Vitamin D Levels and Mortality in Type 2 Diabetes

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OBJECTIVE — To evaluate vitamin D as a predictor of all-cause and cardiovascular mortality and risk of progression to micro- or macroalbuminuria in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — In a longitudinal observational follow-up study, 289 type 2 diabetic patients with normoalbuminuria (n = 172), microalbuminuria (n = 73), and macroalbuminuria (n = 44) at baseline were followed for a median (range) of 15.0 (0.2–23) years. Mean ± SD age was 54 ± 9 years. Plasma 25-hydroxyvitamin D_3 levels were determined by high-performance liquid chromatography/tandem mass spectrometry on baseline samples. Severe vitamin D deficiency was defined as the lower 10th percentile (<13.9 nmol/l).

RESULTS — Median (range) vitamin D level was 35.7 (5–136.7) nmol/l. Vitamin D levels were not associated with age, sex, estimated glomerular filtration rate, urinary albumin excretion rate (UAER), or A1C at baseline, but low levels were weakly associated with elevated systolic blood pressure (R = 0.13, P = 0.03). During follow-up, 196 (68%) patients died. All-cause mortality was increased in patients with severe vitamin D deficiency (hazard ratio 1.96 [95% CI 1.29–2.98]). The association persisted after adjustment for UAER, A1C, diabetes duration, and conventional cardiovascular risk factors (2.03 [1.31–3.13]). Severe vitamin D deficiency was associated with increased cardiovascular mortality (1.95 [1.11–3.44]), and the association persisted after adjustment (1.90 [1.15–3.10]). Severe vitamin D deficiency at baseline did not predict progression to micro- or macroalbuminuria.

CONCLUSIONS — In type 2 diabetic patients, severe vitamin D deficiency predicts increased risk of all-cause and cardiovascular mortality, independent of UAER and conventional cardiovascular risk factors. Whether vitamin D substitution improves prognosis remains to be investigated.

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Levels of vitamin D (25-hydroxyvitamin D_3 [25(OH)D_3]) vary considerably among individuals mainly because of differences in sun exposure and skin color and the presence of risk factors such as diabetes or other comorbidities. Hypovitaminosis is highly prevalent worldwide (1).

The association between vitamin D and survival primarily originated from observational studies of dialysis cohorts receiving therapy with a vitamin D receptor analog (VDRA) (2). Recently, low levels of vitamin D have been associated with an increased risk of cardiovascular disease (CVD) (3) as well as all-cause (4) and cardiovascular mortality (5) in the general population.

An observational study on patients with mainly nondiabetic chronic kidney disease (CKD) stage 2–5 showed that low levels of vitamin D independently predicted death from all-cause and cardiovascular causes (6). Findings from the same study support the hypothesis of vitamin D deficiency playing a role in progression to end-stage renal disease (ESRD).

In the general population, an inverse association was found between vitamin D levels and the prevalence of albuminuria (7). Data from studies in experimental diabetic nephropathy and other kidney disease, as well as limited human evidence, indicate that vitamin D insufficiency may be involved in the pathogenesis of albuminuria (8,9).

Diabetes is the leading cause of ESRD in the Western world, and many diabetic patients will die of cardiovascular complications. Early identification of increased renal as well as vascular risk paves the way for early intervention, thereby contributing to a desirable reduction in incidents of CVD and nephropathy among diabetic patients.

Therefore, we aimed to investigate whether plasma vitamin D has a prognostic value in predicting increased risk of excess all-cause and cardiovascular mortality as well as in initiation and/or progression of diabetic kidney disease in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

— The study population was based on all subjects (n = 363) with type 2 diabetes who were aged <66 years and attending a tertiary referral center at Hvidøre Hospital during 1987 as described previously (10). Type 2 diabetes was defined as either *1*) diabetes treated by diet alone or by diet combined with oral hypoglycemic agents, *2*) diabetes treated with insulin plus onset of diabetes at age >40 years and BMI above normal at the time of diagnosis, or *3*) diabetes treated with insulin, with patients having a normal BMI and a glucagon-stimulated C-peptide value ≥0.60 pmol/ml. Originally, 31 non-Caucasian patients and 4 patients lacking baseline urine collections were excluded. In addition, we excluded 39 patients for whom samples for measurement of plasma 25(OH)D_3 were not available at baseline. The cohort thus consisted of 289 patients, mean age 54 years. Patients were classified as having normoalbuminuria (n = 172, urinary albumin excretion [UAE] <30 mg/24 h), microalbuminuria, (n = 73, UAE 30–299 mg/24 h), or macroalbuminuria (n = 44, UAE ≥300 mg/24 h) at baseline.

