

Vitamin D Levels and Asymptomatic Coronary Artery Disease in Type 2 Diabetic Patients With Elevated Urinary Albumin Excretion Rate

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OBJECTIVE—Coronary artery disease (CAD) is the major cause of morbidity and mortality in type 2 diabetic patients. Severe vitamin D deficiency has been shown to predict cardiovascular mortality in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS—We investigated the association among severe vitamin D deficiency, coronary calcium score (CCS), and asymptomatic CAD in type 2 diabetic patients with elevated urinary albumin excretion rate (UAER) >30 mg/24 h. This was a cross-sectional study including 200 type 2 diabetic patients without a history of CAD. Severe vitamin D deficiency was defined as plasma 25-hydroxyvitamin D (*p*-25[OH]D3) <12.5 nmol/L. Patients with plasma N-terminal pro-brain natriuretic peptide >45.2 ng/L or CCS ≥400 were stratified as being high risk for CAD (*n* = 133). High-risk patients were examined by myocardial perfusion imaging (MPI; *n* = 109), computed tomography angiography (*n* = 20), or coronary angiography (CAG; *n* = 86). Patients' *p*-25(OH)D3 levels were determined by high-performance liquid chromatography/tandem mass spectrometry.

RESULTS—The median (range) vitamin D level was 36.9 (3.8–118.6) nmol/L. The prevalence of severe vitamin D deficiency was 9.5% (19/200). MPI or CAG demonstrated significant CAD in 70 patients (35%). The prevalence of CCS ≥400 was 34% (68/200). Severe vitamin D deficiency was associated with CCS ≥400 (odds ratio [OR] 4.3, 95% CI [1.5–12.1], *P* = 0.005). This association persisted after adjusting for risk factors (4.6, 1.5–13.9, *P* = 0.007). Furthermore, severe vitamin D deficiency was associated with asymptomatic CAD (adjusted OR 2.9, 1.02–7.66, *P* = 0.047).

CONCLUSIONS—In high-risk type 2 diabetic patients with elevated UAER, low levels of vitamin D are associated with asymptomatic CAD.

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Coronary artery disease (CAD) is the major cause of morbidity and mortality in patients with type 2 diabetes. Diabetic patients have been shown to have an increased prevalence of subclinical CAD (1). Coronary calcium score

(CCS), a noninvasive screening method quantifying the extent of coronary artery calcification (CAC), is generally accepted as a marker of increased cardiovascular risk. CCS has been shown to correlate strongly with histopathologic CAD (2,3)

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and the development of adverse coronary events (4,5).

Results from cross-sectional studies examining the relation between low vitamin D levels and presence of CAD in the general population are conflicting (6,7). In type 1 diabetic patients, vitamin D deficiency has been shown to independently predict both prevalence and development of CAC (8). However, a study in type 2 diabetic patients with a history of cardiovascular disease (CVD) found a strong inverse association between low vitamin D levels and prevalent coronary, cerebrovascular, or peripheral CVD (9). Furthermore, low vitamin D levels have been associated with increased cardiovascular morbidity and mortality in the general population (10) and in patients with type 1 (8) and 2 (11) diabetes.

To expand our knowledge on the increased all-cause and cardiovascular mortality seen in type 2 diabetic patients with low vitamin D levels, the current study investigated the association between severe vitamin D (plasma 25-hydroxyvitamin D [*p*-25(OH)D3]) deficiency and the presence of elevated CAC and asymptomatic CAD in type 2 diabetic patients with elevated urinary albumin excretion rate (UAER) >30 mg/24 h.

RESEARCH DESIGN AND METHODS

In a cross-sectional study at Steno Diabetes Center from January 2007 to February 2008, we identified a cohort of 200 type 2 diabetic patients without prior diagnosed CAD or other known cardiac disease but with a high risk of CAD as indicated by persistent UAER >30 mg/24 h. A written invitation to participate in the study was sent to all patients aged 20–70 years from the outpatient clinic (*n* = 613, 69% were male, patients had a mean [SD] age of 47 [8] years). Seventy-two patients refused to participate. Patients were excluded (*n* = 341) if one or more of the following characteristics were present: normal UAER or nonpersistent elevated UAER, significant Q-waves in the 12-lead electrocardiogram,

