25 (OH) Vitamin D Levels and Renal Disease Progression in Patients with Type 2 Diabetic Nephropathy and Blockade of the Renin-Angiotensin System

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Summary

Background and objectives Experimental studies show that 25 (OH) vitamin D is a suppressor of renin biosynthesis and that vitamin D deficiency has been associated with CKD progression. Patients with type II diabetes and CKD have an exceptionally high rate of severe 25 (OH) vitamin D deficiency; however, it is not known whether this deficiency is a risk factor for progression of diabetic nephropathy. This study aimed to investigate whether there is an association of 25 (OH) vitamin D deficiency with disease progression in type II diabetic nephropathy.

Design, setting, participants, & measurements 25 (OH) vitamin D levels were measured at baseline and 4 and 12 months in 103 patients included in a multicenter randomized controlled trial to compare the efficacy of combining an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker with the efficacy of each drug in monotherapy to slow progression of established diabetic nephropathy during 2006–2011. The primary composite endpoint was a >50% increase in baseline serum creatinine, ESRD, or death. All study participants were included in the analysis.

Results Fifty-three patients (51.5%) had 25 (OH) vitamin D deficiency (<15 ng/ml). After a median follow-up of 32 months, the endpoint was reached by 23 patients with deficiency (43.4%) and 8 patients without (16%). Multivariate Cox regression analysis adjusted for urinary protein/creatinine ratio, estimated GFR, and baseline aldosterone showed that 25 (OH) vitamin D deficiency was associated with the primary endpoint (hazard ratio, 2.88; 95% confidence interval, 1.84 to 7.67; P=0.04).

Conclusions These results show that 25 (OH) vitamin D deficiency is independently associated with a higher risk of the composite outcome in patients with type II diabetic nephropathy.

Introduction

The spectrum of activity of vitamin D is much broader than its effect on calcium and phosphate metabolism and bone physiology (1,2). Vitamin D is involved in cell differentiation and antiproliferative pathways and plays a key role in immunity, vascular function, cardiomyocyte health, insulin resistance, and modulation of the renin-angiotensin system (RAS) (3–5). Consequently, vitamin D deficiency has been associated with cancer, hypertension, diabetes, heart failure, and a higher frequency of cardiovascular disease and cardiovascular mortality (3–7).

As renal function declines, serum levels of 1,25 (OH) vitamin D decrease progressively, leading to active vitamin D deficiency. Somewhat less commonly recognized is the high prevalence of nutritional vitamin D deficiency in patients with renal disorders. Serum 25 (OH) vitamin D levels begin to decrease in stage 2 CKD (8,9), and 25 (OH) vitamin D deficiency is prevalent in all subsequent stages of CKD (6,10–13), including ESRD. Proteinuria may be accompanied by high urinary loss of vitamin D-binding protein, leading to increased renal loss of vitamin D metabolites (10,14,15).

Low 25 (OH) vitamin D levels in patients with CKD have been associated with a higher risk of all-cause mortality and faster progression of kidney disease (16–18). In the Third National Health and Nutrition Examination Survey (NHANES III) cohort (6), individuals with 25 (OH) vitamin D levels <15 ng/ml had a higher risk for all-cause mortality despite adjustments for CKD stage and for potential confounders. Individuals with lower 25 (OH) vitamin D levels were more likely to have diabetes.

25 (OH) Vitamin D attenuates renin expression and the compensatory increase in renin levels in patients treated with angiotensin receptor blockers (ARBs) (19). Vitamin D receptor agonists also reduce expression of inflammatory mediators by monocytes and T cells, promote survival of podocytes by inducing
differentiation and preventing apoptosis, and reduce albuminuria and glomerulosclerosis in animal models (20–26). Patients with type II diabetes and CKD have an exceptionally high rate of severe 25 (OH) vitamin D deficiency (27).

