Original Article

Vitamin D, 1,25-Dihydroxyvitamin D, FGF23, and Graft Function after Renal Transplantation

Abstract

Vitamin-D has immuno-modulatory properties besides its role in mineral and bone disorder (MBD) and could have a role in allograft outcome. Fifty-two chronic kidney disease patients on dialysis going for transplantation were prospectively studied before and after renal transplantation. FGF23, 25(OH) vitamin D, 1,25-Dihydroxyvitamin D, PTH, serum Ca, serum PO4, and e-GFR status were evaluated. Vitamin D deficiency was seen in 25.0% of recipients before transplant (26.09 ± 12.19 ng/mL) and in 48.1% at 6 months post-transplant (23.36 ± 15.11 ng/mL). 1,25-$(OH)_2$D levels before transplant were 102.37 ± 108.44 pmol/L, which were less than control (143.30 ± 108.0 pmol/L) and decreased further to 46.20 ± 42.11 pmol/mL at 3 months and started increasing to 78.37 ± 60.12 pmol/mL at 6 months post-transplantation without vitamin D supplementation. The prevalence of hypophosphatemia after transplantation was 32.0%, hyperkalemia was 12.0%, elevated intact PTH levels at 3 and 6 months after transplant were seen in 66.7% and 30.8% patients, respectively. FGF-23 levels were high in 72.5% of patients before transplant (495.94 ± 690.68 pg/mL) and decreased to normal levels at 3 months post-transplant (31.63 ± 14.17 pg/m) (control 32.07 ± 9.78 pg/mL). Serum intact PTH levels were 379.54 ± 281.27 pg/mL before transplant and came down to 103.96 ± 68.34 at 3 months and 69.87 ± 116.03 at 6 months post-transplantation. There was trend of higher e-GFR at 1 year post-transplant in patients without vitamin D deficiency (levels ≥30 ng/mL). The dysregulated mineral metabolism continues in post-transplant despite improvement in renal function and normalization of FGF-23.

Keywords: *1,25-(OH)2 vitamin D, 25(OH) vitamin D deficiency, estimated GFR, FGF23, kidney transplantation*

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Background

Observational studies have demonstrated that vitamin D deficiency, defined as low serum total 25-hydroxy vitamin-D concentration, is associated with increased risks of death and diseases such as various cardiovascular diseases, malignancies, infectious diseases, diabetes, autoimmune diseases, and kidney diseases.[1,2] The prevalence of vitamin D deficiency or insufficiency is high among patients with chronic kidney disease (CKD), especially patients with end-stage renal disease (ESRD) and kidney transplant recipients.[3,4]

1,25-dihydroxy vitamin-D (1,25-$(OH)_2$D), the active functional metabolite of vitamin D, exerts its actions by binding to the vitamin D receptor (VDR) and altering the transcriptional rate of target genes. The protein products of these genes then carry out the functions of vitamin D, including the maintenance of serum Calcium (Ca) and phosphorus (P) homeostasis, regulation of cellular proliferation and differentiation, and modulation of the immune system.[5]

The important final step of 1,25-$(OH)_2$D synthesis is 1α-hydroxylation, which is catalyzed by 1α-hydroxylase. 1,25-$(OH)_2$D deficiency is known to occur during the progression of CKD because the final hydroxylation step of 25-hydroxy vitamin D to 1,25-$(OH)_2$D is mediated by kidney 1α-hydroxylase.[6] 1,25-$(OH)_2$D deficiency plays a major role in the development of secondary hyperparathyroidism, as 1,25-$(OH)_2$D deficiency promotes parathyroid gland growth (hyperplasia) and increased parathyroid hormone (PTH) synthesis through loss of the ability to up-regulate VDR expression and activity within parathyroid cells.[7] The end result is elevated serum PTH and abnormal Ca and *P* balance. Fibroblast growth factor–23 (FGF23), which is markedly

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increased in the early stages of CKD, has also been implicated in causing low 1,25-$(OH)_2$D levels.[8]

