World Journal of

Transplantation

World Journal of Transplantation

| **Contents** | |

ABOUT COVER

Editorial Board Member of *World Journal of Transplantation*, Ahmed M Zidan, MD, MSc, PhD, Associate Professor, Surgeon, Consultant of General, HBP and Transplant Surgery, Assiut University Hospital, Assiut 7111, Egypt. ahmed.zidan@med.au.edu.eg

AIMS AND SCOPE

The primary aim of *World Journal of Transplantation* (*WJT*, *World J Transplant*) is to provide scholars and readers from various fields of transplantation with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJT mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone transplantation, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, *etc.*

INDEXING/ABSTRACTING

The *WJT* is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jia-Ping Yan.*

Retrospective Cohort Study

Vitamin D deficiency may predispose patients to increased risk of kidney transplant rejection

Semih Buyukdemirci, Ebru Gok Oguz, Sanem Guler Cimen, Hatice Sahin, Sertac Cimen, Mehmet Deniz Ayli

Semih Buyukdemirci, Department of Internal Medicine, Sağlık Bilimleri Universitesi, Ankara 65000, Altındağ, Turkey

Ebru Gok Oguz, Hatice Sahin, Mehmet Deniz Ayli, Department of Nephrology, Sağlık Bilimleri Universitesi, Ankara 65000, Altındağ, Turkey

Sanem Guler Cimen, Department of General Surgery, Sağlık Bilimleri Universitesi, Ankara 65000, Altındağ, Turkey

Sertac Cimen, Department of Urology, Sağlık Bilimleri Universitesi, Ankara 65000, Altındağ, Turkey

Corresponding author: Sanem Guler Cimen, Doctor, FEBS, Adjunct Associate Professor, Department of General Surgery, Sağlık Bilimleri Universitesi, Güvenlik Caddesi No 87/6, Ankara 65000, Altındağ, Turkey. sanem.cimen@sbu.edu.tr

Abstract

BACKGROUND

Vitamin D deficiency occurs in more than 80% of kidney transplant recipients. Its immunomodulatory effects can predispose transplant recipients to rejection and chronic allograft nephropathy (CAN). This study determined the association between serum 25 (OH) vitamin D, biopsy-proven allograft rejection, and CAN rates.

AIM

To determine the relationship between serum 25 (OH) vitamin D level and biopsy-proven allograft rejection and CAN rate in renal transplant recipients.

METHODS

Adult renal transplant recipients followed at the clinic between January 2013 and 2018 were included. Recipients requiring graft biopsy due to declined function, hematuria, and proteinuria were reviewed. The two groups were compared regarding collected data, including the biopsy results, immunologic parameters, vitamin D, parathyroid hormone (PTH), phosphorus, albumin levels, and graft function tests.

RESULTS

Fifty-two recipients who underwent graft biopsy met the inclusion criteria. In all,

14 recipients had a vitamin D level > 15 ng/mL (group 1) *vs* ≤ 15 ng/mL (group 2) in 38. In total, 27 patients had biopsy-proven rejection, and 19 had CAN. There was only 1 recipient with biopsy-proven rejection in group 1, whereas there were 24 patients with rejection in group 2. The rejection rate was significantly higher in group 2 than in group 1 ($P < 0.001$). Four patients were diagnosed with CAN in group 1 *vs* fifteen in group 2. There was no significant difference in the CAN rate between the two groups. PTH was higher at the time of graft biopsy ($P = 0.009$, $P = 0.022$) in group 1 with a mean of 268 pg/mL. Donor-specific antibodies were detected in 14 (56.0%) of the recipients with rejection. Vitamin D level was 9.7 ± 3.4 ng/mL in the rejection group *vs* 14.7 ± 7.2 in the non-rejection group; this difference was statistically significant ($P = 0.003$). The albumin levels were significantly lower in patients with rejection than in those without rejection ($P = 0.001$). In univariate regression analysis of risk factors affecting rejection, sex, serum vitamin D, phosphorus and albumin were found to have an impact ($P = 0.027$, $P = 0.007$, $P = 0.023$, $P = 0.008$). In multivariate regression analysis, the same factors did not affect rejection.

CONCLUSION
The serum 25 (OH) vitamin D level in kidney transplant recipients remained low. Although low serum vitamin D level emerged as a risk factor for rejection in univariate analysis, this finding was not confirmed by multivariate analysis. Prospective studies are required to determine the effect of serum vitamin D levels on allograft rejection.

Key Words: Kidney transplantation; Rejection; 25 (OH) vitamin D; Vitamin D; Chronic allograft nephropathy

Core Tip: This study analyzed the results of 130 kidney transplant recipients. Of the 52 recipients who underwent graft biopsy and met the study inclusion criteria, 14 had a vitamin D level > 15 ng/mL *vs* ≤ 15 ng/mL in 38. Although low serum vitamin D level emerged as a risk factor for rejection in univariate analysis, this finding was not confirmed by multivariate analysis. Nonetheless, diagnostic and predictive accuracy is limited when a single test is used, and larger-scale prospective clinical studies are needed to clearly discern the effects of serum vitamin D level on the renal allograft rejection rate.