and relative contraindications to computed tomography angiography or coronary angiography (CAG), including elevated plasma creatinine above the upper normal limit. All patients received multifactorial treatment for the prevention of CAD. The treatment included statins (94%), aspirin (90%), and blockade of the renin-angiotensin-aldosterone system (98%). The *p*-25(OH)D3 levels were determined by high-performance liquid chromatography/tandem mass spectrometry. Severe vitamin D deficiency was defined as *p*-25(OH)D3 <12.5 nmol/L in correspondence with the National Danish guidelines at the time of the study. Plasma N-terminal pro-brain natriuretic peptide (*p*-NT-proBNP) was analyzed by an immunoassay as previously described (12). Clinical measurements and results of the cardiac examinations have been described (13) and are therefore only outlined briefly in the current article. Coronary calcium scanning was performed during a single breath-hold using a 16 multidetector-row computed tomography scanner with 3-mm slice thickness with quantification of Agatston CCS (Heartbeat-CS, EBW; Philips Medical Systems, Andover, MA) (14). According to levels of *p*-NT-proBNP and CCS, patients were stratified into groups with high or low risk for CAD in the following manner: 1) Patients with *p*-NT-proBNP >45.2 ng/L (this cutoff value was the median *p*-NT-proBNP among the first 50 patients examined) or CCS ≥400 were defined as high risk (*n* = 133). 2) All other patients were considered low risk, i.e., patients assumed not to have CAD (*n* = 67). High-risk patients were examined by myocardial perfusion imaging (MPI) (*n* = 109), computed tomography angiography (*n* = 20), or CAG (*n* = 86), according to our study referral algorithm for patients with abnormal results of the noninvasive tests for further invasive examination (13). MPI was performed using a standard 2-day protocol with ^{99m}Tc-Tetrofosmin (600–900 MBq) injected at rest and at peak stress with intravenous dipyridamole (0.6 mg/kg over 4 min). CAG was performed according to standard techniques. Coronary artery stenosis was defined as left main stem luminal diameter stenosis >50% or luminal stenosis >70% of the left anterior descending, right, or left circumflex coronary artery. Elevated CAC was defined by CCS ≥400. Significant CAD was defined as the presence of one or more significant myocardial perfusion defects on MPI or one or more significant major epicardial coronary artery

stenoses on CAG. All patients had normal *p*-creatinine levels and no recent illnesses or history of liver disease. The study was approved by the local ethics committee, and all patients gave written informed consent.

Statistical analysis

Variables with skewed distribution are expressed as medians (interquartile range); data for all other variables are expressed as means (SD). Non-normally distributed variables were log₁₀-transformed before analysis. Because CCS was highly skewed with values of zero, log₁₀ (CCS + 1) was used for analysis. The patients were divided into two groups, in accordance with a vitamin D level ≥ or <12.5 nmol/L. Comparisons between groups were performed using an unpaired Student *t* test. The Pearson χ^2 test was used to compare non-continuous variables. The association of severe vitamin D deficiency with the presence of significant CAD or CCS ≥400 was assessed by logistic regression model and expressed as unadjusted and adjusted odds ratio (OR) with 95% CIs. Covariate adjustments were made for sex, age, and conventional cardiovascular risk factors (systolic blood pressure, *p*-total cholesterol, *p*-creatinine, and smoking). Two-tailed *P* values ≤0.05 were considered statistically significant. All statistical calculations were performed using SPSS for Windows, version 14.0 (SPSS Institute, Inc., Chicago, IL).

RESULTS—The clinical baseline patient characteristics are shown in Table 1. Median (range) vitamin D level was 36.9 (3.8–118.6) nmol/L. The prevalence of severe vitamin D deficiency was 9.5% (19/200). In linear regression analyses, vitamin D level was negatively associated with BMI ($R = -0.26$, $P < 0.01$), and a weak positive association was found with age ($R = 0.159$, $P = 0.025$). Vitamin D levels were not associated with sex, blood pressure, HbA_{1c}, estimated glomerular filtration rate (eGFR), and UAER. Furthermore, neither eGFR nor UAER was associated with CCS scores or prevalence of significant CAD.

