Vitamin D Levels, Microvascular Complications, and Mortality in Type 1 Diabetes

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OBJECTIVE—To evaluate vitamin D as a predictor of all-cause mortality, progression from normoalbuminuria to micro- or macroalbuminuria, and the development of background or proliferative retinopathy in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS—A prospective observational follow-up study in which an inception cohort of type 1 diabetic patients was followed from onset of diabetes diagnosed between 1979 and 1984. Plasma vitamin D [25(OH)D3] levels were determined by high performance liquid chromatography/tandem mass spectrometry in 227 patients before the patients developed microalbuminuria. Values equal to or below the 10% percentile (15.5 nmol/L) were considered severe vitamin D deficiency.

RESULTS—Median (range) vitamin D was 44.6 (1.7–161.7) nmol/L. Vitamin D level was not associated with age, sex, urinary albumin excretion rate (UAER), or blood pressure. During follow-up, 44 (18%) patients died. In a Cox proportional hazards model, the hazard ratio for mortality in subjects with severe vitamin D deficiency was 2.7 (1.1–6.7), $P = 0.03$, after adjustment for UAER, HbA_{1c}, and conventional cardiovascular risk factors (age, sex, blood pressure, cholesterol, smoking). Of the 220 patients, 81 (37%) developed microalbuminuria and 27 (12%) of these progressed to macroalbuminuria. Furthermore, 192 (87%) patients developed background retinopathy, whereas 34 (15%) progressed to proliferative retinopathy. Severe vitamin D deficiency at baseline did not predict the development of these microvascular complications.

CONCLUSIONS—In patients with type 1 diabetes, severe vitamin D deficiency independently predicts all-cause mortality but not development of microvascular complications in the eye and kidney. Whether vitamin D substitution in type 1 diabetic patients can improve the prognosis remains to be investigated.

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Hypovitaminosis D is found to be highly prevalent worldwide (1). Recently, low levels of vitamin D have been associated with an increased risk of excess all-cause and cardiovascular mortality in the general population (2) as well as in type 2 diabetic patients (3). However, to our knowledge the association has never been investigated in type 1 diabetic subjects. The levels of plasma vitamin D (25-hydroxyvitamin D3 [25(OH)D3]) varies considerably among individuals mainly because of differences in sun exposure, skin color, and the presence of risk factors such as diabetes or other comorbidities.

In patients with diabetes, an excess mortality in patients with diabetes complications has been established (4). Development and progression of diabetic microangiopathy in terms of retinopathy and nephropathy is known to be closely related to poor metabolic control, elevated arterial blood pressure, and other risk factors (5,6). Data from studies in experimental diabetic nephropathy indicate that vitamin D insufficiency may also be involved in the pathogenesis of albuminuria. In the general population, an inverse association is found between the level of vitamin D and the prevalence of albuminuria (7), and limited data from clinical trials in nondiabetic chronic kidney disease (CKD) patients suggest that treatment with paricalcitol (vitamin D receptor analog [VDRA]) may reduce proteinuria (8–10). Furthermore, recently published data suggest that administration of a VDRA on top of blockade of the rennin angiotensin aldosterone system (RAAS) in patients with type 2 diabetes and diabetic nephropathy lowers albuminuria (11). Diabetes is the leading cause of CKD and kidney failure in the Western world, but it is unclear if vitamin D insufficiency contributes to the risk of developing diabetic nephropathy or other microvascular complications. With this study we aimed to investigate whether very low levels of plasma 25(OH)D3 could predict increased risk of excess mortality as well as development of microvascular complications in type 1 diabetic patients.

RESEARCH DESIGN AND METHODS

—Our study sample comprised all patients newly diagnosed with type 1 diabetes consecutively admitted to the Steno Diabetes Center between 1 September 1979 and 31 August 1984. The inception cohort included 286 patients. Nine patients were excluded; seven because of serious mental illness and two because of microalbuminuria at the onset of diabetes. Plasma 25(OH)D3 was analyzed in samples from approximately 3 years after diagnosis or the subsequently closest available sample (median [range] years after diagnose = 3.0 [2.3–9.1]) and before any of the patients developed microalbuminuria. Samples were available in 220 patients.

The patients attended the outpatient clinic every 3 or 4 months as part of routine follow-up. They were treated by diabetologists and nurses according to previously described guidelines (12).

