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Original article

Prevalence of Hypovitaminosis D among Renal Transplant Recipients and Its Relation to Graft Interstitial Fibrosis

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ABSTRACT

Background: Vitamin D deficiency is not uncommon among kidney transplant recipients which may lead bone diseases, graft aging and vascular disease. We aimed to evaluate the prevalence of hypovitaminosis D among renal transplant recipients and its relation to graft interstial fibrosis in graft biopsies. **Methods:**We recruited 99 renal transplant recipients with recent graft biopsies performed during the period between 2016 and 2017 in the nephrology department, organ transplant center of Kuwait. We excluded 2nd transplants, previous rejecters, extremes of ages (<18,>70years), postmenopausal women, and conditions that interfered with vitamin D metabolism as hepatic disease, gastric bypass, cystic fibrosis; extensive burns and chronic diarrhea. Patients were divided the into two groups: recent transplants (<1-year post-transplant, n=49) and older transplants (>1- year post-transplant, n=50). We measured serum 25(OH) vitamin D, iPTH, albumin, creatinine, calcium, phosphorus, cholesterol and uric acid. Graft biopsies were assessed according to Banff classification 2013. **Results:**Most of patients (81.8%) had hypovitaminosis D with variable degrees' deficiency (48.5 % had insufficiency, 24.2 % had mild deficiency, and 9.1 % had severe deficiency). In our study, both groups were comparable regarding their demographic data except longer dialysis duration and higher number of patients receiving tacrolimus-based therapy in group 1. Vitamin D level was lower in group 1 but did not rank to significance (p>0.05), however, it had significant negative correlation with iPTH and the degree of renal graft interstitial fibrosis and vitamin D deficiency. **Conclusion:** The prevalence of 25-OH vitamin D deficiency is high post-transplant and it might contribute to the graft interstitial fibrosis.

Keywords: vitamin D , renal transplant , fibosis, rejection

INTRODUCTION

Kidney transplantation is the treatment of choice for patients suffering from end-stage renal disease (ESRD) (**1).** Vitamin D is soluble fat vitamin, its role is calcium and bone homeostasis. Its active form 1,25-dihydroxyvitamin D potentially regulates many other cellular functions. Studies have shown that vitamin D influences muscle function, immune system, cardiovascular mortality and morbidity, metabolic disorders and kidney graft aging **(2).** Reduced 25(OH) vitamin D level is frequently observed in kidney transplant recipients (KTRs), with an extensive prevalence

of deficiency and insufficiency (30% and 81%) respectively. Low 25(OH) vitamin D levels have been observed after transplantation with only 12% of KTRs showing sufficient 25(OH) vitamin D levels (higher than 30 ng/ml) during the first-year post-transplant **(3).**

Physicians advise renal transplant patients to avoid direct sun exposure because their immunosuppressive therapy is associated with high risk of skin carcinomas. So, they are at particular risk of hypovitaminosis D **(4).** Immunosuppressive therapy contributes to vitamin D derangement, although the scientific literature is still scanty on this topic. Glucocorticoids alter vitamin D metabolism, enzymes involved in vitamin D catabolism and increasing PTH andFGF23 levels **(3).**

Among other immunosuppressive agents' discrepancies were observed between the effects of calcineurin inhibitors (CNI) and mammalian target of rapamycin (mTOR) inhibitors on the vitamin D system. CNI was associated with lower 25(OH) vitamin D levels among 289 KTRs and animal models showing CNI-induced vitamin D resistance through VDR downregulation **(5).** On the other hand, Sirolimus has been reported to be a bone sparing immunosuppressive drug, free from side effects on bone and vitamin D metabolism **(6).**

One of the major causes of late graft loss in renal transplant recipients is chronic allograft nephropathy (CAN). CAN is highly prevalent in renal transplant recipients, with moderate to severe CAN present in 24.7% of recipients at 1-year post-transplant and in 89.8% of recipients by 10 years' post-transplant. CAN is defined by the histopathological features of interstitial fibrosis and tubular atrophy, but can also be associated with subclinical rejection and transplant glomerulopathy **(7).** There have been studies about the relation between vitamin D deficiency and graft interstial fibrosis/ tubular atrophy (IF/TA) on graft survival. **Frank B et al2013.,** found unique association between 25(OH)vitamin D deficiency at 12 months and IF/TA progression from 3 months to 1 year after transplantation **(2).**

Aim of the work: we aimed to evaluate the prevalence of hypovitaminosis D among renal transplant recipients and its relation to graft interstitial fibrosis in graft biopsies.

