Vitamin D levels and mortality in type 2 diabetes

Running title: Vitamin D levels and mortality in type 2 diabetes

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**Objective.** To evaluate vitamin D as 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 D₃, 25(OH)D₃ levels were determined by high performance liquid chromatography/tandem mass spectrometry on baseline samples.

Severe vitamin D deficiency was defined as the lower 10% 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 (eGFR), urinary albumin excretion rate (UAER) or HbA₁c 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; HR [95% CI] 1.96 [1.29-2.98]. The association persisted after adjustment for UAER, HbA₁c, diabetes duration and conventional cardiovascular risk factors; HR 2.03 [1.31-3.13]. Severe vitamin D deficiency was associated with increased cardiovascular mortality; HR 1.95 [1.11-3.44]. The association persisted after adjustment; HR 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.

Levels of vitamin D, 25(OH)D₃, vary considerably among individuals mainly due to differences in sun exposure, skin colour 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 analogue (VDRA)(2). Recently, low levels of vitamin D have been associated with an increased risk of cardiovascular disease(3) as well as all-cause(4) and cardiovascular mortality(5) in the general population.

An observational study on patients with mainly non-diabetic chronic kidney disease (CKD) stage 2-5 found low levels of vitamin D to independently predict 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 is 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
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vitamin D insufficiency may be involved in the pathogenesis of albuminuria(8,9). Diabetes is the leading cause of end-stage renal disease in the Western world and many diabetic patients will succumb to cardiovascular complications. Early identification of increased renal as well as vascular risk paves the way for early intervention, and thereby contributes to a desirable reduction in incidents of cardiovascular disease (CVD) and nephropathy among diabetes 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 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 <66 years of age and attending a tertiary referral centre at Hvidøre Hospital during 1987 as previously described(10). Type 2 diabetes was defined as either: 1) diabetes treated by diet alone or by diet combined with oral hypoglycaemic agents; 2) diabetes treated with insulin plus onset of diabetes after the age of 40 years and with patient BMI above normal at 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 four patients lacking baseline urine collections, were excluded. We additionally excluded 39 patients in whom samples for measurement of plasma 25(OH)D₃ were not available at baseline. The cohort thus consisted of 289 patients, mean age 54 years. Patients were classified as having normoalbuminuria, (n = 172, u-albumin excretion < 30mg/24 h), microalbuminuria, (n = 73, u-albumin excretion 30–299 mg/24 h) or macroalbuminuria, (n = 44, u-albumin excretion ≥ 300 mg/24 h) at baseline.

In a prospective observational study design, patients were followed until December 31st 2009 or until death (n = 196) or emigration (n = 3). The study was approved by the local ethics committee, conducted in accordance with the Helsinki Declaration, and all patients gave their informed written consent.

Baseline clinical and laboratory investigations. Patients were interviewed using the WHO cardiovascular questionnaire(11). Prior major cardiovascular events were defined as a history of stroke and/or myocardial infarction. Smoking was defined as persons smoking one or more cigarettes/cigars/pipes a day; all others were classified as non-smokers. UAER was measured by RIA from 24-h urine collections. Blood samples were drawn in the non-fasting state. HbA₁c 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. GFR was estimated by the 4 Variable Modification of Diet in Renal Disease equation, (http://www.nkdep.nih.gov/professionals/gfr_calculators/idms_si.html).

Measurements of plasma 25-Hydroxyvitamin D₃. After the patients had been at rest for at least 10 min in the supine position, blood samples for determination of plasma 25(OH)D₃ were collected in citrated tubes, centrifuged and plasma stored at −80°C. 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(13), making long-term epidemiologic studies of plasma 25(OH)D₃ 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)D₃ were determined by high performance liquid chromatography/tandem mass spectrometry (LC-MS/MS), (Department of Clinical Biochemistry, Lillebaelt Hospital, Vejle, Denmark). The CVs were 12.5% for a sample of 20nmol/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 January 1st 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 analysis of cardiovascular mortality was evaluated until 2004. All death certificates were reviewed independently by two observers and the primary cause of death recorded. All deaths until 2004 were classified as cardiovascular deaths unless an unequivocal non-cardiovascular 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 non-normally distributed variables, comparisons between groups were performed using the Mann-Whitney U test, whereas unpaired Students t-tests were used for comparisons between normally distributed variables.