The prevalence of CCS ≥400 was 34% (68/200). Twelve of 68 patients (18%) with elevated CCS had severe vitamin D deficiency. In contrast, only 6 of 132 patients (4.5%) with CCS <400 had severe vitamin D deficiency ($P = 0.003$). In a logistic regression model, severe vitamin D deficiency was significantly associated with CCS ≥400 (unadjusted OR 4.3, 95% CI 1.5–12.1, $P = 0.005$). This association persisted after adjusting for age, sex, and conventional cardiovascular risk factors (*p*-total cholesterol, *p*-creatinine, HbA_{1c}, systolic blood pressure, and smoking) (4.6, 1.5–13.9, $P = 0.007$). Among 133 high-risk patients with elevated NT-proBNP or CCS ≥400, significant CAD was demonstrated by MPI or CAG in 70 patients. Of these 70

Table 1—Clinical characteristics of 200 type 2 diabetic patients without a history of cardiovascular disease

	All patients	25(OH)D3 ≥12.5 nmol/L	25(OH)D3 <12.5 nmol/L	<i>P</i>
<i>n</i>	200	181	19	
Sex (male/female)	152/48	135/46	17/2	0.1
Age (years)	59 (9)	59 (9)	60 (5)	0.5
Diabetes duration (years)	32.6 (5.8)	12.5 (7.4)	15.5 (6.5)	0.1
BMI (kg/m ²)	32.6 (5.8)	32.4 (5.7)	33.8 (6.3)	0.3
HbA _{1c} (%)	7.9 (1.3)	7.8 (1.3)	8.4 (1.4)	0.05
Urinary albumin excretion (mg/24 h)	103 (39–230)	43 (41–45)	42 (39–44)	0.2
<i>p</i> -Creatinine (μmol/L)	76 (18)	77 (19)	74 (14)	0.5
eGFR (mL/min/1.73 m ²)	90 (25)	90 (25)	96 (24)	0.3
Systolic blood pressure (mmHg)	130 (17)	130 (17)	129 (22)	0.8
Total cholesterol (mmol/L)	3.9 (0.9)	4.0 (0.9)	3.8 (1.1)	0.6
Current smoker (%)	59 (30)	54 (30)	5 (26)	0.7
<i>p</i> -NT-proBNP (ng/L)	48.7 (18.6–95.0)	45.8 (18.6–91.5)	68.6 (12.7–241.5)	0.3
CCS	183 (6–604)	170 (4–534)	638 (194–1,693)	0.02
Significant CAD (%)	70 (35)	60 (33)	10 (53)	0.1
Vitamin D (nmol/L)	36.9 (21.9–52.1)	39.1 (27.3–54.0)	11.0 (6.3–11.8)	—

Data are *n* (%), mean (SD), or median (interquartile range).

patients, 10 had severe vitamin D deficiency. The prevalence of significant CAD was increased in the patients with severe vitamin D deficiency, although this was not statistically significant ($P = 0.08$) (Fig. 1). In a logistic regression model, severe vitamin D deficiency was associated with significant asymptomatic CAD (unadjusted OR 2.24, 0.87–5.81, $P = 0.097$). After adjustment, the OR was 2.9 (1.02–7.66, $P = 0.047$). Adjustment for interaction between vitamin D levels and season at time of study did not change the effect of vitamin D on CAD.

Neither moderate vitamin D deficiency ($p\text{-}25(\text{OH})\text{D}3 = 12.5\text{--}24.9$ nmol/L) nor vitamin D insufficiency ($p\text{-}25(\text{OH})\text{D}3 = 25.0\text{--}49.9$ nmol/L) was significantly associated with $\text{CCS} \geq 400$ or increased prevalence of subclinical CAD.

CONCLUSIONS—In this cross-sectional study including 200 asymptomatic type 2 diabetic patients with elevated UAER and no history of CAD, severe vitamin D deficiency was associated with subclinical CAD evaluated as $\text{CCS} \geq 400$ and with significant CAD detected by MPI or CAG. Our findings add to those of our previous prospective study in which low levels of vitamin D were associated with increased cardiovascular mortality in type 2 diabetic patients who had not undergone cardiovascular investigation.

CCS is a continuous measurement of the coronary arteries atherosclerotic burden, and CCS has been shown to be strongly correlated with histopathologic CAD (2,3).