METHODS

By this cross-sectional study, we recruited 99 kidney transplant recipients in the nephrology department, organ transplant center in Kuwait with the following criteria: males and females, above 18 years and below 70years, with recent kidney graft biopsy done during the period between 2016 to 2017. We excluded patients with the following criteria: Re-transplant patients, Previous rejection episode, Children and elderly more than 70 years, Postmenopausal female, Liver and gastrointestinal disease, those with gastric bypass surgery, Cystic fibrosis, Extensive burns, Patients maintained on drugs that interfere with vitamin D absorption e.g. Phenytoin, phenobarbital, Nephrotic syndrome, Patients with malabsorption syndrome.

The study was performed according to the Declaration of Helsinki guidelines for studies involving humans, and written informed consent was obtained from each subject.

Study design**:**

We divided the patient into two groups: group 1(n=49 patients) who were transplanted recently (less than 1 year) and group 2(n=50 patients) who were transplanted more than year. All patients received calcineurin inhibitor (CNI)-based or rapamycin-based immunosuppression along with azathioprine or mycophenolate mofetil and prednisolone.

All patients were evaluated concerning:

A- Pre-transplant data including:

Patient age and sex, donor age and sex, cause of end-stage renal disease. duration of dialysis, types of dialysis prior to transplant, donor type.

B - Post transplant data:

Clinical evaluation with special stress on:

- Medical complications and surgical complications
- Laboratory assessment:

- Serum creatinine measurements at 6, 12 months, 24-hour urinary protein, fasting blood sugar, blood cholesterol, calcium, phosphorus and uric acid, viral profile, immunosuppressive drug level, serum AST, serum ALP.
- At the time of the study 25(OH) Vitamin D was measured and its deficiency was classified as per KDIGO guidelines 2017.
- Intact parathormone (iPTH) assay used for measurement of serum iPTH.
- The event graft biopsies of all patients were revised with special stress on evidence of interstial fibrosis and will be scored according to Banff 2013.

Statistical analysis:

All variables (clinical, pathological, immunological and non-immunological) were correlated with patients and graft outcome at 3, 6 months, and one year. Statistical analyses were carried out using the SPSS software version 20. Results were presented as mean ± SD or number (%) when appropriate. For the comparison of quantitative parameters (t test, variance analysis) were used. For the comparison of qualitative parameters, chi-squared or Fisher exact tests were used. Statistical significance was indicated by a two-tailed P< 0.05 was considered significant.

RESULTS

Table (1) showed the demographic data of the patients in the studied groups. In our study 99 kidney transplant recipients were chosen according to the duration post-transplant, 49 patients represented group I (less than 1-year post-transplant) and 50 patients represented group II (more than 1-year post-transplant). We found no significant difference between the two groups regarding their gender as male recipients represented 67.3 % in group I and 60 % in group II(p=0.44). The two groups were comparable regarding the mean age of the studied patients (38.3± 13.5 years for group I and 36.7± 13years for group II, p=0.54). Also, we found that the two groups were comparable regarding the gender of the donors with male donors comprised 81.6 % in group I and 86 % in group II with their mean age 42 ± 8.3 years in group I and 43.8 ± 8.3 years in group II(p>0.058). We observed that hemodialysis duration before transplant was significantly longer in patients of group I patients (2.8± 1.3 years) compared to that recorded among patients in group II (2.1 ±1.3 years) (P value <0.01). We found no statistically significant difference between the two groups regarding original kidney disease (p>0.05).

The majority of patients in both groups received basiliximab as induction (36 cases, 73.5 % in group 1 and 39 cases, 78 % in group 2 respectively, p=0.59). We observed that the number of patients who were maintained on tacrolimus-based maintenance immunosuppression was significantly higher in group 1 (30 cases, 61.2 % in group 1 and 22 cases, 44 % in group 2, p=0.035). Moreover, the number of patients who were maintained on rapamycin-based therapy was significantly higher in group 2 (2 cases, 4.1 % in group 1 and 10 cases, 20 % in group 2, p=0.035).