In a prospective observational study design, patients were followed until 31 December 2009 or until death (n = 196) or emigration (n = 3). The study was approved by the local ethics committee and conducted in accordance with the Decla-

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ration of Helsinki, and all patients gave their informed written consent.

Baseline clinical and laboratory investigations

Patients were interviewed using the World Health Organization cardiovascular questionnaire (11). Prior major cardiovascular events were defined as a history of stroke and/or myocardial infarction.

Smoking was defined as individuals smoking ≥1 cigarettes/cigars/pipes per day; all others were classified as nonsmokers. UAE rate (UAER) was measured by radioimmunoassay from 24-h urine collections. Blood samples were drawn with patients in the nonfasting state.

A1C levels were determined by an isoelectric focusing method (normal range: 4.1–6.1%) (12), serum creatinine by a kinetic Jaffé method, and serum cholesterol by standard methods. Glomerular filtration rate (GFR) was estimated by the four-variable Modification of Diet in Renal Disease equation (http://www.nkdep.nih.gov/professionals/gfr_calculators/idms_si.htm).

Table 1—*Baseline clinical and laboratory characteristics of 289 type 2 diabetic patients according to levels of 25(OH)D_3*

	25(OH)D_3 ≥13.9 nmol/l	25(OH)D_3 <13.9 nmol/l	*P* value
n	260	29	
Sex (male/female)	161/99	16/13	0.55
Age (years)	53.7 ± 8.9	54.6 ± 9.6	0.59
Known duration of diabetes (years)	6 (2.0–11.0)	11 (6.5–15.5)	<0.001
Retinopathy (nil/simplex/proliferative)	179/72/9	12/14/3	0.03
History of cardiovascular disease	23 (9)	3 (10)	0.73
Antihypertensive medication	98 (38)	10 (34)	0.84
BMI (kg/m^2)	28.6 ± 4.9	27.5 ± 5.5	0.25
HbA_{1c} (%)	8.0 ± 1.8	8.6 ± 1.8	0.1
Nephropathy (normo/micro/ macroalbuminuria)	158/66/36	14/7/8	0.14
UAER (mg/24 h)	18 (7–65.5)	31 (6–364)	0.03
Serum creatinine (μmol/l)	74 (64–88)	70 (62–90)	0.85
eGFR (ml/min per 1.73 m^2)	93 ± 26	89 ± 29	0.48
Systolic blood pressure (mmHg)	150 ± 23	154 ± 24	0.32
Diastolic blood pressure (mmHg)	86 ± 12	82 ± 15	0.2
Serum cholesterol (mmol/l)	6.3 ± 1.6	6.1 ± 1.7	0.53
Serum HDL cholesterol (mmol/l)	1.2 ± 1.0	1.3 ± 1.7	0.63
Serum triglycerides (mmol/l)	1.85 (1.27–2.84)	1.45 (1.08–2.4)	0.24
Smokers (%)	43.1	48.3	0.69
25(OH)D_3 (nmol/l)	38.6 (24.2–57.9)	11.0 (5.0–12.7)	—

Data are *n*, means ± SD, *n* (%), or medians (interquartile range).

Measurements of plasma 25(OH)D_3

After the patients had been at rest for at least 10 min in the supine position, blood samples for determination of plasma 25(OH)D_3 were collected in citrated tubes and centrifuged, and plasma was stored at −80°C. All samples were treated and stored under the same conditions. Plasma 25(OH)D_3 is found to be stable when tested after >10 years of storage (13), making long-term epidemiological studies of plasma 25(OH)D_3 possible. Before initiating the present study, we also tested the stability of plasma vitamin D in samples taken from a cohort of type 1 diabetic patients followed with regular sampling since 1979 and stored under similar conditions. We analyzed vitamin D in samples taken from the same subjects at the same time of year and stored for 5, 10, 15, 20, and 25 years. No statistically significant difference between mean levels of plasma vitamin D was shown (data not shown). Plasma levels of 25(OH)D_3 were determined by high-performance liquid chromatography/tandem mass spectrometry (Department of Clinical Biochemistry, Lillebaelt Hospital, Vejle, Denmark). The coefficients of variation were 12.5% for a sample of 20 nmol/l, 8.3% for a sample of 56 nmol/l, and 6.7% for a sample of 231 nmol/l.