The purpose of this study was to analyze the association between 25 (OH) vitamin D levels and progression of type II DN in a substudy of the Spanish Progésion de Nefropatía Diabética (PRONEDI) trial (28), which was designed to compare the efficacy of combining the angiotensin-converting enzyme inhibitor (ACEi) lisinopril and the ARB irbesartan with the efficacy of each drug in monotherapy (at high and equipotent doses) for slowing progression of kidney disease in patients with established type II diabetic nephropathy (DN).

We measured 25 (OH) vitamin D levels in the patients included in this study and followed them for 4 years to evaluate the association between 25 (OH) vitamin D levels and progression of established type II DN in patients receiving optimal doses of RAS blockers.

Materials and Methods

Patients
The Spanish PRONEDI trial (EUDRACT 2004-002470-31) enrolled 133 patients from 17 centers located throughout Spain (age >35 years) with type II diabetes and a clinical diagnosis of DN, stage 2 or 3 CKD, and a urinary protein/creatinine ratio (UPCR) >300 mg/g (morning urine spot) on two separate occasions. All of the patients had hypertension, with a resting BP <180/95 mmHg. The exclusion criteria were myocardial infarction, cerebrovascular accident, heart failure, or myocardial revascularization in the last 3 months, and any condition that could affect long-term survival. Serum and plasma samples were only collected from 13 centers, leaving a final study population of 103 patients. We determined levels of 25 (OH) vitamin D at baseline, 4 months, and 12 months. The protocol fulfilled the criteria of the Declaration of Helsinki and was approved by the regulatory authorities and local ethics committees. All patients provided informed consent.

Intervention
During the 4-week washout period, patients continued to receive their standard antihypertensive therapy. If they had been taking an ARB or ACEi, these medications were discontinued and replaced by alternative open-label medications in doses sufficiently high to control BP. After the washout period, patients were randomly assigned (1:1:2) to receive once-daily doses of lisinopril (10 mg), irbesartan (150 mg), or a combination (5 mg of lisinopril plus 75 mg of irbesartan), along with conventional antihypertensive therapy. The dose was titrated up to the maximum recommended study dose after 8 weeks (40 mg of lisinopril, 600 mg of irbesartan, or 20 mg of lisinopril plus 300 mg of irbesartan). Treatment was administered while the patients remained in the study.

Follow-Up Assessment
Median follow-up was 32 months (interquartile range [IQR], 18–48). Serum creatinine, UPCR, hemoglobin, and other laboratory values including serum cholesterol (total lipoprotein, HDL, and LDL), triglycerides, and glycosylated hemoglobin were measured. Visits were scheduled every 4 months, or more often if necessary, to monitor systolic BP, diastolic BP, use of concomitant medication, adherence (pill counts at each visit), and laboratory values. We also assessed whether adverse events had occurred or endpoints had been reached. Cholecalciferol or other forms of 25 (OH) vitamin D were not prescribed during the follow-up period; calcitriol or paricalcitol was prescribed in those patients with secondary hyperparathyroidism, according to the policy of the individual center.

Routine clinical and biochemical variables were measured using standardized methods in automated analyzers. The serum creatinine level was determined using the kinetic Jaffé assay, which is standardized for all laboratories according to a certified program (ISO 9000:2008) of the Spanish Society of Clinical Biochemistry. Urinary protein excretion was determined at a central laboratory using immunonephelometry. The 25 (OH) vitamin D level was determined using a chemiluminescent immunoassay (Clia; Liaison DiaSorin, Dartford, Kent, UK), with a 5% intraassay coefficient of variation (CV), 8% interassay CV, and sensitivity between 4 and 150 ng/ml. The accuracy of the method was identical in both the normal and low ranges. Aldosterone was measured using RIA (Abcam, Cambridge, UK) and parathyroid hormone (PTH) was determined using an immunoassay (normal range, 14–72 pg/ml; ADVIA Centaur Siemens, Erlangen, Germany).

Outcome Measures
The primary efficacy measure was the time to the first event of the composite endpoint (>50% increase in serum creatinine concentration, ESRD, or death). The renal endpoint was a >50% increase in serum creatinine concentration or ESRD. The >50% increase in serum creatinine concentration was defined as the first serum creatinine value that was >50% higher than the baseline value, as confirmed by a second serum creatinine value a month later. ESRD was defined as the need for long-term dialysis or renal transplantation. Physicians reviewed each event on an individual basis at each visit.

