Renal function and 25-hydroxyvitamin D concentrations predict parathyroid hormone levels in renal transplant patients

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Abstract

Background. Recent guidelines suggest supplementation with ergocalciferol (vitamin D2) in chronic kidney disease stages 3 and 4 patients with elevated parathyroid hormone (PTH) levels and 25-hydroxyvitamin D (25OHD) levels <75 nmol/l. These guidelines are also applied to renal transplant patients. However, the prevalence rates of 25OHD deficiency and its association with PTH levels in renal transplant populations have not been extensively examined. We aimed to document the prevalence rates of 25OHD deficiency [defined by serum levels <40 nmol/l (<16 ng/ml)] and insufficiency [<75 nmol/l (<30 ng/ml)] in a single renal transplant centre, and examine its relationship with PTH levels.

Methods. Serum 25OHD and PTH concentrations were measured in 419 transplant patients attending a single renal transplant clinic over a 4-month period. Demographic and biochemical data were also collected, including serum creatinine, calcium, phosphate and albumin. Simple and multiple linear regression analysis were performed.

Results. In 27.3% of the patients, 25OHD deficiency was present, and 75.5% had insufficiency. On univariate analysis, 25OHD, serum albumin and estimated glomerular filtration rate (eGFR) were significantly associated with PTH levels (P < 0.0001, P = 0.004 and P < 0.0001, respectively). Multiple linear regression demonstrated that only 25OHD, eGFR and serum phosphate were significantly predictive of PTH levels (R² = 0.19, P < 0.0001). In this model, a 75 nmol/l increase in 25OHD will only result in a maximal reduction in PTH of 2.0 pmol/l.

Conclusions. We conclude that 25OHD deficiency and insufficiency are common in renal transplant patients and may exacerbate secondary hyperparathyroidism. However, 25OHD, eGFR and phosphate only account for 19% of the variability in PTH levels. In addition, even a large increase in serum 25OHD levels is likely to result in only a small reduction in PTH. Therefore, alternative approaches to managing hyperparathyroidism in renal transplant recipients rather than supplementation with ergocalciferol are warranted.

Keywords: cholecalciferol; 25-hydroxyvitamin D; hyperparathyroidism; renal transplant; transplantation; vitamin D

Introduction

Low 25-hydroxyvitamin D (25OHD) concentrations have been shown to be associated with the development of hyperparathyroidism, osteomalacia, osteoporosis, increased falls and hypertension [1–5]. Concentrations previously thought to be adequate have now been documented to increase the risk of some of these outcomes [6–8] and as a result the threshold serum level, at which nutritional supplementation is recommended, has been rising in recent years [7,9–11].

Recently published clinical practice guidelines (National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF K/DOQI)) recommend measurement of 25OHD concentrations in all patients with chronic kidney disease (CKD) stages 3 and 4 (i.e. glomerular filtration rate (GFR) of 15–60 ml/min) and elevated parathyroid hormone (PTH) concentrations [12]. Subsequent vitamin D supplementation is also recommended in all individuals with a 25OHD concentration <75 nmol/l (30 ng/ml), in order to reduce the PTH concentrations.
Renal transplant patients do commonly have persistently elevated PTH concentrations for many months post transplantation [13–15]. The NKF K/DOQI Guidelines recommend the same management as for CKD patients. While there is some evidence for this recommendation in CKD patients, the data in renal transplant patients is scant [16,17]. Our aim was to document the prevalence rate of low 25OHD concentrations and examine its association with PTH concentrations in a renal transplant population.

Subjects and methods

Serum 25OHD was measured in all patients attending the renal transplant clinic at the University Campus of the London Health Sciences Centre, in London, Ontario, Canada between December 2003 and March 2004. London, Ontario is situated at 43° 2′ N latitude. All patients were over the age of 18 years and had a renal transplant for at least 1 month. Of the 419 patients studied, 63% of the subjects were men. Multivitamin or vitamin D supplementation was not routinely recommended at that time. All procedures performed were in accordance with the Ethics Committee for the University of Western Ontario.

Using the Sorin radioimmunoassay (Stillwater, MN, USA), 25OHD was measured in which the sample is initially treated with acetonitrile, to dissolve the lipid, including 25OHD, and the protein is precipitated. The antibody used in this assay is specific to 25OHD, even in the event of limited cross-reaction, the absolute concentration of 1,25 dihydroxy-vitamin D in the assay volume (1000-fold less) would be well below the detection limits. The assay does not detect other metabolites, such as 24,25 dihydroxyvitamin D. Twenty-five hydroxyvitamin D deficiency was defined at concentrations below the detection limits. The assay does not detect other metabolites, such as 24,25 dihydroxyvitamin D. Twenty-five hydroxyvitamin D deficiency was defined at concentrations <40 nmol/l (16 ng/ml) and insufficiency at concentrations <75 nmol/l (30 ng/ml) [9,11].

Serum PTH concentrations were assayed by a solid-phase, two-site chemiluminescent enzyme-labelled immunometric assay (Immulite 2000 intact PTH from Diagnostic Products Corporation, Los Angeles, CA, USA). Serum creatinine, calcium, phosphate, alkaline phosphatase and albumin levels were measured by standard autoanalyser techniques. GFR was estimated using the four-variable MDRD formula [18]. Patient charts were reviewed and 29 patients were prescribed either calcitriol or doxercalciferol to manage persistent hyperparathyroidism, with these patients being excluded from the regression analysis. In addition, note was made of the number of transplants a patient had received, duration of transplant, a etiology of end-stage renal failure, weight and age.