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They received no specific intervention. Twenty-four hour urinary albumin excretion rate (UAER) was measured in each patient at least once a year (12). Development of persistent microalbuminuria and persistent macroalbuminuria were defined as UAER between 30 and 300 mg/24 h and >300 mg/24 h, respectively, in at least two of three consecutive samples, with an increase of at least 30% above the baseline level (13,14).

Plasma 25(OH)D3 was measured from samples stored at −20°C until analysis. All samples were treated and stored under the same conditions. Plasma 25(OH)D3 is found to be stable when tested after more than 10 years of storage (15), making long-term epidemiologic studies of circulating plasma 25(OH)D3 possible. Before initiation of the current study, we tested the stability of plasma 25(OH)D3 in samples taken from this exact cohort. We analyzed plasma 25(OH)D3 in samples taken from the same subjects at the same time of year and stored for 5, 10, 15, 20, and 25 years. No statistical significant difference between mean levels of plasma 25(OH)D3 was shown (data not shown). Plasma levels of 25(OH)D3 were determined by high performance liquid chromatography/tandem mass spectrometry (Department of Clinical Biochemistry, Lillebælt Hospital, Vejle, Denmark). A plasma 25(OH)D3 value equal to or below the 10% percentile (15.5 nmol/L) was considered severe vitamin D deficiency in accordance with our previous study on vitamin D and mortality in type 2 diabetes (3).

Patients were classified as smokers if they smoked more than one cigarette a day; smoking history was elicited by questionnaire. Retinopathy was assessed through dilated pupils and graded as absent, background, or proliferative (12).

Statistical analysis

Baseline data are from first assessment 6 months after the onset of type 1 diabetes, after initial glycemic stabilization. Variables with skewed distribution are expressed as medians (interquartile range); values for all other variables are means (SD).

For nonnormally distributed variables, comparisons between groups were performed using the Mann-Whitney *U* test, and unpaired Student *t* tests were used for normally distributed variables. A χ^2 test was used for comparison of categorical variables between groups.

To evaluate whether low vitamin D levels predicted all-cause mortality in an explanatory model, a Cox proportional hazards regression analysis was performed. Initially, a univariate analysis was performed using baseline variables (sex, age, plasma total cholesterol, systolic blood pressure, UAER, smoking), all which have previously been shown to be associated with increased all-cause mortality. Results are described as hazard ratios (HRs) with 95% CIs.

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 above or below the lower 10% percentile. Two-tailed *P* values ≤0.05 were considered statistically significant. All statistical calculations were performed using SPSS for Windows, version 14.0 (SPSS, Chicago, IL)

RESULTS—We followed 220 patients newly diagnosed with type 1 diabetes for a median (range) of 26.0 (1.0–29.0) years. The main baseline patient characteristics are shown in Table 1. The median (range) vitamin D concentration was 44.6 (1.7–161.7) nmol/L.

The patients were divided into two subgroups based on their vitamin D level being either equal to and below or above the value of the lower 10% percentile. The cut off value for the lower 10% percentile was vitamin D ≤15.5 nmol/L in both men and women, and 22 (10%) of the 220 included patients with a vitamin D value below this level. Vitamin D level was not associated with age, sex, UAER, and blood pressure, but a weak negative association was found with HbA_{1c} (R = 0.14, *P* = 0.04).

During follow-up, 44 (20%) of the 220 patients died. Seven of the 22 (32%) patients with vitamin D levels ≤15.5 nmol/L died compared with 37 (19%) of the patients with vitamin D levels >15.5 nmol/L (*P* = 0.06). Figure 1 shows a Kaplan-Meier curve for mortality according to a vitamin D level equal to and below or above the lower 10% percentile. In a Cox proportional hazards model, the unadjusted HR (95% CI) for mortality in subjects with vitamin D levels equal to or below the lower 10% percentile was 2.0 (0.9–4.4), *P* = 0.1. The association persisted and became statistically significant after adjustment for UAER, HbA_{1c}, and conventional cardiovascular risk factors (age, sex, blood pressure, cholesterol, smoking) (covariate adjusted HR 2.7 [1.1–6.7], *P* = 0.03). An analysis of vitamin D as a continuous variable in the Cox model could not demonstrate a significant relation to all-cause mortality, suggesting the relationship is not linear over the range of vitamin D values.