Statistical Analyses
Quantitative data are expressed as the mean ± SD or median with IQR. Qualitative data are expressed as absolute numbers and percentages. Differences between patients with 25 (OH) vitamin D deficiency (<15 ng/ml) were studied using a univariate analysis. Qualitative data were analyzed using the chi-squared test, and quantitative data were analyzed using the t test. The correlation between variables was assessed using the Pearson correlation coefficient.

Time-to-event curves are based on the Kaplan–Meier analysis and Cox regression model with adjusted valid and accurate hazard ratios (HRs) and with time to renal event as a function of the factors studied. The covariates considered for adjustment included sex, age, treatment (monotherapy and combined treatment), clinical baseline characteristics, estimated GFR (eGFR) calculated using the four-variable Modification of Diet in Renal Disease study equation (MDRD4), UPCR, and levels of albumin, PTH, aldosterone, and phosphorus.
Variables were eliminated manually by monitoring variations in the regression coefficient exposure to identify those variables that could be removed as nonconfounders. The assumption of proportionality was monitored by applying a log minus log plot and testing the interaction between the variables in the model and time.

Mixed models were adjusted to study longitudinal data. The model included time, treatment (monotherapy or dual blockade of the RAS), and their interaction as the fixed effect and patient as the random effect, with an unstructured covariance matrix.

All tests were two sided, and a $P$ value $<0.05$ was considered statistically significant.

**Results**

**Patient Characteristics**

The study population comprised 103 patients with established type II DN (78% men, mean age 69±8 years, mean eGFR 47±16 ml/min per 1.73 m², geometric mean UPCR 1.37±2.13 g/g). Twenty-six patients were randomized to lisinopril, 26 to irbesartan, and 51 to combination treatment. Median baseline 25 (OH) vitamin D levels were 14.9 ng/ml (IQR, 8.1–21.2). Ninety-six patients (93%) had 25 (OH) vitamin D levels $\geq$15 ng/ml and 53 patients (51.5%) had 25 (OH) vitamin D levels $<15$ ng/ml, which are the thresholds for 25 (OH) vitamin D insufficiency and deficiency, respectively.

The characteristics of the patients classified by serum 25 (OH) vitamin levels are summarized in Table 1. No significant differences were found, apart from a higher percentage of women, lower serum albumin, higher serum phosphate, and high level of proteinuria in patients with 25 (OH) vitamin D deficiency. We did not find differences in BP. At the end of the follow-up period, the mean BP was 139±18/71±10 mmHg in the lisinopril group, 138±20/70±9 mmHg in the irbesartan group, and 140±19/72±11 mmHg in the combination group. No differences were detected for other habitual risk factors (cholesterol, glycosylated hemoglobin) at baseline or during follow-up. At baseline, 25 (OH) vitamin D levels were directly associated with serum albumin ($r=0.32$, $P=0.002$) and were inversely associated with UPCR ($r=-0.23$; $P=0.04$); however, no correlations were observed between 25 (OH) levels and eGFR ($r=0.25$, $P=0.81$). According to the policy of the individual center, active vitamin D compounds were taken by six patients in the group with 25 (OH) vitamin D deficiency and four patients in the group without deficiency. No patients were taking calcimimetics.

No differences were detected between the number of samples obtained during the cloudy months (53%) or during the sunny months (47%).

