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# Vitamin D Deficiency in Kidney Transplant Recipients: Risk Factors and Effects of Vitamin D3 Supplements

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ABSTRACT

Introduction. The Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines in chronic kidney disease (CKD) give some recommendations about diagnosis and treatment of vitamin D deficiency. These guidelines may also be applied to renal transplant recipients. The aim of the present study was to assess the vitamin D status and the effects of vitamin D3 supplements among a cohort of kidney graft recipients.

Patients and Methods. Five hundred nine renal transplant recipients with a follow-up of more than 12 months were included in this retrospective cross-sectional study. A total of 189 patients were treated with vitamin D3 supplements, 171 with calcitriol (0.25 or 0.5 $\mu$g $\times$ 3 weekly) and 18 with cholecalciferol (400 IU/d).

Results. 25OHD deficiency was present in 38.3% of patients, insufficiency in 46.9%, and normal levels in 14.7%. There were no differences in the prevalence of deficiency or insufficiency between patients who were not treated or those who were treated with vitamin D3 supplements. Upon multivariate analysis, 25OHD concentrations correlated with gender, length of follow-up, season of 25OHD determination, iPTH and 1.25OHD concentrations, and treatment with *ACEI/ARB* ($R^2 = 0.17$; $P = .000$).

Conclusions. 25OHD deficiency or insufficiency is frequent after renal transplantation even in sunny regions. The clinical significance of such a high prevalence of apparent 25OHD deficiency/insufficiency is unclear and requires further study.

MEASUREMENT of serum 25-hydroxyvitamin D (25OHD) is the best indicator of vitamin D status as it correlates with total body stores. Vitamin D deficiency is common among the general population, particularly in some at risk groups.[1,2] The National Kidney Foundation has elaborated clinical practice guidelines that suggest that measurement of 25OHD concentrations is important in patients with chronic kidney disease (CKD) stages 3 and 4 who have hyperparathyroidism.[3] According to the target levels, the prevalence of 25OHD deficiency and insufficiency in this population is high, namely 70% to 80%, regardless of geographic location.[4,5] Kidney graft recipients have various degrees of renal functional impairment with increased levels of parathyroid hormone (PTH). In several reports vitamin D status has been investigated. As in CKD patients, the incidence of 25OHD deficiency or insufficiency was high, but in some of these studies the number of patients was small, or the studies were performed in countries from the north of Europe or America and they excluded recipients on treatment with vitamin D.[6–10] The aim of the present study was to document the vitamin D status among a cohort of renal transplant recipients in Central Spain, seeking to analyze variables related to 25OHD concentrations.

## PATIENTS AND METHODS

Among 522 adult renal transplant recipients the 509 who had serum level measurements of intact PTH (iPTH) and vitamin D metabolites in the last 6 months of follow-up were included in this study. Madrid is located at 40°26′ latitude in Spain. The region has between 2590 and 3023 hours of sunshine annually according to reports from the last 5 years. The mean age of the patients was 45.4 ±

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14.5 years (range 18–74 years); there were 295 males and 214 females. The follow-up after transplantation was at least 12 months (mean, 113 ± 76 months; range, 12–324 months). At the time of the study 245 patients were on tacrolimus-based immunosuppression; 205, were on cyclosporine-based regimen; 469 were on steroids. In addition, 222 patients were on treatment with mycophenolate mofetil associated either with tacrolimus or with cyclosporine. Patients receiving any vitamin D supplement were not excluded from the present analysis.