From table 2, we can observe no statistically significant difference between both groups regarding serum creatinine at 3months, 6 months and 12 months' post-renal transplantation (p=>0.05). However, the mean serum creatinine at the time of graft biopsy was significantly higher in `group 2 (2.8±0.3mg/dl in group 2 vs. 2.1± 0.4mg/dl in group 1, p<0.01). We observed that patients in both groups were suffering hypovitaminosis D (mean vitamin D level was 20.3 ± 9.8 in group I vs. 23.2 ± 13.9 ng/ml in group II) and we foun.d no significant difference between the two groups (P value = 0.229). We found high significant difference between the groups regarding iPTH. The mean iPTH in group I was 197.9 ± 101.8 pg/ml vs. 78.2 ± 82.2 pg/ml in group II (P value <0.01). In our study, we did not find any statistically significant difference between the two groups regarding 24 hours' urine protein g/day, mean serum calcium and mean serum alkaline phosphatase (p>0.05). However, we found that mean serum phosphorus was significantly higher in group 1 (3.1± 0.7 mg/dl in group I vs. 4.5± 0.9 mg/dl in

group 2, P value <0.01). We found that the mean serum cholesterol was significantly higher in patients of group 1 (233.2 ± 27.5 mg/dl in group 1 vs. 206.8 ± 36.8 mg/dl in group 2, P value <0.01). Mean serum albumin was significantly higher in group 2 (3.6± 0.4 g/dl in patients of group II vs. 3.1± 0.4 g/dl in patients of group 1 P value <0.01). Both groups were suffering different degrees of low 25(OH) vitamin D levels. The majority of patients in both groups had mild deficiency or insufficiency with no significant difference between both groups (p>0.050). Most patients in both groups were not receiving vitamin D supplement (91.8% in group 1 and 88 % in group 2) and the two groups were comparable (P value 0.526). There was no statistically significant difference between the studied groups regarding fasting blood sugar (p>0.05). Most of patients had within normal fasting blood sugar. Moreover, the majority of them had targeted drug level without significant difference between the studied groups (p=0.83).

Table (3) showed the histological findings of the graft biopsies at the time of the study in both groups. We observed that most of graft biopsies in both groups showed tubular necrosis (30.6% in group 1 and 26 % in group 2) and we found comparable number of acute rejection episode between both groups (P value 0.512). Both groups showed different degrees of interstitial fibrosis and tubular atrophy (93.9 % in group 1 vs. 82 % in group 2). The number of biopsies showing mild to moderate fibrosis was significantly higher in group 1(44 cases, 89.8%) vs. (34 cases, 68%) in group 2(p=0.036). Moreover, the number of biopsies showing severe fibrosis was significantly higher in group 2(12 cases, 24%) vs. (2 cases, 4.1%) in group 1(p=0.036). We found that 81.8% of the patients had hypovitaminosis D; 48.5 % had insufficiency, 24.2 % had mild deficiency, and 9.1 % had severe deficiency.

Figure 1 showed further analysis of subgroups of vitamin D status (sufficient, insufficient, mild deficiency and severe deficiency). It illustrated that irrespective of the transplant duration, more than 81 % of patients in both groups showed degree of vitamin D deficiency. We observed high mean 25(OH) vitamin D level in rapamycin-based group than the other groups, however, it did not rank to significance (P =0.08).

Significantly higher 25(OH) vitamin D was found among patients without or with mild degree of graft interstitial fibrosis compared to cases with moderate and severe graft interstitial fibrosis (Figure 2, p <0.01). Moreover, significant negative correlation between serum vitamin D level and iPTH was observed (Figure 3, p value < 0.01).

Table 1. Demographic data of the studied renal transplant recipients.

