Vitamin D Affects Survival Independently of Vascular Calcification in Chronic Kidney Disease

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Background and objectives: Cardiovascular disease is the main cause of mortality in chronic kidney disease (CKD) patients. Vitamin D might have beneficial effects on vascular health. The aim of this study was to determine the prevalence of vitamin D deficiency (25-hydroxyvitamin D [25D] ≤ 15 ng/ml) and insufficiency (25D levels between 16 and 30 ng/ml) in a cohort of patients at different CKD stages and the relationships between vitamin D serum levels, vascular calcification and stiffness, and the mortality risk.

Design, setting, participants & measurements: One hundred forty CKD patients (85 men, mean age 67 ± 12 yr; CKD stages 2 [8%], 3 [26%], 4 [26%], 5 [7%], and 5D [33%]) were allocated for a prospective study. Serum levels of 25D and 1,25-dihydroxyvitamin D, aortic calcification score, and pulse wave velocity (PWV) were evaluated.

Results: There was a high prevalence of vitamin D deficiency (42%) and insufficiency (34%). Patients with 25D ≤ 16.7 ng/ml (median) had a significantly lower survival rate than patients with 25D >16.7 ng/ml (mean follow-up, 605 ± 217 d; range, 10 to 889; P = 0.05). Multivariate adjustments (included age, gender, diabetes, arterial pressure, CKD stage, phosphate, albumin, hemoglobin, aortic calcification score and PWV) confirmed 25D level as an independent predictor of all-cause mortality.

Conclusions: Vitamin D deficiency and insufficiency were highly prevalent in this CKD cohort. Low 25D levels affected mortality independently of vascular calcification and stiffness, suggesting that 25D may influence survival in CKD patients via additional pathways that need to be further explored.


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physiologic doses (i.e., just enough to correct secondary hyperparathyroidism) protect against aortic calcification (21). In a CKD setting, a recent study in adult hemodialysis patients described an association between 25D deficiency and arterial stiffness (13), whereas dialyzed children showed a bimodal association between 1,25D levels and vascular calcification and stiffness (22).

We therefore decided to determine the prevalence of vitamin D deficiency and insufficiency in a cohort of adult patients at different stages of CKD. Moreover, we investigated the relationships between vitamin D serum levels, vascular calcification and stiffness, and the risk of mortality in this population.

Materials and Methods
Patient Selection
Over an 18-mo period (from January 2006 to June 2007), a total of 140 Caucasian CKD patients were recruited from the nephrology department's outpatient clinic at Amiens University Hospital. All patients gave their informed, written consent. The study was approved by the local Institutional Review Board and was performed in accordance with the ethical principles of the Declaration of Helsinki.

Included patients had to be over the age of 40, with a confirmed diagnosis of CKD (defined as being on hemodialysis or having two previous, estimated creatinine clearances—calculated according to the Cockcroft and Gault formula [23]—with an interval of 3 to 6 mo and values <90 ml/min/1.73 m²). CKD stage 5D patients had been receiving thrice-weekly hemodialysis for at least 3 mo. Exclusion criteria included the presence of chronic inflammatory disease, atrial fibrillation, complete heart block, abdominal aorta aneurysm, aortic and/or femoral artery prosthesis, primary hyperparathyroidism, kidney transplantation, and any acute cardiovascular event in the 3 mo before screening for inclusion.

Study Protocol
All patients were hospitalized for the day for laboratory blood tests, blood pressure (BP) measurement, a pulse wave velocity (PWV) determination, lateral lumbar x-ray, and multislice spiral CT scanning. For a given patient, all examinations were performed between 9:00 a.m. and 2:00 p.m. on the same day. Hemodialysis patients were preferentially seen on a dialysis-free day or the morning before the dialysis session. A patient interview focused on comorbidities and the personal disease history. The patients' medical charts were reviewed to record concomitant medications.