Follow-up

All patients were traced through the National Register during January 2010. If a patient had died before 1 January 2010, the date of death was recorded. Information on the cause of death was obtained from the death certificate until 2004 but was not available thereafter; thus, cardiovascular mortality was evaluated until 2004. All death certificates were reviewed independently by two observers, and the primary cause of death was recorded. All deaths until 2004 were classified as cardiovascular deaths unless an unequivocal noncardiovascular cause was established (14).

Statistical analysis

Variables with skewed distribution are given as medians (interquartile range); data for all other variables are means ± SD. For nonnormally distributed variables, comparisons between groups were performed using the Mann-Whitney *U* test, whereas unpaired Student *t* tests were used for comparisons among normally distributed variables. A χ^2 test was used for comparison of categorical variables between groups.

To evaluate whether vitamin D is a predictor of all-cause and cardiovascular mortality in an explanatory model, a Cox proportional hazards regression model was used. The relationships were first analyzed without adjustment, followed by an adjustment for baseline variables (sex, age, smoking, systolic blood pressure, history of cardiovascular disease, duration of diabetes, total cholesterol, and kidney function (estimated GFR [eGFR] and UAER), all of which have previously been shown to be associated with increased all-cause and cardiovascular mortality.

Using the Cox proportional hazards regression model, we did additional uni- and covariate analysis on the cohort when it was divided according to the median diabetes duration of the group with low vitamin D levels (11 years). Results are presented as hazard ratios (HR) with 95% CI. All time-to-event variables were analyzed with a log-rank test and displayed as Kaplan-Meier plots according to levels of vitamin D either greater than or less than the 10th percentile. Two-tailed $P \leq 0.05$ was considered statistically significant. All statistical calculations were performed using SPSS for Windows (version 14.0; SPSS, Chicago, IL).

RESULTS — The main baseline characteristics of the patients are given in Table 1. The median (range) vitamin D concentration was 35.7 (5–136.7) nmol/l. The patients were divided into two sub-

groups based on their vitamin D level at baseline being either in the lower 10th percentile or above. The cutoff value for the lower 10th percentile was vitamin D <13.9 nmol/l in both men and women. Patients with low levels of vitamin D had more advanced retinopathy ($P = 0.03$), a higher UAER ($P = 0.03$), and a longer known duration of diabetes ($P < 0.001$), but vitamin D levels were not associated with diabetes duration ($R = 0.07$, $P = 0.26$). Vitamin D levels were not associated with age, sex, eGFR, UAER, or A1C at baseline, but low levels were weakly associated with elevated systolic blood pressure ($R = 0.13$, $P = 0.03$).

During 15 (0.2–23) years of follow-up, 196 (68%) of the 289 patients died. Figure 1*A* shows Kaplan-Meier curves for all-cause mortality in patients according to a vitamin D level less than or greater than the lower 10th percentile. During follow-up, all-cause mortality was significantly increased in patients with severe vitamin D deficiency: 25 (86%) patients with vitamin D <13.9 nmol/l and 171 (66%) patients with vitamin D ≥13.9 nmol/l died ($P < 0.01$). In a Cox proportional hazards model the unadjusted HR (95% CI) was 1.96 (1.29–2.98). The association persisted after adjustment for UAER, eGFR, A1C, diabetes duration, and conventional cardiovascular risk factors (adjusted HR 2.03 [1.31–3.11]). Known duration of diabetes at baseline was significantly different in groups according to levels of vitamin D, being longer in the patient group with low levels of vitamin D. Therefore, duration was adjusted for in the Cox models. Table 2 shows crude and adjusted HRs for predictors of all-cause mortality used in the Cox proportional hazards model.