	Group I < 1-year post-transplant N = 49	Group II > 1-year post-transplant N = 50	P value
Recipient gender in years			
Male	33(67.3%)	30(60 %)	
Female	16(32.7 %)	20 (40 %)	0.447
Recipient age in years Mean ±SD	38.3± 13.5	36.7± 13	0.545
Donor gender in years			
Male	40 (81.6 %)	43 (86 %)	
Female	9 (18.4 %)	7 (14 %)	0.555
Donor age in years Mean ±SD	42 ± 8.3	43.8 ± 8.3	0.286
Dialysis duration in years Mean ±SD	2.8± 1.3	2.1 ±1.3	**<0.01**
Original kidney disease			
Diabetes mellitus	7 (14.3 %)	7 (14 %)	
Hypertension	10 (20.4 %)	15 (30 %)	
Obstruction	7 (14.3 %)	5 (10 %)	
unknown	25 (51.1 %)	23 (46 %)	0.709
Induction immunosuppression			
Basilixmab	36 (73.5 %)	39 (78 %)	
ATG*	13 (26.5 %)	11 (22 %)	0.599
Maintenance immunosuppression			
Cyclosporine based	17 (34.7 %)	18 (36 %)	
Tacrolimus based	30 (61.2 %)	22 (44 %)	
Rapamycin based	2 (4.1%)	10 (20 %)	0.035

*ATG= antithymocyte globulin, RR= renal replacement

Table 2. Laboratory parameters of the studied patients at the time of the study.

	Group I < 1 year post-transplant (N = 49)	Group II > 1 year post-transplant (N = 50)	P value
S.cr. at 3 months in mg/dl (Mean ±SD)	1.2± 0.2	1.1±0.2	0.121
Serum creatinine at 6 months mg/dl Mean ±SD	1.3± 0.1	1.3±0.1	0.680
Serum creatinine at 12months mg/dl Mean ±SD	1.6±0.3	1.7±0.2	0.181
Serum creatinine at time of graft biopsy mg/dl Mean ±SD	2.1± 0.4	2.8±0.3	**<0.01**
25(OH) Vitamin D level ng/ml Mean ±SD	20.3 ± 9.8	23.2 ± 13.9	0.229
iPTH pgm/ml Mean ±SD	197.9 ± 101.8	78.2 ± 82.2	**<0.01**
24 hours urine protein g/day Mean ±SD	1.8 ± 0.6	1.6 ± 0.9	0.250
Serum cholesterol mg/dl Mean ±SD	233.2 ± 27.5	206.8 ± 36.8	**<0.01**
Serum calcium mg/dl Mean ±SD	8.3± 1.1	8.6± 0.4	0.255
Serum phosphorus mg/dl Mean ±SD	3.1± 0.7	4.5± 0.9	**<0.01**
Serum alkaline phosphatase Mean ±SD IU/L	149.3 ± 39.5	95.3 ± 36.5	**<0.01**
Serum albumin g/dl Mean ±SD	3.1± 0.4	3.6± 0.4	**<0.01**
25(OH) Vitamin D status **Severe deficiency** **Mild deficiency** **Insufficiency** **Sufficient**	 4 (8.2 %) 16 (32.7 %) 21 (42.9 %) 8 (16.3 %)	 5 (10 %) 8 (16 %) 26 (52 %) 11 (22 %)	 0.287
Drug level **Below target level** **Within target level** **Above target level**	 11 (22.4 %) 35 (71.4 %) 3 (6.1 %)	 13 (26 %) 35 (70 %) 2 (4 %)	 0.837

S.cr.= serum creatinine

Table 3. Histological findings of the graft biopsy at the time of the study.

	Group I < 1 year post-transplant (N = 49)	Group II > 1 year post-transplant (N = 50)	P value
Graft biopsy			
ACR	14(28.6 %)	8 (16 %)	
AMR	7(14.3 %)	8 (16 %)	
CAMR	2(4.1 %)	6 (12 %)	
ACR+AMR	4(8.2 %)	7 (14 %)	
CNI toxicity	36.1 %)	2 (4 %)	
Acute tubular necrosis	15(30.6 %)	13 (26 %)	
Normal	4 (8.2 %)	6 (12 %)	0.512
IFTA SCORE			
No fibrosis	3 (6.1 %)	4 (8 %)	
Mild fibrosis	16 (32.7 %)	12 (24 %)	
Moderate fibrosis	28 (57.1 %)	22 (44 %)	
Sever fibrosis	2 (4.1 %)	12 (24 %)	**0.036**

