Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 1, 2021, Pages. 6915 - 6922
Received 15 December 2020; Accepted 05 January 2021.

Vitamin D Status in Kidney Transplant Recipients, a Single Center Study

Mohammed Hannon Alsodani*, Mohammed MukadderMakki, Dina NabeelAlkhayyat****

*Ass. Professor, Consultant Nephrologists,Department of Medicine, College of Medicine, University of Baghdad, Iraq

**Specialists Nephrologists, Iraqi center for kidney disease and transplantation.

***Corresponding author**: Dr. Mohammed Hannon Alsodani, Email: mhannon267@yahoo.com

Abstract

Background: Vitamin D deficiency is a well-known complication of chronic kidney disease patients and with kidney transplants. In addition to its effect on bone heath, vitamin D has an additional effect in kidney transplant recipients including immunodulatory and antimicrobial effects.

Aim of the study: To evaluate vitamin D level in kidney transplant recipients, and to determine any correlation between vitamin D level and kidney graft function and duration, steroid dose ,type of calcineurin inhibitors and important biochemical parameters (PTH,calcium,phosphorus and to talalkaline Phosphatase levels).

Patients and methods: This is across sectional study was performed at Kidney diseases and Transplantation Center, Medical City Teaching Hospital Baghdad,Iraq, from 1st of March 2018–1st of April 2019. Fifty one kidney transplant recipients were enrolled in the study, Clinical data of patients were collected included age, gender, duration of transplantation, steroid dose, on cyclosporine or tacrolimus , serum creatinine,Serum intact parathyroid hormone (iPTH), 25(OH)D, serum calcium phosphorus, and total alkaline Phosphatase were measured. The patients classified to deficient, insufficient and sufficient vitamin D groups according to their serum vitamin D level.

Statistical analysis: All data were analyzed using SPSS20 software package for statistical analysis, p value was<0.05 considered significance.

Results: Mean age of patients was 33.94 (± 10.33) years. Mean time after transplantation was17.7(±13.84)months,35(68.6%)ofthepatientsweremalesand16(31.4%)werefemales.Mean25(OH)Dlevel forpatientswas15.18(±8.28)ng/mL,only4(8%)patientshadsufficientvitaminD,while26(51%)patientshad deficiency and 21(41%) had insufficiency in vitamin D. There was no significant difference between the genders in regard to distribution of vitamin D level. Vitamin D insufficiency and sufficiency were higher in older than younger age groups (p value 0.006). Vitamin D level did not show significant correlation with the duration of transplant whether above or below 1 year (p value 0.278). Vitamin D level had inverse correlation withPTH (r=-0.329, p value 0.018), steroid dose (r =-0.52 p value<0.001) and total alkaline Phosphatase (r= -0.503,p value<0.001.Graftfunction(serumcreatinine), calcium and phosphorus not correlated significantly with vitamin D level. The use of either tacrolimusorcyclosporine did not associated with significant effect on vitamin D level.

Conclusion: There was a high prevalence of vitamin D deficiency and insufficiency in renaltransplantrecipients and the measurement of serum vitamin D level is highly recommending in all kidney transplant recipients.

Keywords: Vitamin D, kidney transplantation.

INTRODUCTION

Vitamin D is a hormone involved in the regulation of calcium, phosphorus and bone metabolism. It is a critical hormone controlling mineral homeostasis. It promotes phosphate and calcium absorption by the gut and increases calcium reabsorption by the distal renal tubule, thereby providing the positive calcium and phosphorus flux required for bone mineralization [1]. The formation of fully active vitamin D requires two-step hydroxylation of its precursors, either cholecalciferol or ergocalciferol. Hepatocytes mediate the first hydroxylation on carbon 25 to produce 25-hydroxyvitamin D (25[OH] D) [2]. The complete activation of vitamin D requires further hydroxylation on carbon 1by the enzyme CYP27B1 resulting in the formation of calcitriol or 1, 25dihydroxyvitaminD (1, 25[OH] D).This step takes place mainly in the proximal tubular cells of the kidney [3].Parathyroid hormone (PTH) and hyperphosphatemia increase CYP27B1 expression in the proximal tubular cells, whereas the phosphatonin fibroblast growth factor-23 (FGF-23) decreasesit[4].

