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Low 25(OH) Vitamin-D levels are associated with inferior graft function in living related kidney transplant recipients

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ABSTRACT

Introduction: Vitamin D deficiency can impact post-transplant outcomes due to its effect on graft function and rejection. The effect of pre- and post-transplant serum vitamin D levels was evaluated on graft function.

Objectives: This study aims to determine the incidence of vitamin D deficiency and its effect on post kidney transplant allograft function in a North Indian cohort.

Patients and Methods: We evaluated 57 patients on dialysis, going for transplantation. Estimated glomerular filtration rate (eGFR) was measured using modification of diet in renal disease (MDRD) formula at 2 weeks and 3, 6, 12 months interval after kidney transplantation.

Results: Pre- and post-transplant (3 months) vitamin D levels were evaluated for vitamin D deficiency and graft function. Before transplant vitamin D levels were 25.77 ± 13.68 ng/mL, 40.4% of these recipients had vitamin D deficiency (levels <20 ng/mL). After transplant, vitamin D levels at 3 months were 22.08 ± 11.15 ng/mL and 54.4% of recipients had vitamin D deficiency. No patient was on vitamin D supplementation after transplantation. At 3 months post-transplant, recipients with vitamin D levels <20 ng/mL, had significantly lower eGFR and higher serum creatinine value as compared to the group with vitamin D levels >20ng/mL. Recipients were divided into 3 groups based on pre- and post-transplant vitamin D levels (<20, 20-30 and >30ng/mL). Pre-transplant vitamin D levels correlated with graft function at 14 days. On multiple regression analysis, 3-month post-transplant vitamin D levels correlated with 12 months eGFR. There was increased incidence of acute rejection episodes in vitamin D deficiency group.

Conclusion: There is a high incidence of vitamin D deficiency and insufficiency in kidney transplant recipients. Low levels of post-transplant vitamin D levels at 3 months were associated with inferior allograft function (eGFR) at 1 year.

Implication for health policy/practice/research/medical education:
Vitamin D deficiency needs to be evaluated as an important risk factor for allograft function after renal transplantation.

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Original

Introduction

The prevalence of vitamin D deficiency or insufficiency is high in patients with end-stage renal disease and in kidney transplant recipients (1,2). Observational studies have demonstrated that vitamin D deficiency, defined as low serum total 25-hydroxyvitamin D (25[OH] D) concentration, is associated with increased risks of death and diseases such as cardiovascular diseases, malignancies, infectious diseases, diabetes and autoimmune diseases (3,4). The chronic kidney disease (CKD) patients have vitamin D deficiency associated with increased co-morbidities and mortality associated with high concentration of parathyroid hormone with bone mineral disorders (5,6).

The Kidney Disease Improving Global Outcomes (K/DIGO) guidelines recommend measurement of vitamin D levels in patients with CKD to monitor for vitamin D deficiency (7). The definition of vitamin D deficiency or insufficiency varies in various guidelines and recommendations. Vitamin D (25(OH)D) levels of less

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than 20 ng/mL is an indicator of deficiency (8). Many other reports support the predictable concentration of 30 ng/mL as cut off to define vitamin D insufficiency (Kidney Disease Outcomes Quality Initiative [KDOQI] guidelines) (9,10). In post-transplant patients, there are no clear guidelines regarding normal serum total 25(OH) D levels or need for nutritional vitamin D supplementation. Vitamin D is an active hormone in kidney controlling mineral homeostasis. The estimated glomerular filtration rate (eGFR) at 1 year after transplantation is associated with long-term allograft outcome (11,12). After renal transplantation graft function and high PTH levels recover (13). The vitamin D status correlates with kidney allograft function. After renal transplantation, PTH and FGF23 concentrations also start normalizing as compared to CKD patients (14,15).

Vitamin D could have immunologic effects resulting in tolerance induction and support to defending immunity. As antigen presenting cells (macrophages and dendritic cells), T cells and B cells have the capability both to synthesize and also to respond to 1,25 (OH)2, vitamin D (16).

Objectives

This study aims to determine the incidence of vitamin D deficiency and its effect on post kidney transplant allograft function in a North Indian cohort.