**Primary and Renal Outcomes**

After an 18-month inclusion period, the median follow-up was 32 months (IQR, 18–48), during which 26 patients (25.2%) achieved the renal endpoint (>50% increase in serum creatinine concentration or ESRD) and 7 patients died (6.7%). Six patients (85%) who died had 25 (OH) vitamin D

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**Table 1. Baseline clinical characteristics of the patients with DN: Comparison of those with 25 (OH) vitamin D levels $\geq$15 ng/ml and 25(OH) vitamin D levels $<15$ ng/ml**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>25 (OH) Vitamin D</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\geq$15 ng/ml ($n=50$)</td>
<td>$&lt;15$ ng/ml ($n=53$)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>68.6±8.4</td>
<td>69.4±7.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.3±12.4</td>
<td>82.4±12.4</td>
</tr>
<tr>
<td>Male sex</td>
<td>43 (87.8)</td>
<td>38 (71.7)</td>
</tr>
<tr>
<td>ACEi, ARB, or combination ($n$)</td>
<td>12/12/26</td>
<td>14/14/25</td>
</tr>
<tr>
<td>Sample in cloudy months (%)</td>
<td>46</td>
<td>62.3</td>
</tr>
<tr>
<td>UPCR (1.37 g/g)</td>
<td>149.7±20.3</td>
<td>148.5±14.4</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>79.2±10.0</td>
<td>78.5±11.1</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>13.6±1.8</td>
<td>13.1±1.5</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.6±0.4</td>
<td>4.4±0.6</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>25.3±3.2</td>
<td>25.8±2.4</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.3±0.5</td>
<td>9.1±0.6</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>3.3±0.5</td>
<td>3.6±0.7</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>7.0±1.3</td>
<td>7.3±1.2</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>4.2±0.4</td>
<td>3.9±0.4</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>47.7±16</td>
<td>46.4±17</td>
</tr>
<tr>
<td>UPCR (g/g)</td>
<td>1.1 (0.6–2.4)</td>
<td>2.4 (1.0–5.1)</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>7.1±1.6</td>
<td>6.8±1.5</td>
</tr>
<tr>
<td>25 (OH) vitamin D (ng/ml)</td>
<td>22.6±6.1</td>
<td>9.2±3.4</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>66.3±55.7</td>
<td>84.4±65.2</td>
</tr>
<tr>
<td>Baseline aldosterone (ng/dl)</td>
<td>204.8±58.3</td>
<td>195.8±58.3</td>
</tr>
<tr>
<td>Calcitriol/paricalcitol ($n$)</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD or median (interquartile range) unless otherwise indicated. GFR was estimated using the four-variable Modification of Diet in Renal Disease study equation. DN, diabetic nephropathy; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HbA1C, glycosylated hemoglobin; eGFR, estimated GFR; UPCR, urinary protein/creatinine ratio; PTH, parathyroid hormone.
deficiency. The causes of death were as follows: sudden death (one patient), tumor (two patients: one with a prostatic tumor and one with an esophageal tumor), myocardial infarction (one patient), heart failure (one patient), death from complications of abdominal surgery (one patient), and unknown (one patient). The number of patients who were eventually prescribed an active compound of vitamin D during the study period was higher in the group with 25(OH) vitamin D deficiency (22 versus 12 patients).

The primary endpoint was reached by 23 patients with deficiency (43.4%) and 8 patients without (16%). The Kaplan–Meier survival curves for the primary endpoint are shown in Figure 1. Significantly higher renal survival was observed in patients with 25(OH) vitamin D deficiency (>15 ng/ml) compared to those with 25(OH) vitamin D levels ≥15 ng/ml.

Table 2. HRs of the primary endpoint (>50% increase in serum creatinine concentration, ESRD, or death) and renal endpoint (>50% increase in serum creatinine concentration or ESRD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Primary Endpoint</th>
<th>Renal Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>25(OH) vitamin D (&lt;15 ng/ml)</td>
<td>2.88 (1.84 to 7.67)</td>
<td>3.79 (1.20 to 12.02)</td>
</tr>
<tr>
<td>UPCR (g/g)</td>
<td>1.35 (1.14 to 1.6)</td>
<td>1.54 (1.26 to 1.87)</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>0.98 (0.95 to 1.01)</td>
<td>0.99 (0.95 to 1.03)</td>
</tr>
<tr>
<td>Baseline aldosterone (ng/dl)</td>
<td>1.00 (1 to 1.01)</td>
<td>1.01 (1.00 to 1.01)</td>
</tr>
</tbody>
</table>

GFR was estimated using the MDRD4 study equation. The covariates considered for adjustment included sex, age, treatment (monotherapy and combined treatment), clinical baseline characteristics, MDRD4, UPCR, and levels of albumin and PTH. HR, hazard ratio; 95% CI, 95% confidence interval; UPCR, urinary protein/creatinine ratio; eGFR, estimated GFR; MDRD4, four-variable Modification of Diet in Renal Disease study equation.