Microvascular complications

During follow-up, 81 (34%) patients developed persistent microalbuminuria. Of these patients, 6 (27%) had a vitamin D level equal to or below the lower 10% percentile. Of the 81 patients who developed microalbuminuria, 27 (12%) progressed to persistent macroalbuminuria, but only 2 of the patients with vitamin D levels equal to or below the lower 10% percentile progressed, corresponding to 9%.

Table 1—*Baseline clinical and laboratory characteristics of 220 type 1 diabetic patients in accordance with levels of 25(OH)D3*

	25(OH)D3 >15.5 nmol/L	25(OH)D3 ≤15.5 nmol/L	*P*
n	198	22	
Sex (male/female)	117/81	14/8	1.0
Age (years)	29 (14)	31 (16)	0.5
BMI (kg/m^2)	20.6 (2.6)	20.2 (2.9)	0.5
HbA_{1c} (%)	9.8 (2.1)	10.6 (2.5)	0.1
Urinary albumin excretion (mg/24 h)	9 (6–14)	9 (5–11)	0.3
Serum creatinine (μmol/L)	80 (14)	77 (16)	0.3
Systolic blood pressure (mmHg)	125 (17)	129 (16)	0.3
Diastolic blood pressure (mmHg)	78 (11)	79 (10)	0.6
Serum cholesterol (mmol/L)	5.5 (1.5)	5.6 (1.4)	0.7
Smokers/nonsmoker/former smoker	85/63/50	11/7/4	0.7
Vitamin D, 25(OH)D3 (nmol/L)	46.6 (30.9–62.7)	11.4 (8.9–11.4)	—

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

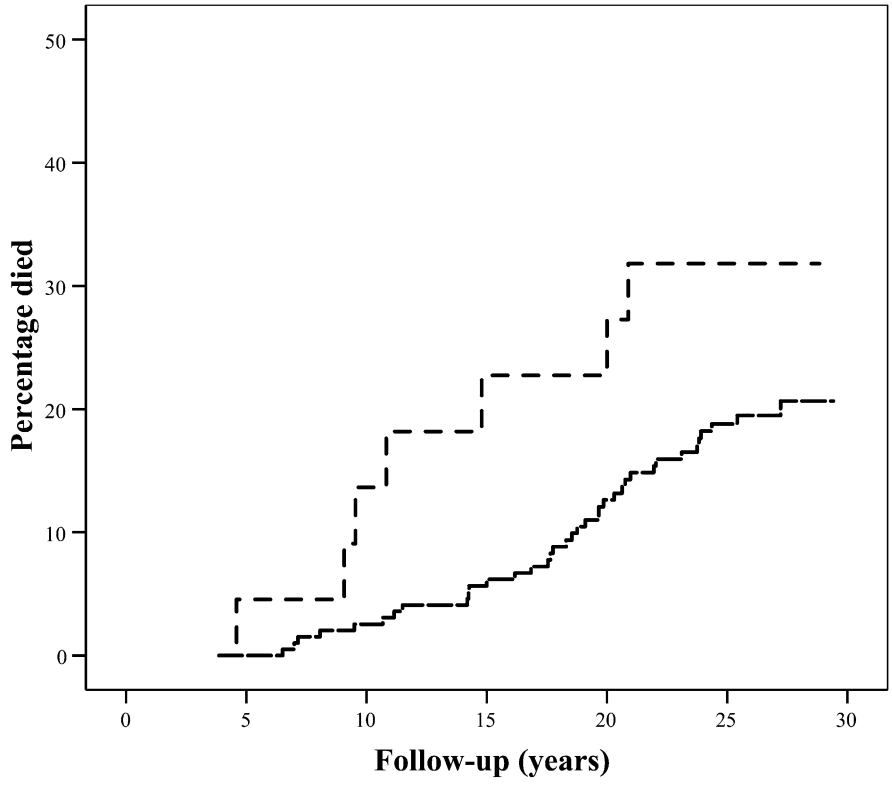

Figure 1—*Kaplan-Meier curves of all-cause mortality in 220 type 1 diabetic patients in accordance with a vitamin D level equal to and below or above the lower 10% percentile, 25(OH)D3 = 15.5 nmol/L. Full black line, 25(OH)D3 >15.5 nmol/L; dashed black line, 25(OH)D3 ≤15.5 nmol/L.*

A Cox proportional hazards model showed that low vitamin D levels at baseline did not predict the development of micro- or macroalbuminuria (unadjusted HR 1.1 [0.5–2.4], $P = 0.8$ and HR 1.3 [0.3–5.4], $P = 0.7$, respectively).