A Chi-square 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, kidney function (eGFR, UAER) all which have previously been shown to be associated with increased all-cause and cardiovascular mortality.

We did additional uni- and covariate analysis using the Cox proportional hazards regression model on the cohort when divided according to the median diabetes duration of the group with low vitamin D levels (11 years). Results are described as hazard ratios (HR) with 95% Confidence Intervals (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 above or below the 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, USA).

**RESULTS**

The main baseline characteristics of the patients are given in table 1. The median (range) vitamin D concentration was 35.7 (5 to 136.7) nmol/l.

The patients were divided into two subgroups based on their vitamin D level at baseline being either in the lower 10% percentile or above. The cut off value for the lower 10% 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 HbA₁c 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 1A shows Kaplan-Meier curves for all-cause mortality in patients according to a vitamin D level below or above the lower 10% 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 to 2.98]. The association persisted after adjustment for UAER, eGFR, HbA1c, diabetes duration and conventional cardiovascular risk factors; adjusted HR 2.03 [1.31 to 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 show crude and adjusted Hazard Ratios 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 (48%) patients had vitamin D < 13.9 nmol/l and 87 (34%) patients had vitamin D levels above the 10% percentile, $p = 0.02$. Cardiovascular mortality according to a vitamin D level below or above the lower 10% percentile is illustrated in Figure 1B. Severe vitamin D deficiency was associated with increased cardiovascular mortality; unadjusted HR 1.95 [1.11 to 3.44], and after adjustment; HR 1.90 [1.16 to 3.10]. Dividing the entire cohort according to known duration of diabetes presented two new subgroups; a group consisting of patients with diabetes duration shorter than 11 years ( $n = 212$) and a group consisting of patients with a diabetes duration of 11 years or more ( $n = 77$). During follow-up until January 1st 2010, 137 (65%) and 59 (77%) patients died in the two groups respectively. Despite reduced power, the analysis shows a similar trend for low levels of vitamin D being predictive of all-cause mortality in both groups. Although weakened and no longer significant in either group, the trend is slightly stronger in patients with long duration (see 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 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 to 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 to 16.71]. After adjusting 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 (below the 10% 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 glycaemic control and conventional cardiovascular risk factors including known ischaemic heart disease, but also 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 diabetes patients, complement recent data from studies suggesting similar associations in the general population(4) and among patients with non-diabetic CKD(6) or ESRD(15).

A cross-sectional study on 13331 participants from the NHANES III found low vitamin D levels to be associated with all-cause mortality(4). Furthermore, a follow-up study on 1739 Framingham Offspring Study participants showed that the incidence of non-fatal cardiovascular events was increased among participants with low vitamin D levels(3).

A study on mainly non-diabetic CKD patients 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 particularly. 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).

Obesity is common among patients with type 2 diabetes. Vitamin D stores 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 are no linear association between BMI and vitamin D in these data. Diabetic patients are more prone to developing cardiovascular disease compared to 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 non-diabetic 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 VDR has clinically important pleiotropic effects involved in CVD development and mortality. Vitamin D has been associated with suppression of the renin-angiotensin-aldersterone 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 a 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 to non-diabetic 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(Christel Joergensen, pers. comm., ASN 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 due to 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(OH)₂D₃ is shown to be a negative endocrine regulator of the RAAS on transcriptional level independent of calcium and PTH(19). Agarwal et al. analyzed data from three randomized controlled clinical trials investigating administration of oral paricalcitol in patients with CKD. They showed that paricalcitol compared to placebo caused reduction in albuminuria as measured by a dipstick method ($p = 0.004$). Importantly, the effects appeared to be independent of concomitant therapies to inhibit the RAAS(9). 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) and Dick de Zeeuw, pers. comm., ASN 2009).