Laboratory
Blood samples were collected the morning before the other investigations. Selected variables were measured after the samples had been frozen and stored at −80°C. Serum calcium, phosphate, albumin, cholesterol, hemoglobin, creatinine (Scr), and C-reactive protein were analyzed in an on-site biochemistry laboratory using standard auto-analyzer techniques (Roche Diagnostics Modular IIP). Serum intact parathyroid hormone (iPTH 1 to 84) and 25D levels were determined using chemiluminescent immunoassays (respectively, the Liaison N-tact PTH CLIA and the Liaison 25OH Vitamin D TOTAL CLIA [which measures both D₂ and D₃]; Diasorin, Stillwater, MN). 1,25D serum levels were determined in an RIA with a 95% reference value for healthy volunteers of 25.1 to 66.1 pg/ml (125I RIA Kit from Diasorin). Serum cystatin C levels were determined by immunonephelometry (N Latex Cystatin C; Dade Behring Marburg, Germany). To better describe glomerular filtration, we calculated the estimated glomerular filtration rate (GFR) combining Scr and CysC measurements for all nondialyzed patients according to the following, recently published (24) “CKD-epi” equation: 177.6 × Scr⁻⁰.²⁰ × CysC⁻⁰.⁶⁵ × Age⁻¹.₂⁰ × (0.82 for female patients). For descriptive purposes, patients were then classified into CKD stages, according to the K/DOQI guidelines (25).

PWV Evaluation
Carotid-femoral PWV was determined automatically with a dedicated, validated device (Complior Colson; Createch Industrie, May, France), as described previously (26). PWV was evaluated by a trained physician with two pressure probes as formerly reported (27).

Abdominal Aorta Imaging with Plain Radiography
A technique similar to that described by Kauppila et al. was used to obtain images of the lower abdominal aorta and generate the aortic calcification score (28). All x-rays were reviewed by two investigators, and a consensus on the interpretation was reached in all cases.

Multislice Spiral CT Scan
All examinations were performed with a 64-detector CT scanner (Lightspeed VCT; GE Healthcare, Milwaukie, WI). The volume acquisition started at the aortic hiatus of the diaphragm and ended at the third lumbar vertebra. The scanning parameters were as follows: collimation, 64 × 0.625 mm; slice thickness, 0.625 mm; pitch, 1; gantry rotation speed, 0.5 s/rotation; tube voltage, 120 kV; tube current, 300 mA.

The volume acquisition was analyzed with commercially available software (Volume Viewer software, GE Healthcare). The abdominal aorta was segmented manually. To reduce errors caused by noise, a threshold of 160 UH was applied. The total calcification volume was calculated as the sum of all voxels in the remaining volume. The aortic calcification score was calculated as follows: [(total calcification volume) ÷ (aorta wall surface area) × 100]].

Survival
Death records were made prospectively, considering all patients that were included at least 1 yr before the study end date (June 30, 2008). Each medical chart was reviewed, and the cause of death was assigned by a physician on the basis of all of the available clinical information. For out-of-hospital deaths, the patient’s general practitioner was interviewed to gain pertinent information on the cause.

Statistical Analyses
Data are expressed as mean ± SD, median and range, or frequencies, as appropriate. For analytical purposes, patients were divided in two groups according to the median 25D level (i.e., 25D ≤ 16.7 ng/ml versus 25D > 16.7 ng/ml). Intergroup comparisons were performed using a χ² test for categorical variables and Student’s t-test or a Mann-Whitney test for continuous variables. Pearson’s correlation coefficient or Spearman’s rank correlation were used to assess the relationships between 25D levels and multiple variables. A Kaplan-Meier actuarial method was used to estimate overall survival in the 25D groups. The log-rank test was used to compare the survival curves. Univariate and multivariate analyses of mortality were performed by using a Cox proportional hazards model of death as a function of 25D levels. In the multivariate analysis, the predefined, noncumulative models included those variables significantly associated with death in univariate analyses and those variables of prognostic importance according to published observations. The limited number of events (n = 25) prevented us from including more than three variables for each model. A P value
of \( \leq 0.05 \) was considered to be statistically significant. All statistical analyses were performed using SAS software 9.1 (SAS Institute Inc., Cary, NC).