A faster decline in eGFR (MDRD4) was observed in patients with 25(OH) vitamin D deficiency. The median rate of decline was 5.8 ml/min per 1.73 m² per year (95% confidence interval [95% CI], 3.6 to 8.15 ml/min per 1.73 m² per year) in the group with 25(OH) vitamin D levels <15 ng/ml and 3.3 ml/min per 1.73 m² per year (95% CI, 1.65 to 5.06 ml/min per 1.73 m² per year) in the group with ≥15 ng/ml ($P=0.06$).

Table 2 shows the results of the multivariate Cox regression analysis for the primary and renal endpoints. The adjusted models included baseline eGFR, UPCR, and levels of aldosterone and 25(OH) vitamin D. UPCR and aldosterone level had a statistically significant effect on both outcomes. 25(OH) vitamin D deficiency was associated with the renal event (HR, 3.79; 95% CI, 1.20 to 12.02; $P=0.02$) and with the primary composite event (HR, 2.88; 95% CI, 1.84 to 7.67; $P=0.04$). Age, sex, phosphorus levels, weight, treatment with RAS blockers (monotherapy versus
combined treatment) and albumin levels were removed as confounders.

**Effect of Aldosterone and 25 (OH) Vitamin D Levels on Renal Progression**

Baseline aldosterone levels decreased, although not significantly, after 4 months of treatment with RAS blockers ($P=0.07$) in all three groups and returned to their previous values at 12 months of treatment. The behavior of 25 (OH) vitamin D was identical but inverse, with significantly increased levels at 4 months (median increase, 2.5 ng/ml; IQR, 0.42–4.54; $P<0.05$) that returned to their previous values at 12 months. No differences were observed between the three treatments. Table 3 shows a comparison of 25 (OH) vitamin D and aldosterone levels at baseline, 4 months, and 12 months in patients who reached the primary endpoint and in those who did not progress.

**Discussion**

Our study shows that 25 (OH) vitamin D deficiency is associated with accelerated progression of CKD in patients with DN. This finding is particularly relevant if we consider the high prevalence of 25 (OH) vitamin D deficiency recorded in this population (18).

Many factors could account for the low levels of 25 (OH) vitamin D observed in patients with CKD, including loss of vitamin D–binding protein in urine (15), ineffective synthesis in skin on exposure to ultraviolet B radiation, reduced nutritional intake, and the progressive increase in fibrolast growth factor 23 levels observed in CKD (29).

Albuminuria is a typical finding in patients with DN. Evidence from clinical trials (30) and association data from the NHANES III cohort demonstrated an inverse relationship between 25 (OH) vitamin D level and degree of albuminuria (31). Our findings were similar; namely, patients with low 25 (OH) vitamin D levels had higher UPCR. Furthermore, diabetes is closely associated with low 25 (OH) vitamin D levels (32,33). Given the above findings, patients with established DN are expected to have even lower 25 (OH) vitamin D levels than patients with CKD of other causes but a similar eGFR (27). In fact, the prevalence of 25 (OH) vitamin D insufficiency (93%) and deficiency (51.5%) was higher in this study than in studies of CKD patients with and without diabetes (18).

Few studies analyze the effect of 25 (OH) vitamin D deficiency on progression of kidney disease in patients with type II DN. In previous studies of patients with CKD of any cause, lower 25 (OH) vitamin D level was associated with an increased risk of incident ESRD (18,34) and contributed to decreased eGFR in early and advanced stages of CKD (35). In the study by Ravani *et al.*, baseline 25 (OH) vitamin D levels correlated directly and significantly with eGFR. Although the prevalence of 25 (OH) vitamin D deficiency was lower than that observed in our study, the Cox regression analysis showed the 25 (OH) vitamin D level to be an independent predictor for death and ESRD. The association between lower 25 (OH) vitamin D levels and reduced eGFR was strongest in patients with diabetes (18).