Due to the circumstantial evidence on beneficial effects seen when 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 below 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 10% percentile (25(OH)D₃ <13.9 nmol/l) in both men and women. International consensus is lacking in regards to definitions of what vitamin D levels are to be thought of as normal, insufficiency and deficiency. 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(24), storing could affect absolute concentrations due to evaporation, thus we chose the 10% percentile. As mentioned, 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 comparing different years of storage.

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 CKD patients is known to predict increased all-cause and cardiovascular mortality(25). 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 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 which 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 this finding. Randomized controlled clinical trials administrating VDRA are necessary in order to prove causality between vitamin D status and survival prognosis in diabetic patients.

In conclusion, baseline levels of 25(OH)D$_3$ below the 10% percentile predict increased risk of all-cause and cardiovascular mortality in type 2 diabetic patients.

Baseline levels of 25(OH)D$_3$ below the 10% percentile do not predict progression to micro-or macroalbuminuria.

**Author contributions:** Christel Joergensen wrote manuscript. Mari-Anne Gall, Lise Tarnow and Peter Rossing researched data and reviewed/edited manuscript. Anne Schmedes measured 25(OH)D$_3$ on baseline samples. Hans-Henrik Parving reviewed/edited manuscript.

**AKNOWLEDGEMENTS**

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**REFERENCES**


**Table 1.** Baseline clinical and laboratory characteristics of 289 type 2 diabetic patients according to levels of 25(OH)D₃.

<table>
<thead>
<tr>
<th></th>
<th>25(OH)D₃ ≥ 13.9 nmol/l (n = 260)</th>
<th>25(OH)D₃ &lt; 13.9 nmol/l (n = 29)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>161/99</td>
<td>16/13</td>
<td>0.55</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.7 (8.9)</td>
<td>54.6 (9.6)</td>
<td>0.59</td>
</tr>
<tr>
<td>Known duration of diabetes (years)</td>
<td>6 (2.0-11.0)</td>
<td>11 (6.5-15.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retinopathy (nil/simplex/proliferative)</td>
<td>179/72/9</td>
<td>12/14/3</td>
<td>0.03</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>23 (9%)</td>
<td>3 (10%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>98 (38%)</td>
<td>10 (34%)</td>
<td>0.84</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.6 (4.9)</td>
<td>27.5 (5.5)</td>
<td>0.25</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>8.0 (1.8)</td>
<td>8.6 (1.8)</td>
<td>0.1</td>
</tr>
<tr>
<td>Nephropathy (normo/micro/macrouinaria)</td>
<td>158/66/36</td>
<td>14/7/8</td>
<td>0.14</td>
</tr>
<tr>
<td>UAER (mg/24 h)</td>
<td>18 (7-65.5)</td>
<td>31 (6-364)</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum Creatinine (µmol/l)</td>
<td>74 (64-88)</td>
<td>70 (62-90)</td>
<td>0.85</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>93 (26)</td>
<td>89 (29)</td>
<td>0.48</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>150 (23)</td>
<td>154 (24)</td>
<td>0.32</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>86 (12)</td>
<td>82 (15)</td>
<td>0.2</td>
</tr>
<tr>
<td>Serum Cholesterol (mmol/l)</td>
<td>6.3 (1.6)</td>
<td>6.1 (1.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>Serum HDL-cholesterol (mmol/l)</td>
<td>1.2 (1.0)</td>
<td>1.3 (1.7)</td>
<td>0.63</td>
</tr>
<tr>
<td>Serum Triglycerides (mmol/l)</td>
<td>1.85 (1.27-2.84)</td>
<td>1.45 (1.08-2.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>43.1</td>
<td>48.3</td>
<td>0.69</td>
</tr>
<tr>
<td>Vitamin D, 25(OH)D₃ (nmol/l)</td>
<td>38.6 (24.2-57.9)</td>
<td>11.0 (5.0-12.7)</td>
<td>-</td>
</tr>
</tbody>
</table>

Data are n, means (SD) or medians (IQR). UAER: urinary albumin excretion rate.
Table 2. Crude and adjusted Hazard Ratios for predictors of all-cause mortality

