Low 25-Hydroxyvitamin D Is Associated with Increased Mortality in Female Nursing Home Residents

Stefan Pilz, Harald Dobnig, Andreas Tomaschitz, Katharina Kienreich, Andreas Meinitzer, Claudia Friedl, Doris Wagner, Claudia Piswanger-Sölkner, Winfried März, and Astrid Fahrleitner-Pammer

Department of Internal Medicine (S.P., H.D., A.T., K.K., C.P.-S., A.F.-P.), Division of Endocrinology and Metabolism; Clinical Institute of Medical and Chemical Laboratory Diagnostics (A.M., W.M.); Division for Transplantation (C.F.), Department of Surgery; and Department of Internal Medicine (D.W.), Division of Nephrology, Medical University of Graz, 8036 Graz, Austria; Department of Epidemiology and Biostatistics and EMGO Institute for Health and Care Research (S.P.), VU University Medical Center, 1081 BT Amsterdam, The Netherlands; Synlab Academy (W.M.), Synlab services LLC, D-68165 Mannheim, Germany; and Mannheim Institute of Public Health (W.M.), Ruperto Carola University Heidelberg, Medical Faculty Mannheim, D-68167 Mannheim, Germany

Context: Vitamin D deficiency contributes to skeletal diseases and is highly prevalent among institutionalized elderly patients. Whether low 25-hydroxyvitamin D (25[OH]D) concentrations are an independent risk factor for mortality in these patients is, however, unclear.

Objective: We aimed to evaluate whether 25(OH)D concentrations are associated with mortality.

Design, Setting, and Participants: This is a prospective cohort study among elderly female patients (age >70 yr) recruited from 95 nursing homes in Austria.

Main Outcome Measures: We calculated Cox proportional hazard ratios (HR) for all-cause mortality according to 25(OH)D quartiles.

Results: We examined 961 study participants (age 83.7 ± 6.1 yr). Median 25(OH)D concentration was 17.5 (interquartile range 13.7–25.5) nmol/liter, and 93% of our cohort had 25(OH)D levels below 50 nmol/liter. During a mean follow-up time of 27 ± 8 months, 284 patients died. Compared with the fourth quartile (25[OH]D >25.5 nmol/liter), the age-adjusted HR (with 95% confidence interval) was 1.49 (1.07–2.10) in the first 25(OH)D quartile (25[OH]D <14.0 nmol/liter), and this association remained significant after multivariate adjustments (HR = 1.56; 95% confidence interval = 1.01–2.40).

Conclusions: This Austrian study suggests that the majority of institutionalized female patients are vitamin D deficient during winter and that there was an inverse association of 25(OH)D and mortality. These data underscore the urgent need for effective strategies for the prevention and treatment of vitamin D deficiency, in particular in the setting of nursing homes. (***J Clin Endocrinol Metab*** **97: E653–E657, 2012)**

Vitamin D deficiency is considered a causal risk factor for skeletal diseases, which justifies recommendations for dietary vitamin D intakes (1, 2). Particular attention is paid to institutionalized elderly patients because prevalence of vitamin D deficiency is extraordinarily high among these individuals (2, 3). This in turn led to recommendations for vitamin D intake doses in the elderly (mostly 800 IU/d) that are higher than for any other age

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Abbreviations: BMI, Body mass index; HR, hazard ratio; 25[OH]D, 25-hydroxyvitamin D.

group (1, 4, 5). In this context, it should also be noted that a previous meta-analysis suggests that vitamin D supplementation may decrease total mortality in older individuals, but this has not been specifically addressed in elderly institutionalized patients (6). Meta-analyses of observational studies showed an inverse relationship between vitamin D status and mortality (7, 8). It has been documented that low 25-hydroxyvitamin D (25[OH]D) concentrations are associated with increased risk of mortality in the general population as well as in patients with chronic kidney disease (7, 8). By contrast, the situation is less clear for institutionalized elderly patients because only one previous study addressed this topic in such individuals (9). In that study, Sambrook *et al.* (9) examined 842 older people (mean age 81.9 yr; 78.4% females) residing in hostels and nursing homes in Northern Sydney. Higher 25(OH)D was associated with decreased mortality in age- and gender-adjusted analyses, but there was no significant relationship after multivariate adjustments (9). Therefore, the independent association of 25(OH)D with mortality remains to be further studied. We addressed this in a large prospective cohort of female nursing home residents in Austria (10, 11).