When the glomerular filtration rate (GFR) is approximately 33% of normal, the renal reserve of 1α-hydroxylase becomes inadequate, thereby resulting in reduced concentrations of 1,25-$(OH)_2$D.[9-12] This causes development of secondary hyperparathyroidism. Inadequate levels of 1,25-$(OH)_2$D decreases intestinal Ca absorption, resulting in reduced serum ionized Ca concentrations.[13]

Vitamin D deficiency has been defined as 25(OH) vitamin D concentration <20 ng/mL, and insufficiency between ≥20 and <30 ng/mL. As defined in KDIGO guidelines, about 97% of patients in CKD stage 5 have vitamin D deficiency or insufficiency.[14] In a rat model of chronic allograft nephropathy, administration of 1,25-$(OH)_2$D prolonged allograft survival, decreased episodes of acute rejection, reduced proteinuria, and prevented histological changes associated with chronic allograft nephropathy.[15] This suggests that vitamin D supplementation may reduce acute rejection and chronic allograft nephropathy through its interactions with the immune system.

1,25-$(OH)_2$D analogues can act as adjuvant immuno-modulator therapy. They have been shown to prolong the survival of heart,[16] liver,[17] and kidney[18] allograft and inhibit not only acute but also chronic allograft rejection[19] in experimental models.

Methods

Fifty-two CKD patients on dialysis going for transplantation were prospectively studied before and after renal transplantation. FGF23, 25(OH) vitamin D, 1,25-$(OH)_2$D, PTH, serum Ca, serum PO4, and estimated glomerular filtration rate (eGFR) were evaluated. All these patients received vitamin D supplementation (calcirol D2, 60,000 IU weekly for 6 weeks followed by once a month to maintain vitamin D level >30 ng/mL) before transplantation as per the requirement if they were vitamin D deficient. After transplantation, they were not given vitamin D supplementation.

Biochemical parameters were measured using biochemistry analyzer (AU480, Beckman Coulter). Human FGF23 (Intact) Elisa Kit (Immutopics, Inc. San Clemente, CA) was used to measure FGF-23 plasma concentration (https://www.quidel.com/research/immutopics/human-fgf-23-intact, Cat. 60-6100). 1,25-$(OH)_2$D levels in serum were measured by ELISA (Immunodiagnostic Systems Ltd., https://www.idsplc.com/products/125-dihydroxy-vitamin-d-eia/, code: AC62F1) on an BIORAD-ELISA ELISA reader. 25(OH) vitamin D levels (http://www.laboratoireduquaivalliere.fr/notices%20analyses/FicheTechniqueVITD.pdf) and I-PTH (http://www.ilexmedical.com/files/PDF/IntactPTH_ARC.pdf) levels were assayed in serum by chemiluminescent microparticle immunoassay (CMIA) on an Architect i-1000 STAT (ABBOTT).

There is no consensus regarding normal 1,25 $(OH)_2$D levels parameter in transplant recipients. We used 25th percentile of normal control as cutoff, for lower limit to define normal levels of 1,25 $(OH)_2$D in >63 pmoL/lit (25th percentile of control group).[20] Normal FGF-23 levels in our lab is 18.2-58.1 pg/mL. eGFR was measured using the CKD-Epidemiology Collaboration (CKD-EPI) equation which confers less underestimation of GFR in subjects with normal renal function.

25 (OH) Vitamin D levels of >30 ng/mL were considered sufficient and <20 ng/mL were deficient while 20-30 ng/mL were the insufficient vitamin D status (KDOQI guidelines).

Statistical analysis

Data was expressed as mean values ± standard deviation and as absolute and relative frequency for categorical variables. Statistical analysis was performed using SPSS software (Version 20.0). Graft function at 3 months, 6 months, and 1 year was compared between the groups by analysis of covariance (ANCOVA), taking into account covariates like e-GFR value at 1 year and 25-hydroxyvitamin D3 at baseline, 3 months, and 6 months. Various categorical variables were analyzed using Pearson correlation, Chi-square test, and Fisher's exact test. Statistical evaluation was used with eGFR as dependent variable and other factors as independent variables. Other statistical tests as appropriate were applied to various factors and variables.