## Results

Table 1 shows the demographic, clinical and biochemical characteristics of the 140 analyzed patients.

In terms of serum 25D levels, 76% of the patients display either vitamin D deficiency (42%) or insufficiency (34%). Figure 1 illustrates the distribution of 25D and 1,25D serum levels by CKD stage. Serum 25D levels were similar for all CKD stages, whereas serum 1,25D levels were significantly lower in stage 5D patients \((P = 0.035)\). At enrolment, 36% of the patients were receiving vitamin D3 supplementation (either calcifediol [median dose, 14 \( \mu \)g/d; range, 5 to 32 \( \mu \)g/d] or cholecalciferol [median dose, 400 IU/d; range, 250 to 800 IU/d]), whereas only one individual was taking active vitamin D (\( \alpha \)-calcidiol) and bisphosphonate. When comparing patients grouped by study entry date (to evaluate for a possible seasonal bias), we did not find any significant difference in 25D levels between patients who entered during the summer/spring \((n = 67)\) and those who entered during the autumn/winter \((n = 73)\) \((19.7 \pm 12.3 \text{ versus } 21.3 \pm 14.8 \text{ ng/mL}, \text{respectively}; P = 0.669)\). Moreover, there was no difference between these two seasonal groups in terms of the proportion of patients taking vitamin D3 supplementation \((36\% \text{ for summer/spring and } 35\% \text{ for autumn/winter;} \ P = 0.845)\).

When comparing patients divided by the 25D median \((25D \leq 16.7 \text{ ng/mL versus } 25D > 16.7 \text{ ng/mL})\), we found only that patients with 25D \(\leq 16.7 \text{ ng/mL} \) presented significantly lower levels of serum albumin and were less likely to receive vitamin D supplements than patients with 25D \(> 16.7 \text{ ng/mL} \).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All ((n = 140))</th>
<th>25D (\leq 16.7 \text{ ng/mL (n = 71)})</th>
<th>25D (&gt; 16.7 \text{ ng/mL (n = 69)})</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67 ± 12</td>
<td>68 ± 13</td>
<td>66 ± 12</td>
<td>0.299</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>85 (61)</td>
<td>42 (59)</td>
<td>43 (62)</td>
<td>0.702</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>28 ± 6</td>
<td>28 ± 5</td>
<td>28 ± 7</td>
<td>0.646</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>153 ± 26</td>
<td>149 ± 27</td>
<td>157 ± 25</td>
<td>0.089</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>81 ± 12</td>
<td>80 ± 12</td>
<td>82 ± 12</td>
<td>0.387</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>59 (42)</td>
<td>32 (46)</td>
<td>27 (38)</td>
<td>0.317</td>
</tr>
<tr>
<td>Smoking habit, n (%)</td>
<td>55 (40)</td>
<td>24 (35)</td>
<td>31 (46)</td>
<td>0.221</td>
</tr>
<tr>
<td>Presence of CVD, n (%)</td>
<td>44 (31)</td>
<td>23 (32)</td>
<td>21 (30)</td>
<td>0.803</td>
</tr>
<tr>
<td>CKD stage, n (%)</td>
<td>2</td>
<td>11 (8)</td>
<td>6 (8.5)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Calcium, mMol/L</td>
<td>2.3 ± 0.2</td>
<td>2.3 ± 0.2</td>
<td>2.27 ± 0.19</td>
<td>0.390</td>
</tr>
<tr>
<td>Phosphate, mMol/L</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.5</td>
<td>1.3 ± 0.4</td>
<td>0.635</td>
</tr>
<tr>
<td>iPTH, pg/ml (median)</td>
<td>138 ± 138</td>
<td>150 ± 152</td>
<td>126 ± 122</td>
<td>0.537</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>12 ± 1.7</td>
<td>12 ± 1.9</td>
<td>12 ± 1.6</td>
<td>0.834</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>37 ± 6</td>
<td>36 ± 6</td>
<td>38 ± 6</td>
<td>0.030</td>
</tr>
<tr>
<td>C-reactive protein, mg/L (median)</td>
<td>11 ± 23</td>
<td>13 ± 29</td>
<td>9 ± 15</td>
<td>0.812</td>
</tr>
<tr>
<td>Total cholesterol, mMol/L</td>
<td>4.9 ± 1.2</td>
<td>5.0 ± 1.2</td>
<td>4.7 ± 1.0</td>
<td>0.066</td>
</tr>
<tr>
<td>Aortic calcification score on CT, %(^a) (median)</td>
<td>2.9 ± 3.0</td>
<td>3.1 ± 3.3</td>
<td>2.8 ± 2.7</td>
<td>0.910</td>
</tr>
<tr>
<td>Aortic calcification score on x-ray (scale 0-24)(^b\centernot c) (median)</td>
<td>6.2 ± 6.5</td>
<td>6.2 ± 6.7</td>
<td>6.0 ± 6.5</td>
<td>0.812</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>14 ± 4</td>
<td>15 ± 4</td>
<td>14 ± 4</td>
<td>0.701</td>
</tr>
<tr>
<td>Vitamin D supplementation, n (%)</td>
<td>50 (36)</td>
<td>18 (25)</td>
<td>32 (46)</td>
<td>0.009</td>
</tr>
<tr>
<td>25-hydroxyvitamin D, ng/ml (median)</td>
<td>20.5 ± 13.6</td>
<td>10.8 ± 3.9</td>
<td>30.5 ± 12.9</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Data are means ± SD and sometimes (median) for variables with non-Gaussian distribution, or number (frequency) for binary variables. BP, blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; CKD, chronic kidney disease; iPTH, intact-parathyroid hormone; CT, computed tomography; PWV, pulse wave velocity.