Subjects and Methods

Study population

Our study population consists of older (>70 yr) female patients of Caucasian origin who were recruited from 95 nursing homes in Austria. Baseline characteristics and study procedures have been extensively described in two previously published reports (10, 11). In brief, eligible study participants had to be able to walk a short distance independently. Main exclusion criteria were malignancies, hypercalcemia, advanced kidney or liver dysfunction, bilateral hip replacements, history of total gastrectomy, decompensated heart failure, chronic alcoholism, known osteomalacia, untreated thyroid disease, or chronic steroid treatment (10, 11). Mobility scoring was performed as previously published (10, 11): score 1, walking independently and outside the institution; score 2, walking inside nursing home, majority using a walking aid but not a wheelchair; score 3, staying in bed less than 50% during daytime, majority requiring a wheelchair; score 4, staying in bed more than 50% during daytime. We measured quadriceps knee extensor strength in kiloponds. This was done on the nondominant side by using a validated, hand-held isometric device (model DPPH; Industrial Scale Inc., Houston, TX). All study participants were followed up with respect to mortality. Written informed consent was obtained from all study participants, and the study protocol was approved by the local ethics committees.

Laboratory methods

Laboratory procedures have been previously described in detail, and all laboratory parameters were simultaneously measured at a single central laboratory (10, 11). Nonfasting blood samples were collected between 0900 and 1200 h and were immediately stored at −70 C until analysis. 25(OH)D was measured in serum by RIA after extraction (Immunodiagnostic Systems, Boldon, UK). According to manufacturer's instructions, the intraassay coefficients of variation were 5.3 and 5.0% at mean 25(OH)D concentrations of 26.5 and 58.4 nmol/liter, respectively. Interassay coefficients of variation were 8.2 and 8.1% at mean 25(OH)D concentrations of 19.6 and 56.7 nmol/liter, respectively. The detection limit of our 25(OH)D assay is 3 nmol/liter. Other assay methods have been described elsewhere (10, 11).

Statistical analyses

According to their distribution, continuous data are either presented as means ± SD or as medians with interquartile range. Categorical data are presented as percentages. Differences across groups are tested by ANOVA for continuous variables and by χ^2 test or Fisher's exact test for categorical data. We calculated Cox proportional hazard ratios (HR) for mortality according to 25(OH)D quartiles with the fourth quartile as the reference. We present crude HR as well as HR adjusted for age (years) (model 1). Additional adjustments are done for the possible confounders body mass index (BMI) (kilograms per square meter) and albumin (grams per deciliter) in model 2, and for creatinine clearance (milliliters per minute, calculated according to Cockcroft-Gault), glycated hemoglobin (percent), arterial hypertension (yes/no), and coronary artery disease (yes/no) in model 3. Additional adjustments were performed for parameters of mineral metabolism including serum calcium (millimoles per liter), serum phosphate (milligrams per deciliter), and PTH in model 4. Finally, we additionally adjust for mobility score (1–4) and quadriceps knee extensor strength (kiloponds) in model 5. A P value <0.05 was considered statistically significant. SPSS version 17.0 (SPSS Inc., Chicago, IL) was used for statistical analyses.

Results

From the initial cohort of 1664 study participants, 961 agreed to undergo a blood draw with subsequent measurements of 25(OH)D and were thus included into the present work. There were no significant differences in clinical characteristics (*i.e.* age, BMI, or mobility status) between those study participants with and without blood samplings. Blood samplings for 25(OH)D were exclusively performed in February and March 2002. Mean age was 83.7 ± 6.1 yr, and median 25(OH)D concentrations were 17.5 (13.7–25.5) nmol/liter (divide by 2.496 to convert nanomoles per liter to nanograms per milliliter). Only 69 patients (7.2% of the study population) had 25(OH)D levels of 50 nmol/liter or higher. Baseline characteristics of the study population according to 25(OH)D quartiles are presented in Table 1.

We recorded 284 deaths (30% of the study cohort) after a mean follow-up time of 27 ± 8 months (range 2–34 months). Cox proportional HR for mortality according to 25(OH)D quartiles are presented in Table 2. Age-adjusted