Results

Fifty-two CKD (82.7% male, 17.3% female) patients on dialysis going for transplantation were prospectively studied before and after renal transplantation. Patient characteristics and demographic data are given in Table 1. After transplantation, prevalence of hypophosphatemia was 32.0% and of hypercalcemia was 12.0%. Elevated intact PTH levels were seen in 66.7% at 3 months, and in 30.8% at 6 months post-transplantation. Before transplantation, 71.2% of patients had hyperphosphatemia, while hypercalcemia was seen in 3.8% with elevated intact PTH levels seen in 92.2%. Raised FGF-23 levels were seen in 72.5% of patients before transplant (495.94 ± 690.68 pg/mL), which decreased to normal level at 3 months post-transplant (31.63 ± 14.17 pg/mL) (normal control 32.07 ± 9.78 pg/mL) [Table 2]. 25(OH) vitamin D levels indicated vitamin D deficiency in 25.0% of patients before transplant (26.09 ± 12.19 ng/mL). In post-transplant period, vitamin D deficiency was seen at 3 months in 43.1% (23.44 ± 10.64 ng/mL), while at 6 months, vitamin D deficiency further increased and was seen in 48.1% (23.36 ± 15.11 ng/mL). 1,25-$(OH)_2$D levels before transplant were 102.37 ± 108.44 pmol/L which was less than control (143.30 ± 108.0 pmol/L) and decreased further to 46.20 ± 42.11 pmol/L at 3 months but showed an increase to 78.37 ± 60.12 pmol/L at 6 months post-transplantation (which was still less than controls) [Table 2]. Comparison between

Table 1: Patient Demographics

Characteristic	All Patients (*n*=52)	3-Month 25(OH) D Level <20 ng/mL (*n*=22)	3-Month 25(OH) D Level ≥20 ng/mL (*n*=30)	*P**
Patient's Age (years)	34.85±9.95	37.50±9.79	32.90±9.78	0.97
Sex				
Male	43 (82.7%)	15 (68.2%)	28 (93.3%)	0.00
Female	9 (17.3%)	7 (31.8%)	2 (6.7%)	
Induction				
Baxilixmab	41 (78.8%)	15 (68.2%)	26 (86.7%)	0.00
ATG	6 (11.5%)	5 (31.8%)	1 (3.3%)	
Others	5 (9.7%)	2 (9.1%)	3 (10%)	
CNI				
Tacrolimus (ng/ml)	13.47±6.06 (*n*=51)	15.02±5.94	12.29±5.99	0.99
Cyclosporine (ng/ml)	159.50 (*n*=1)			
Rejection				
No Rejection	47 (90.4%)	20 (90.9%)	27 (90%)	0.83
Rejection	5 (9.6%)	2 (9.1%)	3 (10%)	
3 months-post-KT Vitamin-D (ng/mL)	23.44±10.64	15.28±3.08	29.45±10.03	0.00
3 months-post-KT FGF-23 (pg/mL)	31.63±14.17	29.09±12.79	33.56±15.06	0.67
3 months-post-KT Phosphorus (mg/dL)	3.09±0.91	3.09±0.71	3.09±1.05	0.40
3 months-post-KT Calcium (mg/dL)	9.12±1.04	8.86±0.77	9.31±1.17	0.17
3 months-post-KT IPTH (pg/mL)	103.96±68.34	106.02±80.90	102.39±58.53	0.20
Donor's Age (years)	45.36±11.83	44.84±9.58	46.70±16.93	0.03

Values are reported as number of patients (percentage), mean±SD, as appropriate. **P* value represents tests of significance from *t* test, Chi-squared test, or Fisher exact test, as appropriate

Table 2: Descriptive statistics of pre and post kidney transplant data

Characteristic	Pre-KT	3 months-post-KT	6 months-post-KT	Control group	*P*
FGF-23 (pg/mL)	495.94±690.68	31.63±14.17	29.86±16.43	32.07±9.78	0.045*
					0.794**
					0.648***
Phosphorus (mg/dL)	6.93±1.52	3.09±0.91	3.20±0.45	3.87±0.71	0.262*
					0.3.01**
					0.294***
Calcium (mg/dL)	8.25±0.99	9.12±1.04	9.20±1.05	9.15±0.54	0.158*
					0.440**
					0.325***
Vitamin-D (ng/mL)	26.09±12.19	23.44±10.64	23.36±15.11	20.38±8.07	0.649*
					0.282**
					0.485***
$1,25(OH)_2D$ (pmol/L)	102.37±108.44	46.20±42.11	78.37±60.12	143.30±108.07	0.942*
					0.175**
					0.498***
IPTH (pg/mL)	379.54±281.27	103.96±68.34	69.86±116.03	66.28±28.08	0.335*
					0.116**
					0.393***