Patients and Methods

Patients

Fifty-seven CKD patients on dialysis going for transplantation were prospectively studied before and after renal transplantation. Serum 25 (OH) vitamin D, PTH, calcium and serum phosphorous levels and also eGFR were evaluated. Biochemical parameters were measured using biochemistry analyser (AU480-Backman Coulter). Vitamin-D 25(OH) and PTH levels were assayed by chemiluminescent micro-particle immunoassay (CMIA) (Architect i-1000 Stat Abbott).

Ethical issues

The research followed the tenets of the Declaration of Helsinki; 2) informed consent was obtained; and 3). This study was approved by the Ethics Committee of Sanjay Gandhi Post Graduate Institute of Medical Sciences, (intramural project code #PGI/DIR/RC/303/2013).

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 version 20.0.

Graft function at baseline (2 weeks), 3 months, 6 months and 1 year post-transplant was correlated by analysis of covariance (ANCOVA), taking into account covariates like eGFR at one year and 25-hydroxyvitamin D levels (at baseline and at three months). Various categorical variables were analyzed using Pearson's correlation, chi-square test, Fisher's exact test, paired *t* test, independent *t* test. Multiple linear regression statistics was used with eGFR as dependent variable and other factors as independent variables. Various statistical tests as appropriate were applied to various variables.

Results

The impact of pre-transplant and 3-month post-transplant, 25(OH)D levels was evaluated on subsequent graft function (GFR) in a group of kidney transplant recipients. The pre- and post-transplant serum vitamin D levels were evaluated for insufficiency or deficiency. Effect on subsequent graft function was evaluated by calculating eGFR up to one year after transplant. We analyzed CKD patients for vitamin D deficiency in pre-transplant period while they were all on vitamin D supplements, after transplant they were not on vitamin D supplements. We measured eGFR using the modification of diet in renal disease (MDRD) formula at 14 days, 3 months, 6 months and 12 months interval after kidney transplant. We measured PTH, serum calcium and serum phosphorous levels in patients before and after kidney transplant and compared with controls.

Mean values of pre-transplant vitamin-D levels before transplant were 25.77 ± 13.68 ng/mL. In 40.4% of recipients before transplant, vitamin D levels were <20 ng/mL, indicating vitamin D deficiency. Post-transplant (at 3 months), mean vitamin D levels were 22.08 ± 11.15 ng/mL. After transplant (at 3 months) 54.4% of recipients had vitamin D deficiency (levels <20 ng/mL).

Before transplant, hypocalcemia was seen in 29.8% while hypercalcemia was seen in 3.5% while after transplant (at three months) hypocalemia was seen in 27.2% of recipients. Pre-transplantation hyperphosphatemia was seen in 96.5% of patients while majority of them developed hypophosphatemia (54.2%) after transplantation. Serum PTH levels were high in pre-transplantation period, while after transplantation PTH levels came down but were still higher than control healthy population.

We analyzed 67 normal controls for vitamin D levels. Mean of vitamin D levels in controls (normal population) were 19.88 ± 8.34 ng/mL with a creatinine mean value of 0.85 ± 0.20 mg/dL. The control population had 77.6% females and 22.6% males. Majority of normal control population (63.8%) had vitamin D deficiency (vitamin D levels <20 ng/mL).

Kidney transplant recipients were divided into two groups <20 ng/mL and >20 ng/mL vitamin D levels at 3-months post-transplant (Table 1). Then post-transplant graft function was compared between two groups. Recipients with vitamin D deficiency (<20 ng/mL) at 3-months post-transplant showed lower eGFR and higher serum creatinine levels at 3-month, 6-month and 1-year post-transplantation as compared to the group with vitamin D levels >20 ng/mL. Vitamin D levels before transplant did not correlate with graft function at 3, 6 or 12-month but