Until 2004, 101 (72%) of the observed 141 deaths were due to cardiovascular causes. Of these, 14 patients had vitamin D <13.9 nmol/l and 87 patients had vitamin D levels above the 10th percentile ($P = 0.02$). Cardiovascular mortality according to a vitamin D level less than or greater than the lower 10th percentile is illustrated in Fig. 1*B*. Severe vitamin D deficiency was associated with increased cardiovascular mortality (unadjusted HR 1.95 [1.11–3.44] and after adjustment HR 1.90 [1.16–3.10]).

Dividing the entire cohort according to known duration of diabetes presented two new subgroups: a group consisting of patients with diabetes duration <11 years ($n = 212$) and a group consisting of patients with a diabetes duration of ≥11 years ($n = 77$). During follow-up until 1 January 2010, 137 (65%) and 59 (77%) patients, respectively, in the two groups died. Despite reduced power, the analysis shows a similar trend for low levels of vitamin D being predictive of all-cause mor-

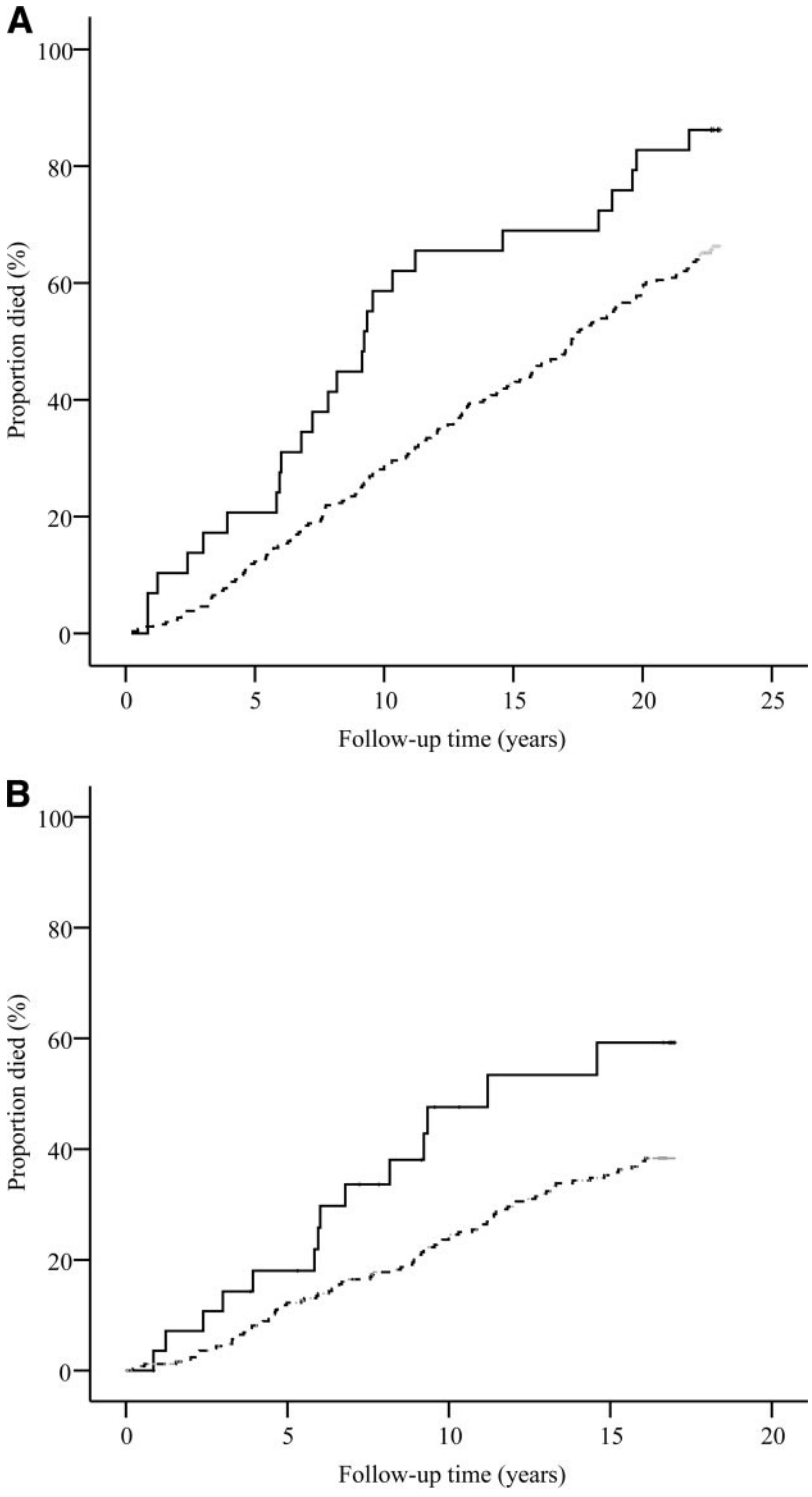

Figure 1—A*: Kaplan-Meier curves of all-cause mortality in 289 type 2 diabetic patients according to a vitamin D level less than or greater than the lower 10th percentile [25(OH)D_3 = 13.9 nmol/l]. ——, 25(OH)D_3 <13.9 nmol/l; · · · · ·, 25(OH)D_3 ≥13.9 nmol/l. Log-rank test for overall difference,* P = *0.002.* B*: Kaplan-Meier curves of cardiovascular mortality in 289 type 2 diabetic patients according to a vitamin D level less than or greater than the lower 10th percentile [25(OH)D_3 = 13.9 nmol/l]. ——, 25(OH)D_3 <13.9 nmol/l; · · · · ·, 25(OH)D_3 ≥13.9 nmol/l. Log-rank test for overall difference,* P = *0.015.*

Table 2—*Crude and adjusted HRs for predictors of all-cause mortality*

Predictors of all-cause mortality	HR_{crude} (95% CI)	HR_{adj} (95% CI)	HR_{adj} (95% CI), diabetes duration <11 years*	HR_{adj} (95% CI), diabetes duration ≥11 years*
n			212	77
Age (years)	1.08 (1.06–1.11)	1.06 (1.05–1.10)	1.09 (1.06–1.12)	1.07 (1.02–1.11)