After an overnight fast, plasma concentrations of creatinine, total calcium, phosphate, and alkaline phosphatase activity were measured using an autoanalyzer. Serum calcium was adjusted according to the following formula: adjusted Ca (mg/dL) = total calcium (mg/dL) + 0.0176× (34 − serum albumin [g/L]). Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated form of the Modification of Diet in Renal Disease (MDRD) study equation: eGFR = exp (5.228 − 1.154 × ln (serum creatinine) − 0.203 × ln (age) − (0.299 if female). Proteinuria was assessed using the urine protein-to-creatinine ratio. Fasting iPTH, 25OHD, and 1.25-dihydroxyvitamin D (1.25OHD) were measured at the same time. Serum iPTH levels were determined using an immunocheminomatric assay (Elecsys; Roche Diagnostic Gmbh, Mannheim, Germany). The 25OHD levels (calcidiol) were measured using enzyme-immun assay (ELISA; IDS systems; Boldon, United Kingdom) and 1.25OHD levels (calcitriol) were determined using radioimmunoassay (RIA; Biosource Europe, Nivelles, Belgium). In analyzing serum 25OHD, the results were stratified as follows: 25OHD deficiency (<16 ng/mL) or insufficiencicy (16–30 ng/mL) or normal (>30 ng/mL), according to the Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines for bone metabolism and disease in CKD.[3] The results were expressed as mean values ± SD. Normality was assessed using the Kolmogorov-Smirnov test. Phosphate, eGFR, iPTH, calcidiol by 25OHD, calcitriol 1.25OHD, and duration of transplant required natural logarithmic transformation as they were not normally distributed. When assessing differences between more than 2 groups, analysis of variance (ANOVA) and Kruskal-Wallis test were performed for parametric and nonparametric continuous data, respectively. The chisquare test was used to compare categorical data. Simple regression analysis was performed with the logarithm of 25OHD as the dependent variable. Multiple linear regression analysis with backward selection included the variables with $P$ values of $< .1$ as well as those previously reported in the medical literature to influence serum 25OHD levels. A $P$ value $< .05$ was considered significant.

## RESULTS

Overall mean serum creatinine level was 1.7 ± 0.8 mg/dL (range, 0.6–7.5 mg/dL) and the eGFR level was 47.0 ± 18.4 mL/min/1.73 $m^2$ (range, 8–146). There were 160 patients (31.4%) with proteinuria >0.3 g/mg. The iPTH levels were 144 ± 149 pg/mL (range, 36–1853 pg/mL), the serum 25OHD levels were 20.0 ± 10.6 ng/mL (range, 0.1–111 ng/mL), and the 1.25OHD levels were 37.4 ± 25.3 pg/mL (range, 0.5–360 pg/mL). At the time of the study, 189 patients (36.6%) had been on treatment with vitamin D supplements for at least 3 months: 171 patients with calcitriol (0.25 or 0.5 $\mu$g/d × 3 d/wk) and 18 patients with cholecalciferol (400 IU/d). Vitamin D supplements were administered because of persistent high iPTH levels after 6 or 12 months or due to findings of osteopenia. The differences between the 2 groups were older age, shorter follow-up after transplantation, higher serum calcium levels, lower serum phosphate levels, higher total $CO_2$, and greater percentage of patients on treatment with calcium supplements among the patients on vitamin D therapy. There were no differences in graft function or iPTH, 25OHD, and 1.25OHD concentrations. According to 25OHD concentrations: 14.7% of recipients showed normal concentrations; 46.9% had vitamin D insufficiency; and 38.3% had vitamin D deficiency. The characteristics of these 3 groups of patients are shown in Table 1. Similar results were observed when untreated versus treated patients were analyzed separately (data not shown). However, to avoid bias, we performed simple linear regression analysis with 25OHD as the dependent variable in only nontreated recipients. Upon univariate analysis, 25OHD concentrations correlated with age (coefficient = −0.003; $P = .003$), gender (coefficient = −0.084; $P = .005$), time of follow-up (coefficient = 0.117; $P = .005$), season of 25OHD determination (coefficient = −0.095; $P = .001$), eGFR (coefficient = 0.189; $P = .016$), total $CO_2$ ($r = 0.015$; $P = .003$), iPTH ($r = -0.256$; $P = .000$), and 1.25OHD (coefficient = 0.138; $P = .008$) concentrations as well as treatment with ACEI/ARB ($r = -0.069$; $P = .025$). Upon multivariate analysis: gender, length of follow-up, season of 25OHD determination, iPTH, and 1.25OHD concentrations, as well as treatment with ACEI/ARB, were the variables that remained in the model ($R^2 = 0.17$; $P = .000$).

## DISCUSSION

According to the cut-off values recommended by the National Kidney Foundation (NKF)/DOQI guidelines for the definition of vitamin D status,[3] most of our recipients had low 25OHD levels: 38.3% revealed a deficiency and 46.9% had an insufficiency. We did not observe differences between subjects who were untreated and those who were treated with vitamin D supplements. Our results are similar to those reported by other authors from America[9] or from Europe.[6] They are slightly better than those observed by Stavroulopoulus et al[10] from the United Kingdom, in which 94% had 25OHD deficiency or insufficiency. These results may be explained at least in part by differences in sunlight exposure. Moreover, a similar prevalence of low levels of 25OHD has been observed among patients on dialysis at the time of transplantation, most of them treated with vitamin supplements[11] and in elderly patients with chronic renal disease.[5] Furthermore, mean 25OHD serum levels in our transplant recipients were even slightly higher than those observed among a population of elderly individuals from the north of Spain.[2] All of these findings suggested that vitamin D insufficiency/deficiency is almost universal, affecting the CKD population as well as the general population. The causes of low 25OHD concentrations are not clear. In the transplant recipients, vitamin D deficiency may be due to reduced skin synthesis, urine losses, and increased catabolism. We have observed correlations of 25OHD concentra-