Statistical analysis

Results are given as mean ± SD. Normality was assessed for all variables, with PTH, phosphate, estimated GFR (eGFR) and duration of transplant requiring logarithmic transformation. Simple linear regression analysis was then performed with PTH as the dependent variable and the independent variables as serum calcium, phosphate, 25OHD, albumin, eGFR, gender, number of transplants, duration of transplantation, age and weight. Multiple linear regression analysis with forward selection included all variables with a P-value of <0.1 on univariate analysis, plus the variables calcium, phosphate, age and duration of transplant that were selected a priori. Interaction terms were included into the model and retained if there was significant improvement in the coefficient of determination. Residual plots and multicollinearity diagnostics were performed to ensure adequacy of the model produced. STATA 8.2 (StataCorp, College Station, TX, USA) was used to assist with the analysis.

Results

The mean age of the 419 patients studied was 51 ± 15 years with a mean duration of transplant of 7.2 ± 6.4 years (Table 1). About 88.6% of the transplant recipients were on their first transplant, with 9.9% on their second and 1.5% on their third. The aetiology of end-stage renal failure included glomerulonephritis (48%), diabetes mellitus (12.8%), hypertension (7.5%), polycystic kidney disease (11.9%) and reflux nephropathy (10.3%). Three hundred and ninety of the patients were not taking any type of vitamin D supplement. Amongst all patients, the mean 25OHD level was 57.3 ± 26.2 nmol/l, with patients not taking supplements recording 56.9 ± 25.8 nmol/l and those taking supplements recording a mean level of 57.8 ± 29.3 nmol/l (P = 0.82 for difference).

The median serum creatinine was 132 μmol/l and the median eGFR was 49.2 ml/min. About 27.3% of the transplant patients had 25OHD levels <40 nmol/l, and 75.5% had a level <75 nmol/l. PTH levels were above the upper limit of the recommended range for CKD stage 3 (7.7 pmol/l), according to KDOQI Guidelines, in 73.8% of the subjects, with 20.6 and 6.9% recording levels above 20 and 30 pmol/l, respectively. Of the 279 patients with a PTH level above 7.7 pmol/l, 30.8 and 79.6% had 25OHD levels <40 and 75 nmol/l, respectively (Figure 1).

On univariate analysis, 25OHD, eGFR and serum albumin were significantly associated with PTH levels (Table 2). On inclusion of these variables plus calcium, phosphate, age and duration of transplant, the only variables that were statistically significant were 25OHD, eGFR and serum phosphate, P < 0.0001 and R² = 0.19 (Table 3). No significant interaction terms or multicollinearity were identified.

Utilizing the 95% confidence intervals (CI) for the coefficients in the multivariate model produced, plots were derived of the predicted change in PTH with changes in each one of the three significant variables (Figure 1). These plots demonstrate that a 75 nmol/l increase in 25OHD concentrations would result in a maximum lowering of PTH by 2.5 pmol/l.

Discussion

Renal osteodystrophy remains an ongoing problem in patients even after successful renal transplantation.
A major factor in the development of this is persistent hyperparathyroidism [13–15]. The NKF K/DOQI Guidelines recommend management of hyperparathyroidism along the same pathways as for CKD patients [12]. Specifically, this would imply the correction of low 25OHD levels in transplant patients with an elevated PTH level. We have demonstrated here that this would produce only a minimal reduction in PTH levels, even with a considerable rise in 25OHD levels.

It has been shown that 25OHD levels have a strong inverse correlation with PTH levels in both the non-uraemic and uraemic populations [6,8,11,16,17]. This relationship persists even up to 25OHD levels of 75–80 nmol/l, much greater than the previously recommended normal level of 40 nmol/l [6,9–11]. The strength of this correlation in renal transplant populations has, however, not been extensively investigated [16,17].

As a result of this documented relationship, ergocalciferol supplementation is recommended for individuals with hyperparathyroidism and serum 25OHD levels <75 nmol/l [12]. However, the effect of the supplementation and subsequent rise in serum 25OHD on PTH levels has not been examined prospectively in a renal failure population.

We have demonstrated a prevalence rate of 25OHD deficiency of 32.5% in our renal transplant population with elevated PTH levels, an average of over 7 years posttransplant. In addition, 81.5% had levels lower than the level the NKF K/DOQI Guidelines recommend for supplementation. The clinical significance of such a high prevalence of apparent 25OHD deficiency/insufficiency is unclear. They are very similar to prevalence rates recently reported in the healthy Canadian population, and may therefore reflect the Canadian diet and northerly latitude in general [19].

While our results do show a significant inverse association between 25OHD and PTH, our multivariate model only accounts for 19% of the variability in PTH concentrations. Therefore, factors exclusive of the ones we have examined affect over 80% of the variability of PTH levels.

Utilizing the multivariate model, increasing 25OHD levels will have relatively little effect on PTH levels. Even with the 97.5th centile of the coefficient for 25OHD, a 75 nmol/l increase will only result in a 2.0 pmol/l reduction in PTH. Compared with this, a 30 ml/min change in GFR will be associated with a 12 pmol/l change in PTH, and a 2 mmol/l change in phosphate will result in a 1 pmol/l change.

Our results need to be confirmed in a prospective, randomized controlled trial but they suggest that supplementation with 25OHD for renal transplant patients with hyperparathyroidism may be largely futile.
Conflict of interest statement. None declared.

References

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