\(^a\)\(n = 129; ^b\)\(n = 122; ^c\) by lateral lumbar x-rays, as previously described.
Table 2 describes the correlations between 25D serum levels and several variables. The only significant linear correlation was between 25D serum levels and albumin.

During the study period (mean follow-up period, 605/11006217 d; median, 591; range, 10 to 889), 25 patients died (18 from cardiovascular causes, 5 from infectious diseases, and 2 from other causes). In the crude analysis (Figure 2), a 25D level of 16.7 ng/ml was a predictor of death ($P$ = 0.05). Age (relative risk [RR] = 1.06; 95% CI, 1.02 to 1.10), CKD stage 5D (RR = 4.6; 95% CI, 1.98 to 10.66), smoking status (RR = 2.23; 95% CI, 1.03 to 5.25), albumin (RR = 0.94; 95% CI, 0.89 to 1.0), hemoglobin (RR = 0.68; 95% CI, 0.54 to 0.87), aortic calcification score on CT (RR = 1.3; 95% CI, 1.16 to 1.44), and aortic calcification score on an x-ray (RR = 1.1; 95% CI, 1.02 to 1.13) were also associated with the risk of death in a univariate Cox regression. There was no association between 1,25D levels and mortality, even after adjustment for age, gender, the presence of diabetes, smoking status, systolic and diastolic BP values, CKD stages, vitamin D supplementation, aortic calcification, PWV, and serum albumin, hemoglobin, and phosphate levels.