VitaminDinrenaltransplantrecipients:VitaminDdeficiencyinthekidney recipient population can be expected for several reasons as some degree of chronic kidney disease exists in most of the recipients [5], and patients are advised to avoid sun exposure because of increased skin cancer risk [6]. Also, corticosteroids commonly used against rejection, increase vitamin D catabolism [7]. Several studies showed

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low levels of vitamin D found in more than 80% of kidney recipients examined in European countries such as Spain andGermany[8-9].Currently,theactiveformofvitaminDisusedafterkidneytransplantation for the prevention of post-transplant bone loss and the treatment of normocalcemic persistent secondary hyperparathyroidism[10].

Immunological effects of vitamin D relevant to renal transplantation: The vitamin D receptor (VDR) is ubiquitously expressed in immune cells, including activated CD4 and CD8 Tlymphocytes,andcellsoftheinnateimmunesystem,suchasmacrophagesanddendriticcells (DCs). Immune cells not only express the VDR but may contain the machinery for producing biologicallyactive1, 25(OH) 2D3throughinducibleexpressionoftheCYP27B1[11].

Vitamin D and allograft outcomes: It has been hypothesized that reduced serum 25(OH) D concentrations are associated with poorer graft outcomes [12]. Notably, in an observational study of 90 Polish RTRs, 25(OH) D deficiency at time of transplantation was significantly associatedwithdelayedgraftfunctioningandanincreasedriskofacuterejectionepisodesover a 2-year follow-up period [13], Another study of 634 patients demonstrated an association betweenlowserum25(OH) Dat3monthsposttransplantationandincreasedriskofinterstitial fibrosis/tubular atrophy on 12-month transplant biopsies at, but not with mortality[14].AccordingtoKidneydisease:improvingglobaloutcomes(KDIGO)clinicalpracticeguideline forthecareofkidneytransplantrecipients,inpatientswithCKDstages1–5T(transplant),there is suggestion that 25(OH)D (calcitriol,vitamin D) levels might be measured, and repeated testing determined by baseline values and interventions [15]. Despite the high prevalence of vitamin D insufficiency in RTR, there is no general consensus regarding vitamin D supplementation dose after transplantation, however it was shown that high doses of vitamin D3 (100,000 IU cholecalciferol every other week for 2 months, equivalent to 6,600 IU/day) were able to correct 25OHD insufficiency in RTRs without significant side effects, and this regimen was also associated with a significant decrease in serum PTHconcentration [16].**Aim of study** to evaluate vitamin D status in kidney transplant recipients, to estimate the prevalence of vitamin D deficiency and insufficiency among them, and to determine any correlation between vitamin D level and kidney graft function, duration of transplantation, steroid dose,type of calcineurin inhibitors and some biochemical parameters (PTH, calcium, phosphorus and total alkaline Phosphatase levels).

Patients and methods

This is an observational cross-sectional study was performed on fifty one kidney transplant recipients who were followed at Kidney Diseases and Transplantation Center, medical complex, Baghdad, Iraq. Duration of study was 13 months from March 1st, 2018 to April 1st, 2019, and the patients were including if they were older than 18 years and had kidney transplantation for more than 3 months.Exclusion criteria were: acute illness, chronic diarrhea, patients on vitamin D compounds, and calcium, patients with prior parathyroidoctomy,Stage5CKD,needfordialysisandpatientsonanticonvulsantsorheparin.Clinical assessment of the enrolled patient included age and gender, duration of transplantation, prednisolone dose, and type of calcineurin inhibitor weather cyclosporine or tacrolimus.Blood samples were collected for measurement of serum levels of intact parathyroid hormone (iPTH), 25 hydroxy vitamin D, Creatinine (estimated GFR measured depending on CKD-EPI equation) , total calcium (corrected to albumin level), phosphate, and total alkaline Phosphatase.The intact PTH level and vitamin D level were measured with *cobas E411* machine depending on *Chemiluminescence immunoassay*. The normal values of PTH are 15-65 Pg/ml according to our laboratory standards.Vitamin D levels were divided into three groups; sufficient (more than 30 ng / ml), insufficient (16 –30 ng/ml) and deficient less than 15 ng / ml. These values adopted from the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [17].