*Pre transplant, **Post-transplant 3 month, ***Post-transplant 6 month, all compared to control group

groups with e-GFR <60 and ≥60 mL/min/1.73 m^2 showed that post-transplant eGFR at 12 months did not correlate with vitamin D deficiency [Table 3] but showed correlation with vitamin D sufficiency [Table 4].

Serum intact PTH levels were 379.54 ± 281.27 pg/mL before transplant and came down after transplant to 103.96 ± 68.34 pg/mL at 3 months and to 69.87 ± 116.03 pg/mL at 6 months.

All patients except one were on tacrolimus-based immunosuppression. Tacrolimus levels at 1 month were 13.47 ± 6.06 ng/mL with baseline normal target range of 10–15 ng/mL at 1 month.

There was no statistically significant difference (*P* value > 0.05) in all the parameters of mineral metabolisms studied in rejection and without rejection groups.

Table 3: Descriptive Statistics of vitamin D (pre and post kidney transplant) compared with graft e-GFR category at 12 months (post-KT)

Parameters (*n*=52)	e-GFR 12 months (POST-KT) <60 mL/min/1.73 m² (*n*=20)	e-GFR 12 months (POST-KT) ≥60 mL/min/1.73 m² (*n*=32)	*P*
PRE-KT1,25 Dihydroxy vitamin-D (pmol/L)	98.02±78.5	108.07±124.08	0.297
PRE-KT Vitamin -D (ng/mL)	22.95±8.47	28.00±13.89	0.342
3 MONTHS-POST-KT 1,25 Dihydroxy vitamin-D (pmol/L)	41.70±44.52	44.32±32.59	0.810
3 MONTHS-POST-KT Vitamin -D (ng/ml)	21.09±8.74	25.23±11.27	0.570
6 MONTHS-POST-KT 1,25 Dihydroxy vitamin-D (pmol/L)	79.74±60.28	78.59±61.78	0.789
6 MONTHS-POST-KT Vitamin -D (ng/ml)	20.72±15.35	25.55±14.73	0.908
3 MONTHS-POST-KT Creatinine (mg/dL)	1.240±0.30	1.01±0.26	0.563
6 MONTHS-POST-KT Creatinine (mg/dl)	1.42±0.26	1.11±0.20	0.175
12 MONTHS-POST-KT Creatinine (mg/dL)	1.97±1.33	1.11±0.18	0.016

Table 4: Three-month Vitamin D status and graft eGFR at 1 year

25(OH) Vitamin D 3 months post-transplant (ng/mL)	Estimated GFR 12 months post-transplant (mL/min/1.73 m²)	*P*
Vitamin D <30	64.18±22.8	0.026
Vitamin D >30, sufficient	81.75±24.9	
Vitamin D <20, deficient	63.00±26.0	0.185
Vitamin D >20	72.07±22.5	

Discussion

Our study shows that there is high prevalence of vitamin D deficiency and insufficiency in patients with CKD going for transplantation, and it persists even after kidney transplantation in majority of patients , and this is also associated with secondary hyperparathyroidism (SHPT). This has also been shown in reports of publications of chronic kidney patients going for transplantation.[3,21]