ACR : Acute cellular rejection
AMR : Acute antibody mediated rejection
CAMR : Chronic antibody mediated rejection
CNI : Calcineurin inhibitors
IFTA: Interstitial fibrosis and tubular atrophy

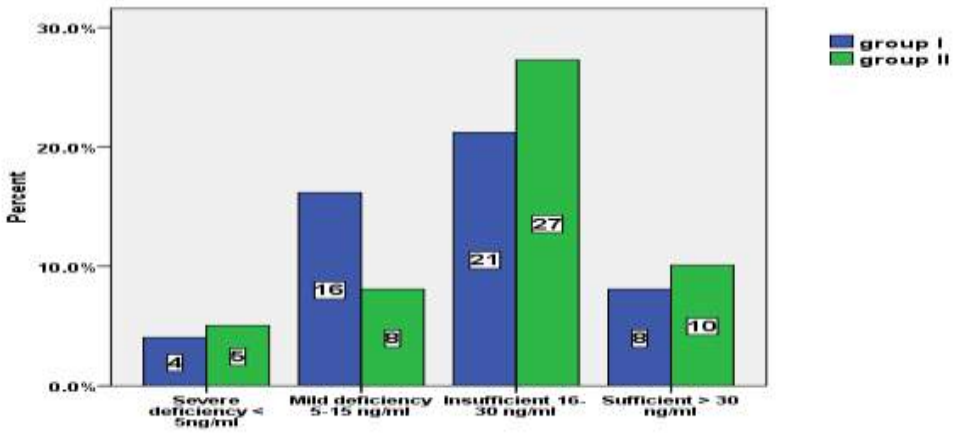

Figure 1. Distribution of both groups according to vitamin D status.

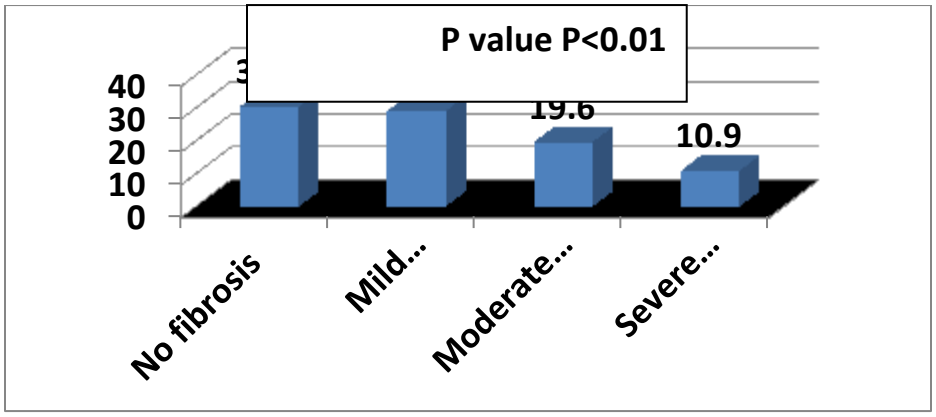

Figure 2. Mean 25(OH) vitamin D level (ng/ml) in relation to the degree of interstitial fibrosis.

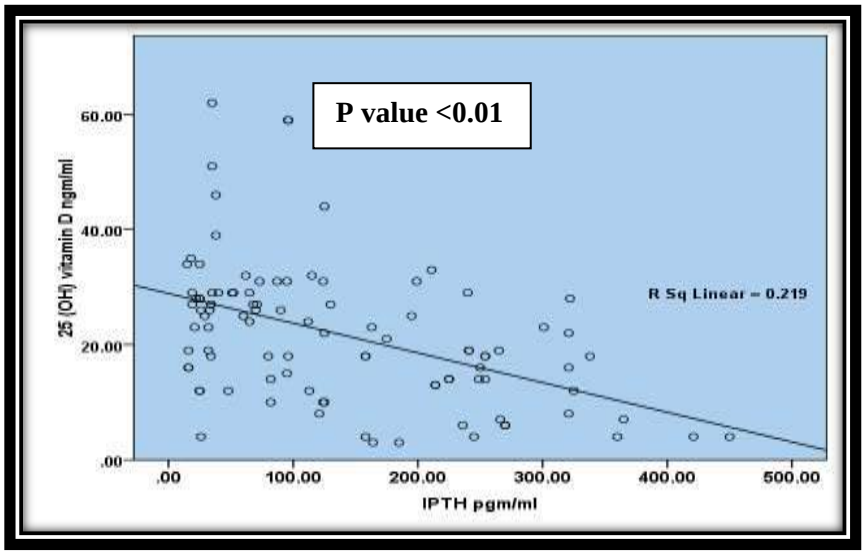

Figure 3. The correlation between iPTH and 25 (OH) vitamin D level.