A total of 192 (80%) patients developed background retinopathy, and 18 (82%) of the patients had vitamin D levels equal to or below the lower 10% percentile. Of the 192 patients, 34 (15%) patients progressed to proliferative retinopathy, and one of these patients had low vitamin D level at baseline, corresponding to 5%. Vitamin D levels equal to or below the lower 10% percentile at baseline did not predict development of background retinopathy or proliferative retinopathy (HR 1.1 [0.7–1.7], $P = 0.8$ and HR 3.1 [0.4–22.9], $P = 0.3$, respectively).

After adjusting for progression promoters, the associations between severe vitamin D deficiency at baseline and development or progression of microvascular complications weakened further.

CONCLUSIONS—In this 26-year prospective observational follow-up study, we found very low levels of plasma 25(OH)D3 (equal to or below the 10% percentile) after onset of diabetes to be a strong and independent predictor of all-cause mortality in type 1 diabetic patients. This association was not only independent of glycemic control and conventional cardiovascular risk factors, but also independent of UAER. Severe vitamin D deficiency at baseline did not predict development or progression of microvascular complications in the eye and kidney.

Our finding of an association between severe vitamin D deficiency and increased risk of mortality complement recent data from epidemiological studies suggesting similar associations in other populations. For the general population, a cross-sectional study of 13,331 participants from the National Health and Nutrition Examination Survey (NHANES) III (2) showed low vitamin D levels to be associated with all-cause mortality. A study of mainly nondiabetic CKD patients (16) found vitamin D to independently predict all-cause mortality and increased risk of progression to dialysis. Also among patients with nondiabetic end-stage renal disease, low levels of vitamin D have been associated with all-cause mortality (17).

In healthy subjects, vitamin D deficiency mainly results from inadequate sunlight exposure, skin color, and inadequate nutritional supply of vitamin D–containing foods. Seasonal variations in vitamin D levels occur depending on geographic latitude and sun exposure in particularly. A study (18) done in 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%. Furthermore, several conditions such as obesity and absorption, liver, or kidney disorders pose an increased risk of developing vitamin D deficiency.

The mechanisms of action behind the increased mortality risk seen among patients with the lower 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 noncalcemic pleiotropic effects. Activation of the vitamin D receptor is associated with suppression of the RAAS (19), cardiac myocyte hypertrophy (20), vascular calcification, and atherosclerosis lowering, anti-inflammatory (21), and immunomodulatory actions. Also, an inverse relationship is found between vitamin D and increased incident risk of certain cancers as well as a higher mortality from these cancers (1).

Diabetic patients have a higher rate of cardiovascular morbidity and mortality compared with the general population. In a 10 year follow-up study of a cohort of 593 normoalbuminuric patients with type 1 diabetes, we have previously shown that more than one-third died of known cardiovascular causes and 25% died of unknown, potentially cardiovascular causes (4), hence a large number of the observed deaths in the cohort of the current study are likely to be from cardiovascular causes.

In a cross-sectional study of type 2 diabetic patients with mild kidney impairment, vitamin D deficiency was shown to be strongly associated with a higher prevalence of manifest cardiovascular disease when compared with normal vitamin D status (22).

Several of the above mentioned pathways may be important mechanisms in cardiovascular health. In a recent study of type 2 diabetic patients (23), which investigated the mechanism by which vitamin D deficiency mediates increased risk of

cardiovascular disease, investigators found a reduced vitamin D receptor signaling to be a potential mechanism underlying increased foam cell (macrophages that ingested oxidized LDL) formation and accelerated cardiovascular disease in diabetic compared with nondiabetic patients.

Given the observational design, the current study does not elaborate further on underlying mechanisms but indirectly adds to the increasing amount of data suggesting that vitamin D substitution might be a potential therapeutic target to prevent vascular disease progression. However, it is not possible to rule out that low levels of vitamin D may result from a single yet unidentified factor that is at the same time responsible for the increased risk seen in this study.