Table 1. Patient demographics and lab data after kidney transplant

Characteristic	All patients (n=57)	Post 3 months 25(OH)D level <20 ng/mL (Deficient group) (n=29)	Post 3 months 25(OH)D level ≥20ng/mL (Non-deficient group) (n=28)	P value
Patient's age (y)	34.28±11.12	37.38±11.45	31.07±9.99	0.27
Male	50(87.7%)	26(89.7%)	24(85.77%)	0.65
Female	7(12.3%)	3(10.3%)	4(14.3%)	
Induction/No Induction	46/11	23/6	23/5	0.19
Baxiliximab	43(75.4%)	20(69.0%)	23(82.1%)	
ATG	3(5.3%)	3(10.3%)	0(0%)	
Tacrolimus (ng/mL)	55(96.5%)	28(96.6%)	27(96.4%)	0.98
Cyclosporine (ng/mL)	2(3.5%)	1(3.4%)	1(3.6%)	
No rejection	50(87.7%)	23(79.3%)	27(96.4%)	
Rejection	7(12.3%)	6(20.7%)	1(3.6%)	0.04
Pre-KT vitamin-D(25OH) (ng/mL)	25.77±13.68	21.78±8.26	29.75±17.45	0.032
3 months post-KT PTH (pg/mL)	136.31±120.38	166.81±149.89	99.47±53.12	0.041
3 months post-KT calcium (mg/dL)	8.64±0.72	8.70±0.58	8.56±0.91	0.520
3 months post-KT phosphorous(mg/dL)	2.98±1.22	3.05±1.31	2.89±1.18	0.679
Post-KT eGFR(ml/min) at 3 months	77.25±31.67	69.32±17.96	85.72±41.60	0.063
Post-KT creatinine at 3 months (mg/dL)	1.22±0.28	1.29±0.25	1.15±0.31	0.074
Post-KT eGFR(mL/min) at 6 months	68.26±20.83	60.30±13.65	76.48±24.62	0.005
Post-KT creatinine at 6 months (mg/dL)	1.34±0.31	1.46±0.28	1.23±0.31	0.010
Post-KT eGFR (ml/min) at 12 months	67.08±19.71	62.38±16.93	72.00±21.26	0.080
Post-KT creatinine at 12 months (mg/dL)	1.36±0.33	1.44±0.35	1.29±0.29	0.095

the group with vitamin D deficiency pre-transplant had higher serum creatinine levels and lower eGFR at 15 days post-transplantation (Tables 2 and 3). The group with vitamin D deficiency (<20 ng/mL) had more episodes of acute rejections as compared to the group with vitamin D levels >20 ng/mL (Table 1, $P<0.04$)

Kidney transplant recipients were classified based on post-transplant vitamin D levels at 3 months, into three groups <20, 20-30 and >30 ng/mL to compare the effect on graft outcome (eGFR). The group with post-transplant vitamin D levels at 3 months of >30 ng/mL had the best graft function at one year. With post kidney transplant (3 months) vitamin D levels as an independent variable, 12 months eGFR values showed a significant difference between 3 groups, ($P<0.022$, Figure 1). On multivariate linear regression analysis, considering graft function as dependent variable, 3-month vitamin-D levels showed significant correlation with 12-month eGFR (Table 4).

Discussion

This study shows that a high prevalence of vitamin D deficiency and insufficiency in patients with CKD going for transplantation and it persists even after kidney transplantation in the majority of patients. This finding as has also been reported in other publications (17,18). Vitamin D deficiency has been defined as 25(OH)D concentration <20 ng/mL, and insufficiency has been defined as 25(OH)D concentration <30 ng/mL (19,20). As defined in KDIGO guidelines, about 97% of patients in CKD stage 5 have vitamin D deficiency or insufficiency (21,22) and this is also associated with secondary hyperparathyroidism. This finding is also shown in our results.