TABLE 1. Baseline characteristics according to 25(OH)D quartiles

Variable	1st quartile	2nd quartile	3rd quartile	4th quartile	*P*
Range (nmol/liter)	<14.0	14.0–17.5	17.6–25.5	>25.5	
Number	241	241	241	238	
Age (yr)	85.5 ± 5.6	83.6 ± 6.2	83.3 ± 6.0	82.2 ± 6.2	<0.001
Height (cm)	153.0 ± 7.7	153.7 ± 6.7	154.2 ± 7.1	153.6 ± 6.8	0.311
Weight (kg)	58.8 ± 11.4	61.3 ± 12.9	61.8 ± 11.8	62.2 ± 11.5	0.002
BMI (kg/m^2)	25.2 ± 4.6	26.0 ± 5.3	26.0 ± 4.4	26.3 ± 4.5	0.013
PTH (pg/ml)	88 (62–135)	71 (49–95)	60 (44–85)	45 (35–62)	<0.001
25(OH)D (nmol/liter)	11.7 (10.7–12.7)	15.7 (14.7–16.7)	20.7 (19.2–22.7)	36.4 (29.2–52.7)	<0.001
Serum phosphate (mg/dl)	3.6 ± 0.8	3.8 ± 0.7	3.8 ± 0.7	3.9 ± 0.7	<0.001
Serum calcium (mmol/liter)	2.42 ± 0.14	2.45 ± 0.11	2.45 ± 0.11	2.49 ± 0.12	<0.001
Calcium supplementation (%)	1.2	0.8	4.6	18.5	<0.001
Vitamin D supplementation (%)	0.4	0	2.1	14.3	<0.001
Albumin (g/dl)	3.9 ± 0.3	3.9 ± 0.3	4.0 ± 0.3	4.0 ± 0.3	0.017
Creatinine clearance (ml/min)	36.4 ± 11.4	37.6 ± 11.8	39.3 ± 11.7	39.0 ± 11.8	0.005
Knee extensor strength (kiloponds)	11.7 ± 4.9	13.3 ± 4.9	13.3 ± 5.3	14.2 ± 5.9	<0.001
Mobility status (%)					<0.001
1	7.0	10.6	14.3	16.4	
2	7.6	7.5	6.0	3.9	
3	10.1	6.6	4.6	4.4	
4	0.3	0.5	0.1	0	
HbA1c (%)	4.9 (4.6–5.1)	4.9 (4.7–5.3)	4.9 (4.7–5.2)	4.9 (4.6–5.2)	0.143
Arterial hypertension (%)	32.8	40.7	39.8	47.9	0.010
Coronary artery diseases (%)	31.5	31.1	24.1	25.1	0.246

Data are presented as medians with interquartile range, as means with SD, or as percentages. Differences across groups were calculated with ANOVA with *P* for trend and with χ^2 test or Fisher's exact test. HbA1c, Glycated hemoglobin.

HR (with 95% confidence interval) for mortality was 1.49 (1.07–2.10) in the first compared with the fourth 25(OH)D quartile, and this association remained significant even after multivariable adjustments (see Table 2).

Discussion

In a large cohort of institutionalized elderly women, we have shown that lower 25(OH)D levels are highly prevalent in winter and are associated with increased mortality.

The observation of extremely low 25(OH)D concentrations in our study participants is in line with previous investigations among institutionalized elderly people (2, 3, 12–15). Hence, our data suggest that although the high prevalence of vitamin D deficiency among frail elderly people in Europe has already been known for several decades, no efficient strategies have meanwhile been implemented to prevent and treat vitamin D deficiency in these individuals. Limited sunlight access in concert with impaired vitamin D synthesis of the aging skin as well as nutritional deficits may likewise contribute to this high prevalence of vitamin D deficiency. In fact, 25(OH)D concentrations were below the recommended level of 50 nmol/liter in almost all (92.8%) of our study participants. These data have implications for the interpretation of our prospective findings because even our highest group had median 25(OH)D levels well below the cutoff for vitamin D deficiency. Considering a meta-analysis that documented a nonlinear relationship between 25(OH)D and mortality with the lowest mortality risk at 25(OH)D levels ranging from 75–87.5 nmol/liter, it could be hypothesized that availability of an adequate reference group with such

TABLE 2. Hazard ratios (with 95% confidence intervals) for mortality according to 25(OH)D quartiles

	1st quartile	2nd quartile	3rd quartile	4th quartile
Range (nmol/liter)	<14.0	14.0–17.5	17.6–25.5	>25.5
Crude	1.74 (1.25–2.43)	1.41 (1.00–1.98)	1.08 (0.75–1.55)	1.00 reference
Model 1	1.49 (1.07–2.10)	1.32 (0.93–1.86)	1.03 (0.72–1.48)	1.00 reference
Model 2	1.45 (1.03–2.06)	1.25 (0.88–1.79)	1.08 (0.75–1.56)	1.00 reference
Model 3	1.57 (1.10–2.23)	1.30 (0.90–1.86)	1.16 (0.80–1.68)	1.00 reference
Model 4	1.88 (1.28–2.76)	1.49 (1.02–2.16)	1.31 (0.90–1.93)	1.00 reference
Model 5	1.56 (1.01–2.40)	1.21 (0.80–1.84)	1.32 (0.88–1.97)	1.00 reference