Statistical analysis

Anderson Darling test of normality was done to assess. Non parametric Kruskal Wallis testto assess the statistical significance between the 3 groups (deficient, insufficient, and sufficient) of vitamin D levels, and between each group weuseMannWhitneyUtest.Hisquaretestusedtoassessthedifferenceinassociationbetween various discrete variables (deficient, insufficient, and sufficient) of vitamin D levels. Linear and multiple regression modules wereuse.All data were analyzed using SPSS20 software package for statistical analysis, p value were<0.05 considered significance.

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 1, 2021, Pages. 6915 - 6922
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Results

This study included fifty one kidney transplant recipients whom had been followed up in our center from March 1st, 2018 to April 1st, 2019. Thirty five (68.6%) of them were males and sixteen (31.4%) were females with a mean age of33.94. All patients were on prednisolone treatment, table (1)

Table 1: basic characteristics of kidney transplant recipients

Age (mean	33.94
Male (no, %)	35 (68.6%)
Female (no, %)	16 (31.4%)
Duration of transplantation(months)	17.17
Medication	
Prednisolone (no,%)	51(100%)
Tacrolimus (no,%)	21(41.2%)
Ciclosporin (no,%)	24 (47.1%)

Overall mean vitamin D was 15.18 (ng/ml) ± 8.28. There were 26 (51%) recipients with vitamin D deficiency, 21(41%) with insufficiency and only 4 (8%) recipient had sufficient vitamin D,figure (1)

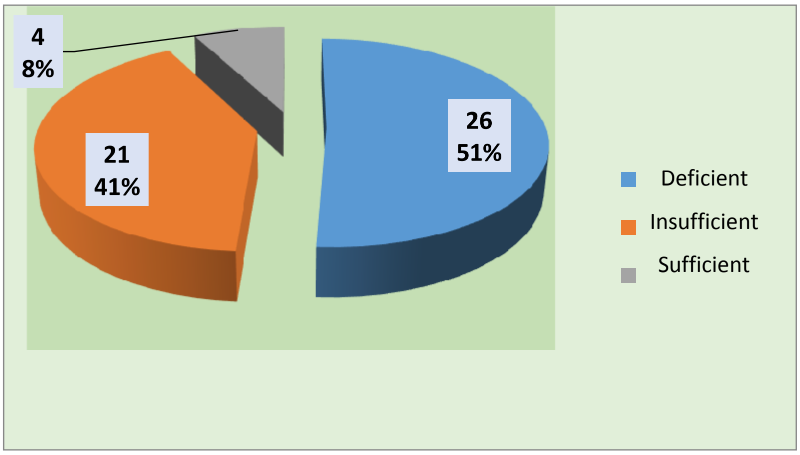

Figure 1: Rate of vitamin D status in kidney transplant recipients

There was no significant difference between male and female in regard distribution of vitamin D level. Mean age of patients differ significantly between deficient and insufficient vitamin D levels (p value 0.006) as seen in table (2)

Table 2: Distribution of vitamin D according to age and gender of kidney transplant recipients

Vitamin D3		Deficient	Insufficient	Sufficient	Total	P value
Number		26	21	4	51	
Female	No %	9 (34.6%)	7 (33.3%)	0 (0.0%)	16 (31.4%)	0.369a
Male	No%±	17 (65.4%) ± 10.97	14 (66.7%)±8.81	4(100%)±5	35 (68.6%) ± 10.33	
Age	MeanSD	37.5	29.8	27.5	33.94	0.017b

Both PTH and alkaline Phosphatase (ALP) showed significant differences with vitamin D level, both were higher in vitamin D deficient group, table (3),while the duration of transplantation, s creatinine, GFR,s.PO_4 and calcium did not differ significantly when vitamin D status.