DISCUSSION

Kidney transplant patients are advised to avoid direct sun exposure because their immunosuppressive therapy is associated with a higher risk of skin carcinomas. Consequently, they are at particular risk of hypovitaminosis D. Renal transplant recipients may be more susceptible to vitamin D insufficiency due to reduced sun exposure and steroid treatment **(4).** Unfortunately, specific recommendations on the optimal 25(OH) vitamin D targets in KTRs and the relative interventions to achieve them are still lacking. However, the KDIGO guidelines 2017 recommended to replenish 25(OH)D levels <30 ng/ml as a first-line therapy against hyperparathyroidism. Not only nutritional vitamin D supplement was recommended for treatment of hyperparathyroidism but also it carried protective effect against post-transplant proteinuria, cardiovascular diseases and post-transplant bone diseases (8).

We aimed from this cross-sectional study to evaluate the prevalence of hypovitaminosis D among renal transplant recipients and its relation to graft interstitial fibrosis in graft biopsies.

Similarly, **Filipov et al.,** demonstrated high prevalence of vitamin D insufficiency after kidney transplantation in their cohort study**.** Similarly, we observed that more than 80 percent of patients had hypovitaminosis D which were subcategorized according to its severity into insufficiency (in 48.5 % of cases), mild deficiency (in 24.2 % of cases) and severe deficiency encountered in 9.1 % of cases **(5).**

In another study by **Aggarwal et al.,** they divided the post-transplant period into three groups; first — the peri-transplant group (within 15 days of transplantation) probably the group representing extension of pre-transplant hypovitaminosis D, second — the intermediate group (16 days to one year), and third — the late transplant group (more than one year). The mean vitamin D levels in each group were 16.13 ± 8.64 ng/ml,18.2 ± 8.26 ng/ml, 16.89 ± 9.57 ng/ml, respectively. They found no statistically significant difference observed between the above-mentioned groups **(9).**

Renal transplant recipients had a high prevalence of vitamin D deficiency versus controls **(10,11).** This arises from several reasons, including the mild-to-moderate degree of renal allograft dysfunction (causing loss of renal tubular CYP27B1), raised serum concentrations of fibroblast growth factor (FGF-23) **(12),**immunosuppressive drugs which induce vitamin D catabolism and medically-advised sun-avoidance behavior **(5**).In the same direction we observed similar risk factors for the high prevalence of low vitamin D among our patients especially impaired graft function (after 1 year of transplant),high prevalence of CNI use in our patients , significantly higher degree of interstitial fibrosis in relation to vitamin D and avoidance of sun exposure because of medical advices and religious factors .

Our patients were divided into 2 groups according to their transplant duration: group I with transplant duration less than year and group II who were older than one-year post-renal transplant. Different degrees of low 25(OH) vitamin D levels were comparable in both groups with the reported mean 25(OH) vitamin Das 20.3 ng/ml in group I and 23.2 ng/ml in group II (P =0.229).Our findings were matched with that reported by **Aggarwal et al.,** who did not find any significant difference (ranged from 16 to 18 ng/ml) in the vitamin D levels early post-transplant and after one year **(9).**

In our study, we found significantly higher mean iPTH in group I compared to group II (P value <0.01) despite the comparable degree of graft function in both groups as represented by serum creatinine at 3 months, 6 months and 1year(p>0.05). The significantly higher iPTH in group I(recent transplant)compared to group II(old transplant) at the time of graft biopsy might be due to multiple factors as persistent tertiary adenoma, post-transplant hypercalciuria, mild graft dysfunction, steroid-induced impaired intestinal calcium absorption, and hypovitaminosis D**. Aggarwal et al.,** added that renal transplant might correct the states of 1-α hydroxylation and hyperparathyroidism over a period of six months to one year after transplant **(9).**