The first large prospective observational study of CCS in diabetic patients

and controls was performed by Raggi et al. in 2004 (15), who demonstrated that CCS is highly associated with all-cause mortality. Of note, low CCS in this study was associated with a low rate of mortality similar to that of controls. Later studies have confirmed and extended this association in asymptomatic diabetic patients without suspected CVD (16–18). In addition, in diabetic patients with proteinuria, a threshold ($\text{CCS} \geq 400$) for clinical significant disease exists (19). For symptomatic patients, the method is somewhat more controversial (20); however, in these patients, a high CCS has been reported to identify symptomatic patients with a high risk of structural coronary artery stenosis as determined by CAG, whereas a low CCS accurately excluded patients with significant coronary artery stenosis (<1%) (21). Subsequently, CCS was suggested by Beller (22) to be valid in risk assessment and screening for asymptomatic CAD.

The association between a low vitamin D level and $\text{CCS} \geq 400$ seen in the current study complements data correlating $p\text{-}25(\text{OH})\text{D}3$ to an increased prevalence or incidence of markers of subclinical CVD. A recent study in 1,370 primarily nondiabetic subjects found 25(OH)D3 levels to be inversely associated with the level of developing CAC (7). The same study found a trend toward an increase in magnitude of this association among participants with impaired kidney function. In 390 consecutive patients with type 2 diabetes, without advanced chronic liver or renal disease, and not taking medications or supplements known to affect vitamin D metabolism, low levels of vitamin D were found to be strongly and independently associated with increased carotid intima-media thickness, a marker of subclinical CVD (23).

Our finding of an association between low vitamin D levels and asymptomatic significant CAD also complements data suggesting an association between hypovitaminosis D and known CVD in the general population (10) and in type 1 diabetic patients (8). In addition, a study of 459 type 2 diabetic patients showed a strong inverse association between 25(OH)D3 levels and prevalent CVD (9). However, some of these patients, unlike the patients in the current study, had a history of CVD. Furthermore, as indicated above, in a prospective observational follow-up study, we found low levels of vitamin D to independently predict cardiovascular mortality among type 2 diabetic patients (11). Unlike in the present cross-sectional study,

in which we have analyzed 25(OH)D3 in fresh plasma samples, the samples used for vitamin D measurements in our previous follow-up study had been stored for many years before analysis. These patients were not examined in regard to CVD, and data were not available in regard to comorbidities, level of physical activity, and seasonal variation in 25(OH)D3. We were therefore not able to rule out the possibility that the low 25(OH)D3 levels were due to such possible confounders. The current study has shown that severe vitamin D deficiency is associated with subclinical CAD in 200 asymptomatic and otherwise healthy type 2 diabetic patients. This finding was not affected by adjustment for interaction between the vitamin D levels and the season of blood sampling for 25(OH)D3 analysis (data not shown).

The exact mechanisms of action behind the increased prevalence of asymptomatic CAD among subjects with low vitamin D levels are unclear. Vitamin D is primarily known for its role in the regulation of the calcium homeostasis in the body. A growing body of evidence indicates that vitamin D through activation of the vitamin D receptor (VDR) exerts extraskelatal pleiotropic effects beneficial to cardiovascular health. Activation of the VDR is associated with suppression of the renin-angiotensin-aldosterone system (24), cardiac myocyte hypertrophy (25), and vascular calcification together with atherosclerosis-lowering, anti-inflammatory (26), and immunomodulatory actions. Clinical data show that administration of a VDR activator causes a reduction in serum levels of inflammatory markers involved in the acute inflammatory response (27,28). Secondary hyperparathyroidism triggered by hypovitaminosis D can also elicit an acute phase response and thereby promote development of CVD, providing a plausible explanation for how hypovitaminosis D is a possible risk factor for CVD. Animal models are supportive of these considerations, where vascular calcification is prevented by calcitriol doses sufficient to correct secondary hyperparathyroidism (29). Interactions between bone and vitamin D may also mediate increased deposition of calcium in the arterial wall mediated by molecules and hormones released by bone (30). However, a recent study investigating the mechanism by which vitamin D deficiency may mediate increased risk of CVD found a reduced VDR signaling to be a potential mechanism underlying increased foam cell formation and accelerated CVD in type 2 diabetic