Table 3: distribution of various variables according to vitamin D_3 status in kidney transplant recipients

Variables	Vitamin D_3 level				P value
	Deficient	Insufficient	Sufficient	Total	
Number	26±10.4	21±15.2	4±21.5	51±13.8	P value
Duration of transplant(months)	13.8	19.3	27.75	17.2	0.087a
Creatinine mg/dl	1.3	1.3	1.15	1.28	0.704a
GFR ml/minute/1.7 m^2	76.5	71.8	92.7	75.8	0.532a
Calcium mg/dl	8.6	9.1	9.0	8.8 1.7	0.845a
PTHc pg/ml	139.5(76.7, 170.8)	54(38.6, 70.1)	49(45, 268.3)	70.1(50, 160)	<0.001a
PO c (mg/dl)4	3(2, 3.4)	3.4(2.5, 3.55)	2.9(2.3, 3.13)	3.2(2.5, 3.37)	0.32a
ALP (I U /L)	143.7	98.2	91.5	121.9	0.004a

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 1, 2021, Pages. 6915 - 6922
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The use of both tacrolimus and ciclosporin did not associated with significant effect on vitamin D, as illustrated in table (4).

Table 4: Correlation between type of calcineurin inhibitor and vitamin D levels

		Vitamin D3				
Drugs		Deficient	Insufficient	Sufficient	Total	P value
Tacrolimus	No (%)	10 (38.5%)	9 (42.9%)	2 (50%)	21 (41.2%)	0.89[a]
Cyclosporine	No (%0	13 (50 %)	10 (47.6%)	1(25 %)	24 (47.1%)	0.646[a]

The following variables were significantly and inversely correlated with vitamin D level; prednisolone dose, ALP, PTH (prednisolone the highest correlation while PTH lowest as indicated by the correlation coefficient), while the rest of the variables did not correlate significantly with vitamin D,tables(5-6) and figures (2-3).

Table (5): univariate regression analysis of various variables against vitamin D_3 in kidney transplant recipients

	Correlation coefficient	F	P value
Duration of kidney transplant	0.228	2.679	0.108
Creatinine	0.077	0.293	0.591
Calcium	0.208	2.226	0.142
PTH	-0.329	5.964	0.018 (SD)
PO_{4m}	-0.178	1.61	0.211
ALP	-0.503	16.58	<0.001 (SD)
Prednisolone dose	-0.52	18.17	<0.001 (SD)

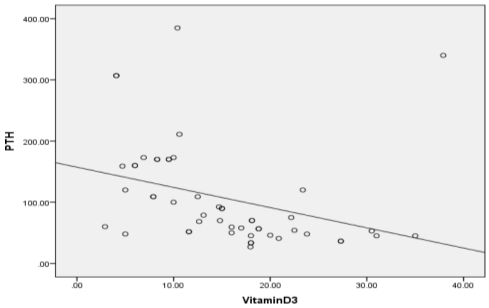

Figure (2): scatter plat of vitamin D and PTH

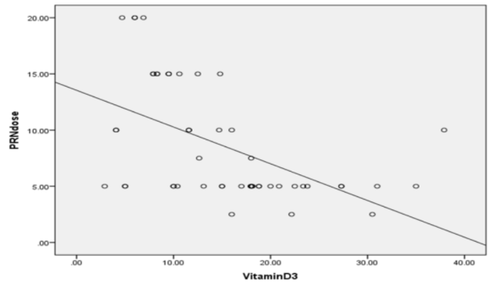

Figure (3): scatter plot of prednisolone dose (mg) and vitamin

Discussion

ThisisthefirststudythatfocusedonevaluationofvitaminDstatusinIraqikidney transplant recipient[18]. This study showed that only 8 % of recipient had sufficientvitaminD while vitamin D deficiency and insufficiency were found 51% and 41% respectively. This might be a part from the highly prevalent vitamin D deficiency in general population in our region.InSaudiArabia,Elsammak*etal*.study,reportedaprevalenceofvitaminDdeficiency of more than 65% among healthy young Saudis [19], and In Iranian study the total prevalence of both vitamin D insufficiency and deficiency was high and seen in 75 % 0f general population. Regarding vitamin D status in renal transplant recipients, Gonzalez and coworkers' study found Hypovitaminosis D (both insufficiency and deficiency) in 86 % of transplant patients [20], and in Boudville and Hodsman's study, 27.3% of kidney transplant recipients had deficiency while 75.5% had insufficiency [21]. Also in Tazik etal. study , only6.5%ofthetransplantedpatientshadenoughbloodlevelofvitaminDand93.5%hadlow serum vitamin D levels (21.7% insufficiency and 67.4% deficiency) [22]. Our study showed therewasnosignificantdifferenceregardingdistributionofvitaminDstatusamongmalesand females; this consists with (Roberto Marcén etal. study [8], however in general population in middle east, number of studies