Table 2. Correlations between serum 25D levels (log transformed) and baseline clinical characteristics, nutritional status markers, mineral metabolism, and arterial calcification/function

<table>
<thead>
<tr>
<th>Variable</th>
<th>$r$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.034</td>
<td>0.380</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.211</td>
<td>0.013</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>-0.021</td>
<td>0.799</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.024</td>
<td>0.777</td>
</tr>
<tr>
<td>Phosphate</td>
<td>-0.119</td>
<td>0.162</td>
</tr>
<tr>
<td>1,25D</td>
<td>0.035</td>
<td>0.733</td>
</tr>
<tr>
<td>iPTH</td>
<td>-0.132</td>
<td>0.123</td>
</tr>
<tr>
<td>Systolic arterial pressure</td>
<td>0.081</td>
<td>0.343</td>
</tr>
<tr>
<td>Diastolic arterial pressure</td>
<td>0.067</td>
<td>0.432</td>
</tr>
<tr>
<td>Aortic calcification score, CT</td>
<td>-0.104</td>
<td>0.241</td>
</tr>
<tr>
<td>Aortic calcification score, x-ray</td>
<td>-0.031</td>
<td>0.738</td>
</tr>
<tr>
<td>PWV</td>
<td>-0.074</td>
<td>0.384</td>
</tr>
</tbody>
</table>

25D, 25-hydroxyvitamin D; 1,25D, 1,25-dihydroxyvitamin D; iPTH, intact parathyroid hormone; CT, computed tomography; PWV, pulse wave velocity.

Discussion

The present study revealed a high prevalence of 25D deficiency and insufficiency in a cohort of patients with CKD. Most important, there was a significant relationship between low 25D levels and mortality, even after adjustment for age, gender, the presence of diabetes, smoking status, BP, CKD stage, serum albumin, hemoglobin, and phosphate levels.

![Figure 1. A) Serum levels of 25-hydroxyvitamin D (25D) and (B) serum levels of 1,25-dihydroxyvitamin D (1,25D) as a function of CKD stage (with dashed lines indicating the reference values). *$P$ < 0.05 for CKD stage 5D versus other groups.](image1)

![Figure 2. Crude patient survival as a function of vitamin D (25D) levels ($\leq$16.7 ng/ml or >16.7 ng/ml).](image2)
CKD patients are at particular risk of 25D deficiency because of a range of factors that do not directly depend on renal function; these include reduced sun exposure, impaired production of the 25D precursor molecule, and reduced dietary intake (29). The present study evidenced a positive correlation between 25D and albumin levels, in accordance with previous observations (30–32). Reduced albumin levels are frequently related to malnutrition, because the latter also lowers levels of vitamin D binding protein (VBP) (6). Because vitamin D metabolites have low aqueous solubility and are mainly bound to plasma proteins (essentially VBP), low plasma protein levels could have contributed to the low observed 25D levels. However, the fact that we did not evaluate proteinuria prevents us from drawing further conclusions in this respect. In contrast to 25D, circulating levels of 1,25D chiefly depend on the ability of renal 1-α hydroxylase to convert 25D into 1,25D. This ability is decreased by (1) a reduction in the nephron mass, and (2) the hyperphosphatemia-induced increase in levels of the phosphaturic hormone FGF-23, which both inhibits the production of 1,25D and increases its degradation (33). Thus, as renal failure progresses and renal production of 1,25D decreases, 25D availability may constitute a rate-limiting step in the production of 1,25D by nonrenal tissues, where it may act either in autocrine or paracrine pathways (6). In accordance with other recently reported data (34), 25D deficiency was a better predictor of death than 1,25D in our cohort of CKD patients. The observed lack of a relationship between 1,25D levels and mortality in the study population may be due to the fact that most patients presented very low levels of 1,25D, and could have attenuated a potential risk. These low levels of 1,25D might result (at least in part) from the very low concentrations of 25D (i.e., the 1,25D precursor) observed in these patients. Nevertheless, this observation may most likely reflect 25D’s advantageous characteristics as a biomarker (a more reproducible assay and a longer half-life) when compared with 1,25D, thus enabling more accurate measurement of exposure over time (6). In addition, it is possible that in CKD patients with markedly deficient renal production of 1,25D, the maintenance of adequate reserves of 25D may be especially important in maintaining VDR activation in cells that rely on autocrine pathways; this is the case for cultured human vascular smooth muscle cells (which have been shown to express functional 1-α hydroxylase [35]) and cultured human endothelial cells (in which the expression of the mRNA and protein for 1-α hydroxylase have been demonstrated [36]). It should be noted that the 25D assay used in the present study measures both ergocalciferol (D2) and cholecalciferol (D3). Hence, the observed high prevalence of vitamin D deficiency is unlikely to result from methodological limitations of the assay used here.