Kidney is the main organ for metabolizing 25(OH) vitamin D to 1,25-$(OH)_2$D (the biologically active form of vitamin D) by the action of the enzyme 1α-hydroxylase.[22] Reduction in the GFR is associated with hyperphosphatemia and hypocalcemia. 1,25-$(OH)_2$D deficiency results in the development of secondary hyperparathyroidism, as low levels of vitamin D stimulate synthesis of PTH, and loss of ability to regulate the expression and activity of VDR in parathyroid cells.[7] Our results show that pre-transplant 1,25-$(OH)_2$D levels were low. But 1,25-$(OH)_2$D levels continued to be still low in the post-transplant period. In our study, we used vitamin D supplements only in the pre-transplant period. No vitamin D analogue was used in the post-transplant period. Transplant patients continued to have both low 25(OH) vitamin D and low 1,25-$(OH)_2$D. This could be due to reduced renal mass after transplant. Although patients after transplant achieved improved renal function (as indicated by serum creatinine levels), the eGFR was still suboptimal in post-transplant period.

After transplant, though there is significant improvement in disorders of mineral metabolism, transplant patients continue to have vitamin D deficiency along with impaired graft function. After transplant, FGF23 levels got rapidly normalized as GFR improved. But 25(OH) vitamin D deficiency and low levels of 1,25-$(OH)_2$D persisted after transplant.

In our study, FGF-23 levels rapidly decreased within normal limits within 3 months after transplantation. PTH and serum phosphorous levels also decreased significantly after kidney transplantation. Serum Ca and 1,25-$(OH)_2$D levels showed an increasing trend after transplantation. In our study, there was no association between FGF-23 and 1,25-$(OH)_2$D levels. This has also been reported in the literature.[23] We did not use any vitamin D analogue supplementation in post-transplant period. Patients in our study showed a trend of increase in 1,25-$(OH)_2$D levels after transplantation. At 6 months post-transplantation, 1,25-$(OH)_2$D levels increased without any vitamin D supplementation. Vitamin D deficiency has been reported to be associated with risk of acute rejections in the post-transplant period. Vitamin D as an immune-modulator has the potential for preventing allograft rejection after transplantation.[24-26] Even patients with good graft function after renal transplantation continue to have significant biochemical changes that can result in deterioration of bone quality, specifically in relation to vitamin D deficiency and hyperparathyroidism.[27] Stavroulopoulos *et al.* showed that after transplant, vitamin D deficiency was very common in all of their renal transplant recipients and correlated with secondary hyperparathyroidism.[4]

Prevalence of 25(OH) vitamin D deficiency at time of renal transplantation has been reported to be quite high.[28] Renal function and vitamin D deficiency predict PTH levels in renal transplant patients. Management of both hyperparathyroidism and vitamin D deficiency needs to be done optimally after transplantation.[29,30] In our study, vitamin D levels higher than 30 ng/mL were seen only in a minority of transplant recipients on follow-up. No association has been reported between 1,25-$(OH)_2$D levels and eGFR after transplantation[31] as was also seen in our study. At 3 months post-transplantation, there was high

prevalence of vitamin D deficiency along with raised PTH levels in our group of patients.

In vitro studies on cell cultures suggest that intra-cellular activity of 1,25-$(OH)_2$D might be required to achieve adequate immune responses.[32,33] Immune cells are both targets for 1,25-$(OH)_2$D and are also able to locally activate 1,25-$(OH)_2$D from circulating 25(OH) vitamin D. The anti-proliferative effects of 1,25-$(OH)_2$D (i.e., stimulation of apoptosis, suppression of proliferation and differentiation, and decreased production of immunoglobulin) on B cells have been reported to be indirectly driven by T-helper cells.[34] In our study, patients with vitamin D deficiency had a trend of decreased eGFR which could have a detrimental effect on graft outcome at 12 months post-transplant.

Conclusion

The dysregulated mineral metabolism continues after kidney transplant despite improvement in renal function and normalization of FGF-23. Although improved, 1,25-$(OH)_2$D levels after transplantation were still less than normal healthy controls. This may be due to reduced renal mass and 1α-hydroxylase activity as compared to healthy controls with two kidneys as compared to transplant patients who have only one functioning kidney. In this study, there was trend of higher e-GFR at 1 year post-transplant in patients without vitamin D deficiency (levels $\geq$20 ng/mL). Future studies are required to test whether vitamin D supplementation early after kidney transplantation could improve allograft outcomes in larger number of patients.

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Conflicts of interest

There are no conflicts of interest.

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