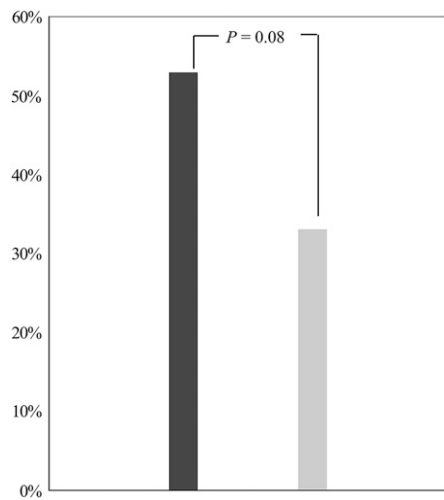


Figure 1—Prevalence of significant CAD among all 200 patients in accordance with vitamin D level. Black bar, 25(OH)D3 <12.5 nmol/L; gray bar, 25(OH)D3 ≥12.5 nmol/L.

patients compared with nondiabetic patients (31). Figure 1 shows the prevalence of significant CAD among all 200 patients according to vitamin D deficiency status in our present study. Although this prevalence is probably a minimum estimate because not all patients underwent extensive examinations aimed at subclinical CAD, the prevalence of significant CAD was considerably higher in the patients with severe vitamin D deficiency, albeit this difference did not reach statistical significance. Furthermore, in the logistic regression analysis, severe vitamin D deficiency was significantly associated with CAD even after adjustment for known confounders, suggesting the possibility of vitamin D playing an independent role in the development of CAD.

In healthy subjects, vitamin D deficiency mainly results from inadequate sunlight exposure, dark 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 particular. A study of the general population in a Northern European country showed a seasonal variation in the prevalence of vitamin D insufficiency of 73 and 29% during winter and summer, respectively. The difference for vitamin D deficiency was likewise found to be 8 and 1%, respectively (32). Furthermore, several conditions, such as obesity, disorders of intestinal absorption, and liver or kidney function, pose an increased risk of developing vitamin D deficiency. However, as seen in Table 1, the mean BMI for our patients with low vitamin D levels was not significantly different compared with the patients with higher vitamin D levels. There was no association between vitamin D level and renal function or UAER, and there was no association between CCS and UAER or eGFR. However, all patients were selected to have normal *p*-creatinine levels to avoid radiocontrast problems (mean [SD] eGFR of 90 [25] mL/min/1.73 m²). All patients had an elevated UAER, mostly in the microalbuminuric range. Had the range of eGFR or UAER been wider, including normal and abnormal values, it is possible there would have been significant associations.

International consensus is lacking in regard to a definition of plasma vitamin D levels representative of normal, insufficiency, and deficiency. In our study, severe vitamin D deficiency was defined as *p*-25(OH)D₃ <12.5 nmol/L in both men and women in correspondence with the National Danish guidelines at the time of the

study, but further studies are warranted to more clearly establish physiologic and pathologic vitamin D levels in health and disease.

Our study has some strengths and limitations. This cohort of type 2 diabetic patients underwent detailed and comprehensive testing including CAG to detect asymptomatic CAD. Therefore, this study contributes to future identification of patients in whom aggressive investigations and treatment aimed at CAD should be considered. Given the cross-sectional design, the current study does not elaborate further on the causative nature of the associations made, but it does add to an increasing amount of data suggesting that vitamin D substitution might be a potential therapeutic mean to prevent cardiovascular disease development or progression. We did not measure parathyroid hormone levels, and therefore we were not able to adjust for this potential confounder in our analysis. Prospective, randomized, placebo-controlled trials administering a VDR activator are needed to examine causality between vitamin D status and CAD in diabetic patients.

In conclusion, we have shown that low levels of vitamin D are associated with asymptomatic CAD in asymptomatic high-risk type 2 diabetic patients with elevated UAER.

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No potential conflicts of interest relevant to this article were reported.

C.J. wrote the manuscript and is the guarantor of this study. H.R., P.R.H., N.W., C.L.P., and P.K.J. researched data and reviewed and edited the manuscript. A.S. measured *p*-25(OH)D₃. K.W. measured *p*-NT-proBNP. H.-H.P. and P.R. reviewed and edited the manuscript.

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