In addition, our current data did not show any association between 25D levels and aortic calcification or stiffness. In this regard, Shroff et al. have recently reported a bimodal association between vascular calcification and 1,25D levels in dialyzed children, but no association between 25D levels and the vascular measurements (22). London et al. observed that in adult hemodialysis patients, 1,25D and 25D levels were negatively correlated with aortic stiffness but not with vascular calcification (13). Our findings seem to suggest that 25D’s effect on cardiovascular mortality may be independent of vascular calcification and stiffness. Hence, other negative effects of vitamin D deficiency on the cardiovascular system may be involved. It has been previously reported that left ventricular hypertrophy in hemodialysis patients is associated with lower survival (37). Interestingly, there is also experimental evidence that VDR gene deletion may induce myocardial hypertrophy and fibrosis (38). The absence of vitamin D-mediated signal transduction and genomic activation reportedly results in cardiomyocyte overstimulation and increased contractility, which ultimately lead to cardiomyocyte hypertrophy (39,40). In fact, low serum 1,25D concentrations have been implicated in poorer clinical outcomes for end-stage chronic heart failure patients (41). Furthermore, low levels of 25D have been associated with heart failure and sudden cardiac death in the general population (40,42). In peritoneal dialysis patients, Wang et al. reported an
association between low 25D levels and left ventricular dilation (43). One must bear in mind that the active form of vitamin D (1,25D) has been shown to operate as a negative hormonal regulator of the renin-angiotensin system, which plays an important role in the cardiovascular system by modulating BP and heart mass (4). In line with these observations, the administration of a VDR activator has been shown to attenuate left ventricular abnormalities in Dahl salt-sensitive rats exposed to a high-salt diet (44). Thus, our findings further corroborate the notion that vitamin D deficiency may affect cardiovascular system and mortality via several pathways other than an increase in vascular calcification or stiffness. Unfortunately, the fact that an echocardiographic evaluation was not performed in the present study prevented us from drawing further conclusions.

It is noteworthy that 28% of the deaths observed in our CKD cohort were attributed to noncardiovascular causes. Indeed, 25D deficiency in the general population has been also associated with higher mortality from noncardiovascular causes (namely colon, prostate, and breast cancer (45)) and augmented susceptibility to aggressive forms of specific infectious diseases (such as tuberculosis (46)). In line with these findings, observational studies in the general population have found that taking ordinary doses of vitamin D supplements is associated with a decrease in all-cause mortality (47). Moreover, two different cohort studies on hemodialysis patients demonstrated that oral (48) or injectable (49) doses of VDR activators increased overall survival. Unfortunately, in these latter studies, 25D status was not determined, but it was probably deficient in the North American cohort (49).

The present study’s limitations include a relatively small cohort and limited follow-up, which may have affected the study power. Second, the conclusions may not apply to non-Caucasian populations living at different latitudes. In contrast, strong points include our assessment of vitamin D deficiency in patients with variable degrees of renal dysfunction, together with evaluation of important surrogate markers of cardiovascular health (namely, vascular calcification and PWV).

Our present findings are in line with recently published data that suggest (1) a high prevalence of 25D deficiency in CKD patients and (2) an association between 25D deficiency and mortality in the same population. Importantly, the effect of low 25D on mortality appeared to be independent of vascular calcification and stiffness, suggesting that 25D may influence survival in CKD patients via additional pathways that need to be further explored. The results highlight the imperative need for randomized clinical trials that evaluate the effects of vitamin D supplementation on mortality in CKD patients.

Disclosures
None.

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