depending on VitD status (Figure 4) (p=0.044).

Discussion

Vitamin D status of German hemodialysis patients. In this study we analyzed a current cohort of incident ambulatory hemodialysis patients and found that almost one third of patients (32.7%) were severely deficient in Vitamin D and an additional 47% had lesser degrees of VitD deficiency. This confirms and expands a study by Krause *et al*. (21) who found 41.2% of CKD patients to be severely VitD-deficient, albeit in an earlier (1997-2006) cohort in Germany. In comparison, a study of dialysis patients in the US (4) also found 78% of patients to be VitD-deficient but only 18% were classified as severely deficient (<10 ng/ml). One reason may be that foods are fortified with VitD in the US, whereas in Germany such a program does not exist. Seasonal variation contributed only a 2-ng/ml increase to measured VitD serum levels in the summer months, which is in keeping with the Northern latitude of Germany (22). However, in the course of seven years, there was a 12% increase of average VitD levels (from 18.0 ng/ml to 23.2 ng/ml) and a corresponding decrease of severe deficiency in incident hemodialysis patients. Although information on the nature and dose of Vitamin D medication was not available, the increase was presumably due to empiric supplementation with native VitD. In spite of this increase, however, most patients did not reach a replete VitD status. For patients at risk, such as with CKD 5, the usual supplemental VitD doses may need to be increased substantially as recently recommended in a practice guideline of the US Endocrine Society (23).

Table II. *Cancer prevalence in incident hemodialysis patients.*

Types of cancer	
Patients n	3633
Genital cancer (%)	419 (11.5)
Renal cancer (%)	407 (11.2)
Gastrointestinal cancer (%)	395 (10.9)
Urinary tract cancer (%)	273 (7.5)
Skin cancer (%)	211 (5.8)
Breast cancer (%)	148 (4.1)
Lung cancer (%)	128 (3.5)
Other types of cancer (%)	1652 (45.5)

Burden of cancer in incident hemodialysis patients. The high prevalence of cancer that was found in this study (22.1%) includes not only active disease but also cured or stable disease states. It, therefore, reflects the cumulative burden of cancer that is carried by patients initiating dialysis. Several factors, such as age and background risk of cancer independent of kidney disease but also the nature of renal disease and a history of immunosuppressive therapy, contribute to this burden. In the general population over 60 years of age, the lifetime prevalence of cancer is between 4 and 14% (24). Recent studies have highlighted that CKD by itself is associated with increased risk of malignancies, particularly of the kidney and urinary tract (19, 20). Correspondingly, renal cancer was the second most frequent type of cancer in the present analysis. Most patients

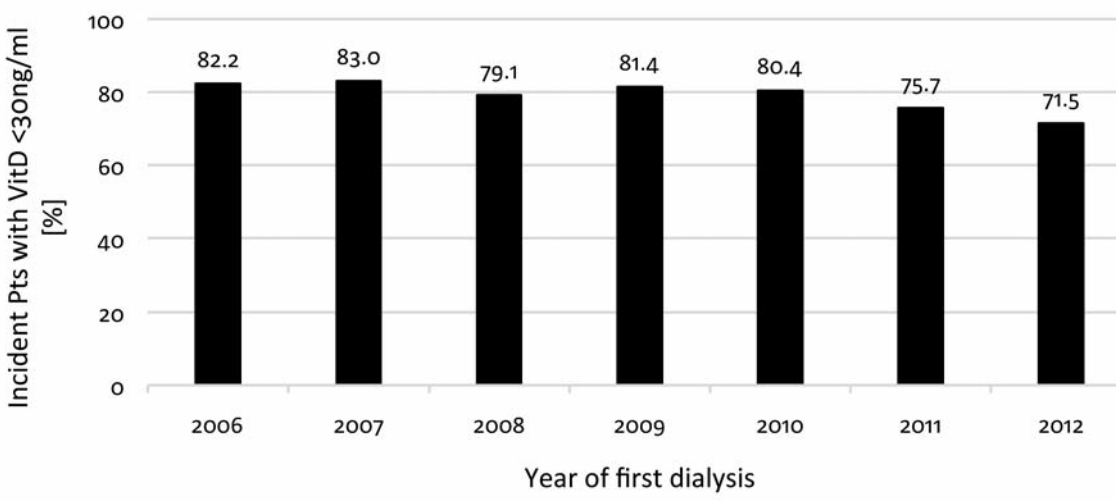

Figure 3. *Percentage of patients initiating dialysis in the years 2006-2012 with first 25(OH) vitamin D levels <30 ng/ml.*