Model 1 was adjusted for age. Model 2 was adjusted for age, BMI, and albumin. Model 3 was adjusted for covariates of model 2 plus creatinine clearance, glycated hemoglobin, arterial hypertension, and coronary artery disease. Model 4 was adjusted for covariates of model 3 plus serum calcium, serum phosphate, and PTH. Model 5 was adjusted for covariates of model 4 plus knee extensor strength and mobility status.

high 25(OH)D levels would have contributed to more significant results for our data on 25(OH)D and mortality (8). On the other hand, not all observational studies, *i.e.* the work by Cawthon *et al.* (16) support a significant association of 25(OH)D and mortality. However, it is noteworthy that in the work by Cawthon *et al.* (16), 25(OH)D levels in the lowest category (<50 nmol/liter) were much higher compared with our study. In our present work, there was an increase in mortality in individuals with lower 25(OH)D levels, but it should be acknowledged that in multivariate models, this was significant only when comparing the fourth quartile (*i.e.* 25[OH]D >25.5 nmol/liter) with the first quartile (*i.e.* 25[OH]D <14.0 nmol/liter). In line with our findings, the only other previous study addressing this issue in institutionalized elderly patients also indicates that low 25(OH)D may be associated with increased mortality (9). Adjustment for possible confounders, however, attenuated this relationship in that work by Sambrook *et al.* (9), which underlines the importance of our work to shed more light into this topic. In this context, it should also be discussed that it is very difficult to differentiate between possible confounders and parameters of the causal chain of vitamin D deficiency because vitamin D may have causal implications for numerous pathophysiological processes (17–20). For example, mobility and muscle strength were associated with lower 25(OH)D in our cohort, but these variables could be partially both the cause as well as the consequence of vitamin D deficiency (2, 17–20). It may also be acknowledged that due to the previously shown nonlinear associations of 25(OH)D and mortality (8), we analyzed categorical data of 25(OH)D in our present study, whereas Sambrook *et al.* (9) presented only results on 25(OH)D concentrations as a continuous variable. Apart from this, we believe that our findings, together with previous data on institutionalized elderly, strongly point to the need for immediate action to prevent and treat vitamin D deficiency in these patients. Considering the high prevalence of vitamin D deficiency, it seems reasonable to initiate vitamin D supplementation (at least 800 IU/d) even without previous 25(OH)D testing in such individuals (1, 5, 14, 18). Regardless of the ongoing debate on putative extraskeletal benefits of vitamin D (*e.g.* cancer or cardiovascular disease), it should be considered that there is only one indication needed to treat vitamin D deficiency, and this is, at least, the proven skeletal benefit (1–8, 17–22). Nevertheless, observational studies like ours and interventional data on vitamin D and mortality may put additional pressure on health authorities to implement more efficient actions to fight vitamin D deficiency, in particular among institutionalized elderly individuals (6–8, 21). The present data are in general agreement with the recent Institute of Medicine statement that circulating 25(OH)D levels below 30 nmol/liter bear the risk of vitamin D deficiency (1). Whereas the Institute of Medicine report relies on bone health, the present study provides evidence that 25(OH)D levels below the aforementioned threshold may also be regarded as risk factor for all-cause mortality (1).

Our results are limited because we examined elderly female Caucasians recruited from nursing homes in Austria. These findings may therefore not be generalizable to other populations. Given that this was a prospective observational study, we cannot draw conclusions regarding causality. Blood samplings in February and March may have contributed to a particularly poor vitamin D status due to the seasonal lowering of 25(OH)D in winter. However, this relatively narrow time window for blood collections may have also minimized the possible influence of season on our prospective analyses. We also have to acknowledge that data on cause-specific mortality as well as on vitamin D supplementation during follow-up were not available. Despite careful adjustments, we cannot rule out the existence of unconsidered confounders. On the other hand, we might have overadjusted our analyses for parameters of the causal chain.

In conclusion, our Austrian study showed that the majority of elderly institutionalized women were vitamin D deficient in winter. We observed a significantly increased mortality risk in those patients with the lowest 25(OH)D levels. In view of these findings and the existing literature on adverse effects of vitamin D deficiency, there exists now an urgent need for effective strategies to improve vitamin D status in older institutionalized patients.

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Address all correspondence and requests for reprints to: Stefan Pilz, Department of Internal Medicine, Division of Endocrinology and Metabolism, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria. E-mail: stefan.pilz@chello.at.

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