Sex (female vs. male)	0.73 (0.55–0.98)	0.76 (0.55–1.05)	0.95 (0.65–1.41)	0.68 (0.37–1.27)
History of cardiovascular disease	3.63 (2.38–5.54)	3.29 (2.11–5.12)	3.72 (2.10–6.59)	2.18 (1.02–4.65)
Systolic blood pressure (mmHg)	1.02 (1.01–1.03)	1.01 (1.01–1.02)	1.01 (1.00–1.02)	1.00 (0.99–1.02)
Cholesterol (mmol/l)	1.12 (1.03–1.22)	1.08 (0.99–1.18)	1.22 (1.08–1.40)	0.99 (0.84–1.16)
eGFR (ml/min per 1.73 m^2)	0.98 (0.98–0.99)	1.00 (0.99–1.00)	0.99 (0.99–1.00)	0.99 (0.98–1.01)
UAER (mg/24 h)	1.61 (1.37–1.90)	1.54 (1.28–1.85)	1.67 (1.32–2.13)	1.45 (1.05–1.97)
Smoking (yes vs. no)	1.03 (0.77–1.36)	1.41 (1.05–1.89)	1.87 (1.30–2.68)	0.94 (0.52–1.68)
Diabetes duration (years)	1.02 (1.01–1.04)	1.01 (0.99–1.02)	—	—
Vitamin D, lowest 10th percentile	1.96 (1.29–2.98)	2.03 (1.31–3.13)	1.58 (0.83–3.03)	2.87 (1.41–5.87)

Columns 2 and 3 show crude and adjusted HRs, respectively, for predictors of all-cause mortality. Columns 4 and 5 show HRs for predictors of all-cause mortality when the cohort is divided according to diabetes duration. *Divided according to median diabetes duration in the patients with vitamin D levels less than the lowest 10th percentile.

tality in both groups. Although weakened and no longer significant in either group, the trend slightly stronger in patients with a long duration of diabetes (Table 2).

An analysis of vitamin D as a continuous variable in the Cox model could not demonstrate a significant relation to all-cause or cardiovascular mortality, suggesting that the relationship is not linear over the range of vitamin D values.

Progression to microalbuminuria and macroalbuminuria

The patients were followed until 2004 in regards to progression in albuminuria. Among the 172 normoalbuminuric patients at baseline, 61 patients developed persistent microalbuminuria during follow-up. A Cox proportional hazards model revealed that low vitamin D levels at baseline did not predict development of microalbuminuria (unadjusted HR 0.72 [0.31–1.70]).