Kidney is the site of conversion of 25-hydroxyvitamin D

Table 2. Vitamin D status at pre-transplant with various biochemical parameters

Characteristic	All Patients		Pre 25(OH)D Level <20 ng/mL		Pre 25(OH)D Level ≥20 ng/mL		*P* value	Control group
	Pre-KT	Post-KT 3 month	Pre-KT	Post-KT 3 month	Pre-KT	Post-KT 3 month		
Vitamin-D (25OH) (ng/mL)	25.77± 13.68	22.08±11.15	14.91±2.94	18.28±6.96	33.12±13.19	24.81±12.79	0.00 0.03	19.88±8.34
PTH (pg/mL)	382.47±322.58	136.31±120.38	343.76±298.12	148.65±150.20	408.29±339.94	126.86±93.04	0.43 0.51	87.36±38.30
Calcium (mg/dL)	8.70±0.88	8.64±0.72	8.69±0.52	8.53±0.92	8.71±1.07	8.71±0.53	0.938 0.396	9.20±0.57
Phosphorous (mg/ dL)	6.35±1.97	2.98±1.22	6.49±1.97	2.99±1.50	6.25±2.00	2.97±1.01	0.654 0.970	3.93±0.79
Creatinine (mg/ dL) 14 days	6.96±2.54	1.25±0.62	7.61±2.59	1.49±0.85	6.50±2.44	1.09±0.30	0.114 0.015	0.85±0.20

Table 3. Pre-transplant vitamin D levels and its effect on post-transplant graft function

Characteristic	All Patients	Pre 25(OH)D Level <20 ng/mL	Pre 25(OH)D Level ≥20 ng/mL	*P* value*
eGFR (mL/min) 14 days	85.49±68.06	66.70±25.70	98.59±84.12	0.085
eGFR (mL/min) 3 months	77.25±31.67	71.30±20.80	81.53±37.352	0.241
Creatinine (mg/dL) 3 months	1.22±0.28	1.27±0.30	1.18±0.26	0.241
eGFR (ml/min) 6 months	68.26±20.83	64.64±17.44	70.75±22.81	0.294
Creatinine (mg/dL) 6 months	1.34±0.31	1.38±0.33	1.31±0.30	0.429
eGFR (mL/min) 12 months	67.08±19.71	65.67±20.36	68.00±19.55	0.678
Creatinine (mg/dL) 12 months	1.36±0.33	1.38±0.33	1.31±0.30	0.832

* *P* value on comparing: <20 and ≥20 ng/mL pre-transplant vitamin D levels.

Table 4. Model Summary of multivariate linear regression analysis

	Coefficients ± SD	*t* value	*P* value
Full Model [a] (Constant)	3.39	16.55	0.00
Creatinine 12 months	-1.19	-8.73	0.00
Post-KT3 months vitamin D[b]	-0.31	-3.28	0.002
Model (ANOVA)	**Sum of squares**	**Mean square**	***P* value**
Regression	6.10	3.051	0.00
Residual	2.74	0.07	
Total	8.84		

Dependent Variable: eGFR 12 months, Predictor Variables: S. Creatinine, 3 Month Post-KT vitamin D

Model Summary	R	R square	Adjusted R square	Std. Error of the estimate
	0.83[b]	0.69	0.67	0.27

Only the variables independently associated with 12 months eGFR are presented (final models after forward selection procedure).
[a] The full model includes all the variables used in this study.
[b] For an increase of 1 unit of the variable.