**Table 1. Demographic and Biochemical Characteristics According to 25OHD Status**

| | Normal (n = 75) | Insufficiency (n = 239) | Deficiency (n = 196) | *P* |
|---|---|---|---|---|
| Age (y) | 41.6 ± 14.0 | 45.3 ± 14.8 | 47.0 ± 14.4* | .021 |
| Gender (male/female) | 53/22 | 149/90 | 93/102 | .002 |
| Time after transplantation (mo) | 140 ± 90 | 110 ± 74† | 108 ± 69† | .027 |
| SCr (mg/dL) | 1.5 ± 0.5 | 1.7 ± 0.6* | 1.8 ± 0.9* | .002 |
| GFR (mL/min/1.73m$^2$) | 55.5 ± 17.6 | 46.7 ± 18.1† | 44.7 ± 18.1† | .000 |
| Serum albumin (g/dL) | 4.6 ± 0.3 | 4.5 ± 0.3 | 4.5 ± 0.4 | .220 |
| Protein-to-creatinine ratio (g/mg) | 0.26 ± 0.34 | 0.43 ± 0.81 | 0.60 ± 1.13* | .035 |
| Adjusted calcium (mg/dL) | 9.6 ± 0.5 | 9.6 ± 0.6 | 9.5 ± 0.6 | .683 |
| Adjusted calcium >10.2 mg/dL (no/yes) | 50/25 | 151/88 | 127/68 | .778 |
| Phosphate (mg/dL) | 3.2 ± 0.7 | 3.2 ± 0.6 | 3.3 ± 0.7 | .254 |
| Total $CO_2$ (mmol/L) | 25.8 ± 2.6 | 25.2 ± 2.8 | 24.6 ± 2.9†‡ | .005 |
| iPTH (pg/mL) | 106 ± 68 | 138 ± 161 | 167 ± 153†‡ | .000 |
| 25 OHD (ng/mL) | 38.3 ± 11.5 | 21.7 ± 3.7 | 10.9 ± 3.3 | .000 |
| 1.25 OHD (pg/mL) | 40.5 ± 22.8 | 38.5 ± 19.4 | 33.3 ± 31.4†§ | .002 |
| Season of determination (spring-summer/autumn-winter) | 53/22 | 108/131 | 77/118 | .000 |
| Vitamin D supplements (no/yes) | 43/32 | 152/87 | 125/70 | .558 |
| Calcium supplements (no/yes) | 50/25 | 151/88 | 127/68 | .831 |
| Treatment with ACEI or ARBs (no/yes) | 50/25 | 162/77 | 126/69 | .784 |

Abbreviations: SCr, serum creatinine; ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.
*$P < .05$ vs normal.
†$P < .01$ vs normal.
‡$P < .05$ vs insufficiency.
§$P < .01$ vs insufficiency.

tions with several variables. In the untreated group, 25OHD was lower in women, during autumn-winter, and increased with length of follow-up. It negatively correlated with iPTH concentrations and positively with 1.25OHD. One surprising finding was the negative relationship between 25OHD concentrations and the use of ACEI or ARBs, as they are given to many patients with proteinuria. 25OHD insufficiency/deficiency could be in part due to uncontrolled urine protein losses. Among renal transplant recipients, treatment with ergocalciferol, calcitriol, and 1-$\alpha$-vitamin D sterols has been recommended, even when patients display normal function, as they may be of benefit for the skeleton and can also help to reduce the PTH to normal. Our findings confirmed the data from previous studies that have shown that low doses of calcitriol supplements did not improve vitamin D deficiency.[12] There were not more treated patients in the group with normal 25OHD, and there were no differences in 25OHD concentrations between treated and untreated patients (data are not shown). Moreover, calcitriol has some immunomodulatory effects in various organ transplants. In animals, treatment with calcitriol prolongs renal graft survival and prevents histological changes associated with chronic allograft nephropathy.[13] However, graft function was similar among untreated and treated patients.

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