The main finding of this study is that 25 (OH) vitamin D deficiency is associated with accelerated progression of CKD in patients with DN over a long-term follow-up. Our analysis took into consideration comorbidities and other clearly demonstrated risk factors, such as eGFR, UPCR, albumin, PTH, and serum phosphate. Progression was present, even though all patients received optimal treatment with high doses of RAS blockers.

In animal models, 25 (OH) vitamin D suppresses the RAS, and lower 25 (OH) vitamin D levels are particularly detrimental in the setting of RAS activation and hyperfiltration, which are characteristic of DN (19). Therefore, at least in experimental models, the use of vitamin D analogs to block RAS activation exerts a therapeutic effect by enhancing the action of currently used RAS blockers (26). In the VITAL clinical trial, the addition of 2 μg/d of paricalcitol to RAS blockers decreased residual albuminuria in patients with DN (36).

Baseline aldosterone level was an independent predictor of renal progression in this study. Interestingly, we observed that treatment with an ACEi or an ARB alone at high

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**Table 3. 25 (OH) vitamin D (ng/ml) and aldosterone levels in patients at baseline, 4 months, and 12 months: Comparison between those patients who reached the renal endpoint and those who did not progress.**

<table>
<thead>
<tr>
<th></th>
<th>Patients with Renal Progression</th>
<th>Patients with No Renal Progression</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 (OH) vitamin D (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9.2 (6.5–12.1)</td>
<td>21.2 (17.4–27.2)</td>
<td>14.9 (8.1–21.2)</td>
</tr>
<tr>
<td>4 mo</td>
<td>11.8 (9.1–17.8)</td>
<td>23.8 (18.2–28.5)</td>
<td>17.5 (10.4–24.5)</td>
</tr>
<tr>
<td>12 mo</td>
<td>9.1 (6.8–14.3)</td>
<td>19.5 (13.4–24.1)</td>
<td>13.9 (8.4–20.3)</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>22.3 ± 5.5c</td>
<td>19.3 ± 5.7</td>
<td>20.1 ± 5.8</td>
</tr>
<tr>
<td>4 mo</td>
<td>18.8 ± 5.1d</td>
<td>18.5 ± 5.1</td>
<td>18.6 ± 5.7</td>
</tr>
<tr>
<td>12 mo</td>
<td>20.3 ± 5.6</td>
<td>20.1 ± 4.8</td>
<td>20.1 ± 5.0</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD or median (interquartile range).

$P<0.001$, comparison of patients with renal progression versus no renal progression.

$P<0.05$, comparison of baseline 25 (OH) vitamin D levels versus levels at 4 months of follow-up.

$P=0.03$, comparison of patients with renal progression versus no renal progression.

$P=0.03$, comparison of baseline aldosterone levels versus levels at 4 months of follow-up.
doses or in combination was associated with a transient and small but significant increase in 25 (OH) vitamin D levels at 4 months; however, this effect disappeared at 12 months. A reverse effect was observed for aldosterone levels, although we do not know whether this finding is related to a beneficial nonhemodynamic effect of RAS blockers on vitamin D metabolism. Further studies are warranted to elucidate this gap in our knowledge.

Almost 25% of our patients experienced a renal event despite optimal treatment with RAS blockers and control of BP. Clearly, many other factors are involved in progression of DN. Our results lead us to believe that 25 (OH) vitamin D deficiency could be one of them and that supplementation could be useful.