Among the 73 microalbuminuric patients at baseline, 25 patients developed persistent macroalbuminuria during follow-up. Of the 25 patients who progressed, 23 had vitamin D levels above the lowest 10% percentile and 2 had lower vitamin D levels (unadjusted HR 3.52 [0.74–16.71]). After adjustment for progression promotors, the association weakened further.

CONCLUSIONS — In our 15-year longitudinal observational follow-up study, we found very low levels of plasma vitamin D (less than the 10th percentile) to be a strong and independent predictor of all-cause mortality in type 2 diabetic patients. Low levels of vitamin D were also predictive of cardiovascular mortality. These associations were not only independent of glycemic control and conventional cardiovascular risk factors including known ischemic heart disease but also were independent of kidney function.

Severe vitamin D deficiency at baseline did not predict progression to microalbuminuria or macroalbuminuria. Our findings of associations between severe vitamin D deficiency and increased risk of all-cause and cardiovascular mortality in type 2 diabetic patients complement recent data from studies suggesting similar associations in the general population (4) and among patients with nondiabetic CKD (6) or ESRD (15).

A cross-sectional study on 13,331 participants from NHANES III found low vitamin D levels to be associated with all-cause mortality (4). Furthermore, a follow-up study on 1,739 Framingham Offspring Study participants showed that the incidence of nonfatal cardiovascular events was increased among participants with low vitamin D levels (3). A study on mainly nondiabetic patients with CKD found vitamin D to independently predict all-cause mortality, cardiovascular events, and increased risk of progression to dialysis (6).

Vitamin D is stored in its inactive form in the liver and in peripheral fat tissue for the body to extract and activate by hydroxylation in the liver and kidney, respectively. In healthy subjects, vitamin D deficiency can result from inadequate intake of vitamin D–containing foods coupled with inadequate sunlight exposure. Seasonal variations in vitamin D levels occur, depending on geographic latitude and sun exposure in particular. A study done on the general population in a Northern European country showed a seasonal variation of vitamin D insufficiency of 73 and 29% for winter and summer, respectively. The difference for vitamin D deficiency was similarly found to be 8 and 1% (16). Furthermore, there are several conditions, such as obesity, absorption, and liver or kidney disorders, in which the risk of developing vitamin D deficiency is increased for physiological reasons.

Obesity is common among patients with type 2 diabetes. Vitamin D stored in fat tissue causes decreased bioavailability, and exposes obese patients at greater risk of developing vitamin D insufficiency. However, in the present study, the patients in the two subgroups did not differ significantly in BMI. There is no linear association between BMI and vitamin D in these data. Diabetic patients are more prone to developing CVD compared with the general population (17). Having a higher risk profile, a greater treatment potential exists if vitamin D is also found to be a risk factor for CVD development and mortality.

The role of vitamin D deficiency in prevalent cardiovascular disease is in a cross-sectional study of type 2 diabetic patients with mild kidney impairment, shown to be strongly associated with a higher prevalence of manifest cardiovascular disease, also after adjustment for baseline kidney function and other known CVD risk factors (18).

With the present longitudinal follow-up study we are now able to show that the predictive value of low vitamin D levels on all-cause and cardiovascular mortality, already shown for the general

population and in patients with nondiabetic CKD, also applies to type 2 diabetic patients.

The mechanisms of action behind the survival benefit seen among patients with the higher levels of vitamin D at baseline are unclear. A growing amount of evidence indicates that vitamin D through activation of the vitamin D receptor has clinically important pleiotropic effects involved in CVD development and mortality. Vitamin D has been associated with suppression of the renin-angiotensin-aldosterone system (RAAS) (19), cardiac myocyte hypertrophy (20), vascular calcification, atherosclerosis-lowering, anti-inflammatory (21), and immunomodulatory actions (1), suggesting cardiovascular and renoprotective effects. Furthermore, vitamin D deficiency has been associated with increased incident risk of certain cancers as well as a higher mortality from these cancers (1).

Several of the above-mentioned pathways may be important mechanisms in cardiovascular health. Inflammation is a key mechanism in atherosclerosis. A recent study in type 2 diabetic patients, investigating the mechanism by which vitamin D deficiency mediates increased risk of cardiovascular disease, found reduced vitamin D receptor signaling to be a potential mechanism underlying increased foam cell (macrophages who ingested oxidized LDL) formation and accelerated cardiovascular disease in diabetic compared with nondiabetic patients (22).