The pathogenesis behind microvascular complications in diabetes is complex and thought to involve multiple pathways. Development of microalbuminuria in diabetic patients is closely associated with an increased risk of both renal and cardiovascular disease. It has been suggested that microalbuminuria often regresses to normoalbuminuria, but in this cohort, spontaneous and permanent regression to normoalbuminuria occurred in only 16% of the patients progressing to microalbuminuria, whereas 34% progressed to persistent macroalbuminuria during follow-up (24). Of particular importance to diabetic nephropathy is an activation of the intrarenal RAAS and the proinflammatory nuclear factor-κB pathway, both promoting progressive renal damage. In a post hoc analysis, Agarwal et al. (10) found that administration of a VDRA compared with placebo caused reduction in albuminuria in nondiabetic CKD as measured by a dipstick method ($P = 0.004$). Importantly, the effects appeared to be independent of concomitant therapies to inhibit the RAAS. Recently the VITAL study, a randomized controlled clinical trial with 281 type 2 diabetic patients with diabetic nephropathy, has shown that administration of a VDRA (paricalcitol) in addition to blockade of the RAAS causes sustained reduction in albuminuria and thereby potentially has clinically relevant renoprotective effects in patients with diabetic nephropathy (11).

A cross-sectional study of 581 type 2 diabetic patients shows significant association between the existence of proliferative retinopathy and a decrease in 25(OH)D3. Also, investigators found a decrease in 25(OH)D3 according to the number of microvascular complications present (25). A cross-sectional design does not contribute to clarification on causality and effect, but fuels speculation that low levels of vitamin D might be a risk marker of development or progression of both diabetic nephropathy and/or retinopathy. In this study, however, we did not find low 25(OH)D3 levels to significantly predict development or progression of microvascular complications. This could be because of the lack of power based on a low number of events as the HR for both retinopathy and albuminuria was above 1 in patients with severe vitamin D deficiency. It is also possible that a potentially damaging effect of low vitamin D is offset by optimized patient treatment aiming at improving blood glucose and lowering blood pressure inclusive of RAAS blockade.

In our study, severe vitamin D deficiency was defined as the lower 10% percentile [plasma 25(OH)D3 ≤15.5 nmol/L] in both men and women. International consensus is lacking in regard to definitions of what vitamin D levels are to be regarded as normal, insufficiency, and deficiency. The limits for a physiological optimal vitamin D level are still a matter of debate in the literature. Although 25(OH)D3 is shown to be stable in stored samples (15), storing could affect absolute concentrations because of evaporation, thus we arbitrarily chose the lower 10% percentile rather than an absolute value. We have previously used the same method to define the cutoff in a follow-up study in type 2 diabetic patients (3). Furthermore, we have recently analyzed plasma 25(OH)D3 in fresh samples from 200 type 2 diabetic patients and we found the lower 10% percentile in these patients to deviate only 0.1 nmol/L from the Danish national definition of severe vitamin D deficiency existing at the time.

The stability of plasma 25(OH)D3 levels in our samples was tested before analysis as previously described. No statistically significant difference in levels was found when compared according to years of storage.

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

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, which could be related to outdoor activity, sun exposure and thereby levels of vitamin D. Vitamin D levels are also influenced by nutritional status. Unfortunately no nutritional parameters were available except BMI, which was not related to vitamin D levels (data not shown). We were therefore not able to adjust for any of these possible cofounders, but in general, the patients were young and healthy apart from newly diagnosed type 1 diabetes.

More observational studies are needed to confirm this finding, but as mentioned, we have performed the same analysis in a cohort consisting of type 2 diabetic patients and found similar results in regards to all-cause mortality and development/progression of diabetic nephropathy. Furthermore, in the study comprising type 2 diabetic patients, very low levels of 25(OH)D3 were also able to predict an increased risk of cardiovascular disease. Another limitation to the current study is that we do not have access to data on the cause of death.

In conclusion, with the present prospective follow-up study we are now able to show that baseline levels of 25(OH)D3 equal to or below the 10% percentile predict increased risk of all-cause mortality in type 1 diabetic patients, as already shown for the general population, in patients with nondiabetic CKD and for patients with type 2 diabetes (3). We were not able to demonstrate an association between baseline levels of 25(OH)D3 equal to or below the 10% percentile and development of microvascular complications in type 1 diabetic patients. Randomized controlled clinical trials administrating VDRA are necessary in order to prove causality between vitamin D status and survival prognosis in diabetic patients.

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C.J., H.-H.P., and P.R. designed the study on vitamin D in this cohort. P.H., P.R., and C.J. collected data. A.S. measured plasma 25(OH)D3 on baseline samples. C.J. analyzed data statistically. P.R., H.-H.P., and to some extent P.H. contributed to the analysis with suggestions

and advice. C.J. drafted the manuscript. P.H., H.-H.P., A.S., and P.R. critically reviewed and edited the manuscript.

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