(25(OH)D) to 1,25-dihydroxyvitamin D3 (1,25(OH)2D), also known as calcitriol (biologically active form of vitamin D) by the action of the enzyme 1-alphahydroxylase (23). The incidence of vitamin D deficiency in patients after renal transplantation has been reported to be above 50%, and its causes are multifactorial, including increased catabolism of the vitamin D by immunosuppressants (24,25). Reduced supply of substrate 25(OH) D for 1-alpha-hydroxylase to active form of vitamin D may also be an important cause for the low levels of calcitriol in chronic renal disease (26), including renal transplant recipients. Successful transplantation significantly improves disorders of mineral metabolism, during the first year post-transplant. Majority of patients after transplant continue to have vitamin D deficiency along with calcium, phosphate and PTH abnormalities. Multiple disturbances of bone mineral disorder due to impaired graft function and the other effects of immunosuppressive drugs aggravate the harmful effects of vitamin D deficiency (27). In our study, there was correlation between low levels of 25-vitamin D levels and renal graft function, suggesting that vitamin D deficiency may be a predictor of poor graft function. In a large prospective observational study of patients receiving renal transplantation, the low concentration of 25(OH) D at three months post-transplantation has been reported to be independently associated with a reduction in glomerular filtration rate at nine months after transplant. Although the reduction was only minor, it was consistent with chronic interstitial and tubular injury (28). Serum levels of 25(OH)D are thousand times greater than 1,25(OH)2D. In renal failure, the levels of 1,25(OH)2D are decreased and low levels of 25(OH) vitamin D also contribute to this deficiency of active Vitamin D (29). Mazzaferro et al (30) found insufficiency or deficiency of 25(OH)D in 69.1% of renal transplant patients. Vitamin D has also been reported to have an immunomodulatory role in transplant recipients. Low 25-hydroxyvitamin D levels have been reported to be associated with increased opportunistic viral infections after kidney transplant (31). Stavroulopoulos et al (2) reported that the prevalence of deficiency or insufficiency of 25(OH)D is extremely high after kidney transplantation, affecting more than 90% of patients, especially in the first year after the procedure. In our study, transplant patients with more than 20 ng/mL vitamin D levels had lower serum PTH levels as compared to the group with vitamin D deficiency. This has been reported in other studies as well (32), The low levels of substrate 25(OH)D can contribute to the reduced synthesis of 1,25(OH)2D but other factors may also be present, interfering with the action of the enzyme (33,34). Mithal et al have reported a high prevalence of vitamin D deficiency (35). They reported vitamin D deficiency in 96% of the neonates, 91% of healthy school girls, 78% of healthy hospital staff, and 84% of the pregnant women. In our study, the healthy control group, consisting mainly of females had a high incidence of vitamin-D deficiency (63.8%). Jabbar et al (36) reported, deficiency of 25(OH) vitamin D3 in all CKD patients and in more than three-quarters of healthy control subjects. Aggarwal et al (37) reported high prevalence of hypovitaminosis D in renal

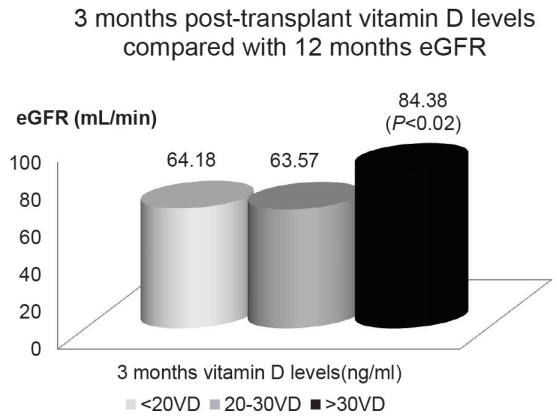

Figure 1. Post-transplant vitamin D levels and 12 months graft function.

transplant recipients. This did not get corrected despite nutritional improvement or normalization of GFR, post-transplantation. Our study highlights that routine evaluation and monitoring of vitamin D levels is required to diagnose vitamin D deficiency after transplantation. There could also be a need for supplementation of 25(OH) vitamin D in post-renal transplant patients. Our study shows that vitamin D deficiency was also associated with an increase in rejection rates and inferior eGFR at one year.

Conclusion

In our study there was a high incidence of vitamin D deficiency and insufficiency in kidney transplant recipients. Low levels of 25 (OH) vitamin D levels before transplantation were associated with significantly inferior kidney allograft function (eGFR) at 14 days. Vitamin D insufficiency was common in normal healthy controls as well. Low levels of post-transplant vitamin D levels at 3 months was associated with inferior allograft function (reduced eGFR) at 12 months and increased acute rejection episodes. There could be need to use vitamin D supplements in the post-transplant period to correct vitamin D deficiency. This may have beneficial effects on graft outcome.

Limitations of the study

The study did not involve supplementation of vitamin D. This study was conducted on a limited proportion of patients. Larger studies are suggested.

Authors' contribution

RKS, SM, NP, AG, DSB, AK and MRP participated in research design. RKS and SM participated in the writing of the paper. RKS, SM, NP, AG, DSB, AK and MRP participated in performance of the research. RKS and SM Contributed to new reagents or analytic tools. RKS, SM and MRP participated in data analysis.

Conflicts of interest

The authors declare no conflict of interest. This study has not been published in or submitted to any other journal for publication.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. An abstract published in Indian Journal of Transplantation (a special abstract issue of Journal of the proceedings of Indian Society of Organ Transplantation meeting, volume 10, Issue 4, October–December 2016, Pages 108-109).

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