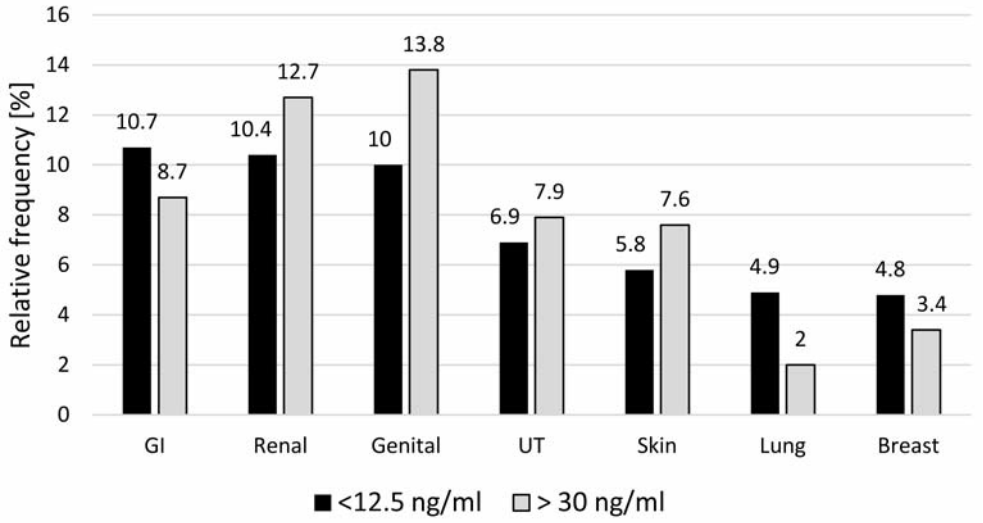

Figure 4. *Relative frequency of cancers depending on vitamin D status. Other types of cancer were 46.5% and 43.9% for patients with a first 25 (OH) Vitamin D <12.5 and >30 ng/ml, respectively. GI, Gastro-intestinal, UT, urinary tract.*

in our cohort have a long history of progressive CKD and, therefore, presumably an increased cumulative risk of developing cancer. A similar study by the USRDS reported a 31% prevalence of cancer in patients initiating dialysis (25).

VitD and cancer prevalence. This analysis did not detect an association between low vitamin D levels and cancer, as has been reported frequently in other studies (26-28). Several explanations may account for this discrepancy. First, the VitD levels measured at the beginning of dialysis may not be representative of a long-standing VitD deficiency, which would be a prerequisite for increasing the risk of cancer development. Second, the documented diagnoses of cancer in this study may reflect past or cured disease in a substantial portion of individuals and, therefore, may be independent of the VitD status analyzed in this study. Third, although the increasing VitD levels between 2006 and 2012 were indicative of increasing supplementation, the blood levels of 25 (OH) vitamin D that were reached may not have been sufficient to have a substantial cancer protective effect (13, 29, 30).

Strengths. The strengths of this study include that it analyzed a large cohort that reflects about a fifth to a quarter of ambulatory hemodialysis patients in Germany. The findings are, therefore, likely to be representative of dialysis patients in Germany. Also, data were collected prospectively according to widely distributed standards in a uniform system of electronic patient records, which ensures a high standard of data quality. Since data were obtained as part of the routine care of patients, these data also reflect actual practice.

Limitations. The nature and dose of medication that were used for supplementation of VitD was not available, which limits the interpretation of these results. Another limitation is that vitamin D levels were not collected systematically such that a selection bias cannot be ruled-out. In fact, there is evidence for a selection bias in that significantly more diabetic patients had VitD levels measured than non-diabetics. However, the frequency and distribution of cancer was not different in patients who did or did not have a VitD level measured.

Conclusion

In this large cohort of incident hemodialysis patients, VitD levels improved from 2006 to 2012 but many patients still remained below recommended levels. Furthermore, there is a high burden of cancer in dialysis patients especially with gastro-intestinal and renal cancer types. Future studies should address the role of vitamin D treatment on the course and progression of cancer in CKD patients.

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