Given the observational design, the present study does not elaborate further on underlying mechanisms but adds to the increasing amount of data suggesting that vitamin D substitution might be a potential therapeutic target to prevent vascular disease progression. In this study there was a significant difference in known diabetes duration between groups with low and higher levels of vitamin D, but duration of diabetes and level of vitamin D were not associated and we adjusted for known duration of diabetes in our Cox models. In a type 1 diabetes cohort, we have recently presented a similar predictive effect of low vitamin D levels (C.J., personal communication, American Society of Nephrology, 2009). Analysis of subgroups based on duration of diabetes of more or less than 11 years, suggested that the effect was stronger in patients with long duration; however, because of the reduced power, such analysis should be interpreted with caution.

The pathogenesis behind diabetic kidney disease is complex and thought to involve multiple pathways. Of particular importance is an activation of the intrarenal RAAS promoting progressive renal injury. In mice, 1,25-dihydroxyvitamin D_3 is shown to be a negative endocrine regulator of the RAAS on transcriptional level independent of calcium and PTH (19). Agarwal et al. (9) analyzed data from three randomized controlled clinical trials investigating administration of oral paricalcitol in patients with CKD. They showed that paricalcitol caused a reduction in albuminuria as measured by a dipstick method compared with placebo ($P = 0.004$). Importantly, the effects seemed to be independent of concomitant therapies to inhibit the RAAS. Furthermore, it has recently been shown that administration of a VDRA in addition to blockade of the RAAS causes sustained albuminuria reduction and thereby has clinically relevant renoprotective effects in patients with CKD (23) (D. de Zeeuw, personal communication, American Society of Nephrology, 2009).

Because of circumstantial evidence on the beneficial effects seen when one is intervening with VDRA, it is tempting to speculate that low levels of vitamin D might be a risk marker of both initiation and/or progression of albuminuria in diabetic patients (9). Our study, however, did not find vitamin D levels <13.9 nmol/l to significantly predict either initiation or progression of albuminuria.

In our study, severe vitamin D deficiency was defined as the lower 10th percentile [$25(OH)D_3$ <13.9 nmol/l] in both men and women. An international consensus in regard to definitions of which vitamin D levels are to be thought of as normal, insufficiency, and deficiency is lacking. The limits for a physiological optimal vitamin D level are still a matter of debate in the literature. Although vitamin D is shown to be stable in stored samples (13), storing could affect absolute concentrations due to evaporation; thus, we chose the 10th percentile. As mentioned, the stability of plasma vitamin D levels in our samples was tested before analysis was done on the present cohort and found not to show any statistically significant difference in levels when samples from different years of storage were compared.

Our study has some strengths and limitations. One element of methodological strength is the longitudinal design and long follow-up period and completeness of follow-up. Given the observational design, it is not possible to infer causality from the associations described.

Secondary hyperparathyroidism in patients with CKD is known to predict increased all-cause and cardiovascular mortality (24). The question arises whether the observed predictive effect of vitamin D is merely to be considered as a marker for other associated risk factors. We did not measure parathyroid hormone at baseline, and therefore we were not able to exclude this vitamin D-dependent variable as a driving confounder in our analysis. However, kidney function was adjusted for, and still the association between vitamin D and increased mortality persisted.

Further limitations of our study are related to possible changes in the level of vitamin D throughout the year. We did not adjust for seasonal change nor did we have baseline data on physical activity that could be related to outdoor activity and sun exposure and thereby level of vitamin D. We were therefore not able to adjust for this.

More observational studies are needed to confirm our findings. Randomized controlled clinical trials administering VDRA are necessary to prove causality between vitamin D status and survival prognosis in diabetic patients.

In summary, baseline levels of $25(OH)D_3$ less than the 10th percentile predict increased risk of all-cause and cardiovascular mortality in type 2 diabetic patients. Baseline levels of $25(OH)D_3$ less than the 10th percentile do not predict progression to micro- or macroalbuminuria.

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C.J. wrote the manuscript. M.-A.G., L.T., and P.R. researched data and reviewed/edited the manuscript. A.S. measured $25(OH)D_3$ in baseline samples. H.-H.P. reviewed/edited the manuscript.

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