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 1, 2021, Pages. 6915 - 6922
Received 15 December 2020; Accepted 05 January 2021.

showed that females had lower vitamin D level than males for example one study that enrolled healthy couples found that Vitamin D was higher in men, and prevalence of vitamin D deficiency was 70% in women, compared with 40% in men.Regarding age of patients, our study showed patients with vitamin D deficiency older than those with vitamin D insufficiency and sufficiency, this might be attributed to decreased cutaneous production of vitamin D with ageing [1].We also studied the correlation of serum creatinine (and estimated GFR) with vitamin D level and we did not find a correlation between them, while Adamson etal. study found significant correlation between kidney graft function and the 25(OH)D level [25], this difference might because our patients had good graft function with mean serum creatinine 1.28 mg L/dl (mean creatinine in the mentioned study was 1.8 mg/dl). In other hand Bettina etal. and Aggarwal etal. studies did not found significant correlation between 25(OH)-vitamin D and graft function [26-27]. In our study serum PTH level had inverse correlation with vitamin D level also founded in a study by (Reinhardt *et al*.), which included 129 renal transplant recipients [28]. Stavroulopoulos*et al*., intheirstudy,alsofoundthesamecorrelation[29]andotherpublishedevidencesshowedthat vitamin D had direct stimulatory effect on parathyroid gland (30,31,32). Regarding other biochemical variables, we found that total calcium level had no correlation with vitamin D status ,the explanation could be that in people with good renal function, normal serum levels of calcium maintained predominantly through the interaction of 2 hormones: parathyroid hormone(PTH)andtheactivevitaminD,andinthesettingofvitaminDdeficiency,elevationof PTH level causes both release of calcium stored in bone and reabsorption of calcium bythe kidney to maintain normal serum calcium and thus, vitamin D deficiency is usually accompanied by normal blood calcium level, unless it is severe and long standing [33].This study also found no correlation between serum phosphate level and vitamin D level,interestingly vitamin D sufficient patients even had less phosphate level than insufficient patients, this might be due to the small number of vitamin D sufficient patients (only four) , in addition to that phosphate level in kidney transplant recipients depend onother factors like FGF23 level [34] andthe correlation between serum phosphate level with vitamin D level becomes more obvious in severe long standing vitamin D deficiency [33]. Total alkaline Phosphatase in our study had inverse correlation with vitamin D level and this go with previous published studies in general population [35-36] and kidney transplant recipients [24] and there were published evidences showed that elevated serum alkaline Phosphatase (ALP) level is a marker for the diagnosis of vitamin D deficiency [37] even with normal serum calcium and phosphate levels[38].Transplant recipients should be maintained on different immunosuppressive medications, on the top of them steroids, so we studied the correlation of prednisolone dose) with vitamin D level and we found significant inverse relationship between dose of steroid and vitamin D level and this may be explained by experimental studies that showed Glucocorticoids had effect on vitamin D metabolism by activating genes involved in the expression of enzymes that catabolized vitamin D [39]. Our study showed no effect of the type of calcineurin inhibitors weather cyclosporine or tacrolimus on the vitamin D status, however in Ophir etal. study which is a study done in middleeastforevaluationofimportanceofimmunosuppressiveregimenonvitaminDlevelin kidney transplant patients ,they found that in addition to the higher doses of steroids, higher doses of tacrolimus were associated with a tendency towards vitamin D deficiency while no association was found between vitamin D levels and cyclosporine dose (40).

Conclusions

This study concludes that there is a high prevalence of vitamin D deficiencyand insufficiency in kidney transplantrecipients. Vitamin D level is inversely correlated with the levels of both serum PTH and alkaline Phosphatase, also it inversely correlated with dose of prednisolone.

Recommendations

We recommend that vitamin D level should be routinely measured in kidney transplant recipients, especially those who are old age,in the first year post transplantation, and those who take higher prednisolone dose.

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