Our treatment paradigm for vitamin D supplementation in CKD has now shifted to ensure that both classic and nonclassic requirements are met. In contrast to the classic endocrine function of vitamin D, the autocrine function of vitamin D appears to remain intact as long as 25 (OH) vitamin D, the necessary substrate, is available. 1-α-hydroxylase activity is maintained, even in anephric patients. In patients with DN, 25 (OH) vitamin D level is almost universally <30 ng/ml; therefore, supplementation should be universally considered in this population. Unfortunately, the level of evidence to support 25 (OH) vitamin D therapy for CKD or DN is low. Several studies of nutritional vitamin D supplementation in patients with type II diabetes are ongoing, although their results are not yet available. Few data are available on combining therapy with both nutritional and active vitamin D compounds; thus, caution should be exercised in clinical practice, because of the possibility of vitamin D intoxication. Further data are necessary in this area.

Our study has several limitations. First, it was not primarily designed to investigate the association of 25 (OH) vitamin D levels with progression of type II DN. Second, the sample size is relatively small. Finally, our findings cannot be considered as robust as those generated by an interventional controlled trial. Consequently, an adequately powered randomized controlled trial should be designed to determine whether 25 (OH) vitamin D therapy is able to slow the progression of type II DN.

In conclusion, we analyzed the association between 25 (OH) vitamin D and long-term progression of type II DN in patients who received optimal treatment with RAS blockers. Our results show that low levels of 25 (OH) vitamin D (<15 ng/ml) are frequent in patients with DN and are independently associated with a higher risk of the composite outcome and renal disease progression in patients with type II DN.

Acknowledgments

Data were analyzed by Elia Pérez from the Statistical Unit of the Alcorcón Hospital Foundation and Jesus Oliva from the National Epidemiology Center.

PRONEDI was sponsored, designed, run, and analyzed by investigators from the following institutions: Alcorcón Hospital Foundation (Alcorcón, Spain), Gregorio Marañón University General Hospital (Madrid, Spain), and 12 de Octubre University Hospital (Madrid, Spain).

The following investigators participated in the PRONEDI study: Dolores Lorenzo (Juan Canalejo Hospital, A Coruña, Spain); José Carlos Rodríguez (Dr. Negrín Hospital, Las Palmas de Gran Canaria, Spain); Francesca Calero (Puigvert Hospital Foundation, Barcelona, Spain); Alberto Martínez Castelao (Bellvitge University Hospital, L’Hospitalet de Llobregat, Spain); Javier Nieto (Our Lady of the Alarcos Hospital, Ciudad Real, Spain); Sergio Barroso (Infecta Cristina Hospital, Badajoz, Spain); Luis Orte (Ramón y Cajal University Hospital, Madrid, Spain); Eduardo Gutierrez and Manuel Praga (12 de Octubre University Hospital, Madrid, Spain); Ana Tato, Gema Fernández-Juarez, and Javier Ocaña (Alcorcón Hospital Foundation, Alcorcón, Spain); Carmen Bernis (University Hospital of the Princess, Madrid, Spain); Gonzalo Gomez Marquez (Son Dureta University Hospital, Palma de Mallorca, Spain); Vicente Lahera and Victoria Cachoefero (Complutense University of Madrid, Madrid, Spain); Vicente Barrio (Infanta Sofia University Hospital, Madrid, Spain); Soledad García de Vinuesa, Marian Goicoechea, and José Luino (Gregorio Marañón University Hospital, Madrid, Spain); Francisco Fernández Vega (Central University Hospital of Asturias, Oviedo, Spain); Isabel García (Dr. Josep Trueta University Hospital, Girona, Spain); Pablo Gómez (Jerez Hospital, Jerez de la Frontera, Spain); Álfonso Pérez García (Valencia General Hospital, Valencia, Spain); and Jesus Oliva (National Center for Epidemiology, Madrid, Spain).

Funding was received from the Spanish Ministry of Science and Innovation, the Spanish Society of Nephrology, and Bristol-Myers Squibb of Spain.

Disclosures

None.

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Received: January 26, 2013 Accepted: June 14, 2013

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.00910113/-/-DCSupplemental.

See related editorial, “Vitamin D Deficiency: Consequence or Cause of CKD?,” on pages 1844–1846.