<table>
<thead>
<tr>
<th>Predictors of all-cause mortality</th>
<th>HR\textsubscript{crude} [95% CI]</th>
<th>HR\textsubscript{adj} [95% CI]</th>
<th>HR\textsubscript{adj} [95% CI]</th>
<th>HR\textsubscript{adj} [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>diabetes duration</td>
<td>diabetes duration ≥</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;11 years* (n=212)</td>
<td>11 years* (n=77)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.08 [1.06-1.11]</td>
<td>1.06 [1.05-1.10]</td>
<td>1.09 [1.06-1.12]</td>
<td>1.07 [1.02-1.11]</td>
</tr>
<tr>
<td>Sex (female vs. male)</td>
<td>0.73 [0.55-0.98]</td>
<td>0.76 [0.55-1.05]</td>
<td>0.95 [0.65-1.41]</td>
<td>0.68 [0.37-1.27]</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>1.02 [1.01-1.03]</td>
<td>1.01 [1.01-1.02]</td>
<td>1.01 [1.00-1.02]</td>
<td>1.00 [0.99-1.02]</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>1.12 [1.03-1.22]</td>
<td>1.08 [0.99-1.18]</td>
<td>1.22 [1.08-1.40]</td>
<td>0.99 [0.84-1.16]</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m(^2))</td>
<td>0.98 [0.98-0.99]</td>
<td>1.00 [0.99-1.00]</td>
<td>0.99 [0.99-1.00]</td>
<td>0.99 [0.98-1.01]</td>
</tr>
<tr>
<td>UAER (mg/24h)</td>
<td>1.61 [1.37-1.90]</td>
<td>1.54 [1.28-1.85]</td>
<td>1.67 [1.32-2.13]</td>
<td>1.45 [1.05-1.97]</td>
</tr>
<tr>
<td>Smoking (yes vs. no)</td>
<td>1.03 [0.77-1.36]</td>
<td>1.41 [1.05-1.89]</td>
<td>1.87 [1.30-2.68]</td>
<td>0.94 [0.52-1.68]</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>1.02 [1.01-1.04]</td>
<td>1.01 [0.99-1.02]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vitamin D, lowest 10% percentile</td>
<td>1.96 [1.29-2.98]</td>
<td>2.03 [1.31-3.13]</td>
<td>1.58 [0.83-3.03]</td>
<td>2.87 [1.41-5.87]</td>
</tr>
</tbody>
</table>

* Divided according to median diabetes duration in the patients with vitamin D levels below the lowest 10% percentile.

Adj.: Adjusted for the other variables in the table.

Column 2 and 3 show crude and adjusted Hazard Ratios, respectively, for predictors of all-cause mortality. Column 4 and 5 show Hazard Ratios for predictors of all-cause mortality when dividing the cohort according to diabetes duration.

UAER: log transformed urinary albumin excretion rate.

FIGURE LEGEND

Figure 1A and B. Figure A shows Kaplan-Meier curves of all-cause mortality in 289 type 2 diabetic patients according to a vitamin D level below or above the lower 10% percentile, (25(OH)D\(_3\) = 13.9 nmol/l). Black line, 25(OH)D\(_3\) < 13.9 nmol/l; dotted line, 25(OH)D\(_3\) ≥ 13.9 nmol/l. Log-rank test for overall difference, \(p = 0.002\). Figure B shows Kaplan-Meier curves of cardiovascular mortality in 289 type 2 diabetic patients according to a vitamin D level below or above the lower 10% percentile, (25(OH)D\(_3\) = 13.9 nmol/l). Black line, 25(OH)D\(_3\) < 13.9 nmol/l; dotted line, 25(OH)D\(_3\) ≥ 13.9 nmol/l. Log-rank test for overall difference, \(p = 0.015\).
Vitamin D levels and mortality in type 2 diabetes

A

B

Follow-up time (years)

Proportion died (%)

Follow-up time (years)

Proportion died (%)

0 5 10 15 20 25

0 10 20 30 40 50 60 70 80 90 100

0 20 40 60 80 100