We observed that the mean iPTH in group I was 197.9 ± 101.8 pgm/ml and 78.2 ± 82.2 pg/ml in group II. However **Aggarwal et al.,** reported that the median serum intact PTH as 358 pgm/ml (with a range of 7.8 pgm/ml-502pgm/ml). The lower mean iPTH among our patients might be explained by the homogeneous nature of our group of patients compared to that reported by Aggarwal **(9).**

We found a highly significant negative correlation between vitamin D and iPTH levels (figure 16, r = - 0.317, P < 0.01). The prevalence of hyperparathyroidism among our patients might be attributed to previous causes **(9).**

Reduced 25(OH) vitamin D levels, assessed 3 months after transplantation, were independently associated with lower GFR at 12-month follow-up **(13)**, and a worse annual eGFR decline **(2)**. The strength of the association between 25(OH) vitamin D levels

and graft function may be negatively influenced by the length of follow-up. **Obi et al.,** observed a significant association between 25 (OH) vitamin D deficiencies and a rapid decline in kidney function only within 10 years after kidney transplantation **(14).**

In our study, we found high significant difference between the two groups regarding serum cholesterol. The mean serum cholesterol in group I was 233.2 ±27.5mg/dl while it was 206.8 ±36.8 mg/dlin group II (P**<0.01)**. This finding could be due to the routine use of statin therapy among patients who were maintained on rapamycin based immunosuppressive regimen. Such group of patients were significantly higher in group II **(p=0.03**, table 2).

We observed that serum phosphorus was significantly lower in patients of group I (3.1± 0.7 mg/dl in group I vs. 4.5± 0.9 mg/dl in group II, **p <0.01**). An observation which could be due to CNI effect on renal tubules.

We found that there was highly significant negative correlation between vitamin D deficiency and degree of renal graft interstitial fibrosis (IFTA score) (**P <0.01)**. This work raised the question of the therapeutic usefulness of vitamin D supplementation in preserving kidney allograft function. These findings were matched with recent studies that showed similar conclusions. **Frank et al.,** found unique association between 25(OH) vitamin D at 12 months and IF/TA progression from 3 months to 1 year after transplantation. They added that vitamin D deficiency had important impact on cardiovascular disease, mortality, and certain types of cancer in addition to eGFR decline **(2).**

The molecular mechanisms responsible for the positive effect of vitamin D in CKD remain unclear because various consequences of VDR signaling had been reported, including preservation of podocyte function, reduction of glomerular inflammation, and reduction of tubular cell proliferation **(15)**.

In our study we found better vitamin D level postrenal transplantation in patients who were maintained on steroid and rapamycin and it was low in patients who were maintained on steroid, tacrolimus and azathioprine. However, this observation did not rank to significance (p=0.08). This observation was in accordance with that reported by **Filipov et al.,** with their cohort of patients. They indicated that CNI intake was associated with lower 25(OH) vitamin D concentrations, while treatment with mTORI did not affect vitamin D status after renal transplantation **(5).** In our study, we observed that CNI associated low vitamin D had no positive impact on the degree of allograft fibrosis (**p>0.05**). This observation should be taken cautiously because of the low number of rapamycin treated patients. Both cyclosporine and tacrolimus similarly promote bone loss via direct osteoclast activation, but sirolimus is administered as a bone-sparing immunosuppressive agent due to its capability to inhibit osteoclast generation **(16)**.

Serum Vitamin D level was significantly deficient in patient whose graft biopsy shows chronic antibody mediated rejection (**p<0.01**). This might be explained by the immune mediated effects of low vitamin D (17 **).**

We found that 89% of our study population were not taking vitamin D supplement. The potential interest of cholecalciferol administration was recently documented in patients with ESRD in whom a significant effect on hyperparathyroidism and left ventricular hypertrophy was recorded **(18)**.

CONCLUSION

We found that the prevalence of 25-OH vitamin D insufficiency and deficiency is extremely high after renal transplantation, affecting more than 80% of our patients, particularly in the first year. This may contribute to the graft interstial fibrosis found in some patients, at least in the long-term renal transplant recipients.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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