INTRODUCTION

Kidney transplantation is the best treatment option for patients with terminal kidney failure. Successful transplantation prolongs longevity and significantly improves quality of life. In addition, following kidney transplantation, 75% of recipients return to work, and approximately 1 in 50 females can get pregnant[1]. For recipients to experience these benefits, close follow-up and optimization of modifiable risk factors are crucial. One of the modifiable risk factors is the serum vitamin D level[2].

It is known that 25 (OH) vitamin D plays a significant role in calcium and phosphate balance. Furthermore, a low vitamin D level can have deleterious effects on renal allografts[3,4]. A large prospective clinical study on kidney transplant recipients reported that a low 25 (OH) vitamin D level was associated with a reduced glomerular filtration rate (GFR) at 9 mo post-transplantation[5]. Moreover, vitamin D has a wide range of effects on the immune, renal, and cardiovascular systems[6]. The vitamin D receptor (VDR) is found in almost every immune cell including macrophages, CD4+/CD8+ T lymphocytes, and dendritic cells. VDR induces allograft tolerance by directing naive T lymphocytes to transform into T helper type 2 cells phenotypically; this process is defined as vitamin D-influenced immunomodulation[7].

The immunomodulatory features of vitamin D have been observed in autoimmune diseases such as psoriasis and rheumatoid arthritis and in experimental transplant models showing that vitamin D analogs amplified cyclosporin A's inhibitory effects on acute and chronic allograft rejection[8,9]. Likewise, vitamin D analogs inhibit adventitial inflammation and intimal hyperplasia in rat aortic allografts [10]; however, the effect of the vitamin D level on the allograft rejection and chronic allograft nephropathy (CAN) rates have not been studied in detail in kidney transplant recipients. Therefore, this study

determined the relationship between serum 25 (OH) vitamin D level and biopsy-proven allograft rejection and CAN rate in renal transplant recipients.

MATERIALS AND METHODS

Study design and population

This single-center retrospective cohort study was performed at the Health Sciences University of Turkey, Diskapi Research and Training Hospital, Department of Nephrology and Transplantation, Ankara, Turkey. All adult renal transplant recipients followed at the transplant clinic between January 2013, and July 2018 were reviewed. Among these patients, recipients requiring allograft biopsy due to progressive graft function decline, new-onset hematuria, and proteinuria were included in the study.

Allograft biopsies were performed as per Kidney Disease Improving Global Outcomes (KDIGO) practice guidelines[11]. Banff 97 criteria were used to evaluate biopsy specimens[12]. Biopsy specimens were considered adequate if they had ≥ 10 glomeruli and two arteries; patients with inadequate biopsy specimens were excluded from the study. Additionally, patients with post-transplant follow-up < 1 year were excluded from the study to establish a homogeneous cohort. The serum vitamin D level was measured every 3 mo, as per the KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder. All recipients received vitamin D replacement therapy considering their serum vitamin D levels, as per KDIGO guidelines[13].

Demographic characteristics, medical history, prior type and duration of dialysis, donor type, human leukocyte antigen (HLA) mismatches, maintenance immunosuppression, biopsy results, and serum vitamin D level at the time of graft biopsy were obtained from hospital records by a research nurse. In addition, as this study determined the relationship between serum vitamin D level and allograft biopsy results, other biochemical parameters associated with rejection and CAN, such as the GFR, and serum creatinine, albumin, calcium, phosphate, and parathyroid hormone (PTH) levels at the time of graft biopsy, were also recorded. The study protocol was approved by the hospital's ethical review committee (06.08.2018-no. 53/20) and was carried out in accordance with the Declaration of Helsinki and the Declaration of Istanbul. All patients provided written informed consent.

Immunosuppression

Recipients of live donor kidneys were induced with interleukin 2 receptor blockers and steroids, whereas recipients of deceased donor kidneys were induced with anti-thymocyte globulin and steroids. Maintenance immunosuppression was based on mycophenolate mofetil (MMF), prednisone, and calcineurin, or mammalian target of rapamycin inhibitors.

Vitamin D status

The serum vitamin D level was measured using the chemiluminescence method (Kit No: A98856; Beckman Coulter Inc., Sykesville, MD, United States). A serum vitamin D level > 30 ng/mL (*i.e.*, > 75 nmol/L) was considered adequate. Concentrations between 15 and 30 ng/mL (40-75 nmol/L) were considered vitamin D insufficiency, whereas < 15 ng/ mL (< 37.5 nmol/L) was considered vitamin D deficiency according to KDIGO guidelines[13].

Biochemistry

The serum PTH concentration was measured *via* immunochemiluminescent assay (Kit No: A16972; Beckman Coulter). Total calcium, phosphate, glucose, blood cell count, albumin, uric acid, total cholesterol, triglyceride, C-reactive protein (CRP), and creatinine levels were measured using standard methods (Kit Nos: OSR61117, OSR6222, OSR 6221, DW20180105, OSR6202, OSR 6298, OSR 6116, OSR6199, and OSR6178, respectively; Beckman Coulter). The GFR was calculated using the modification of diet in renal disease formula.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, United States). The distribution of data was analyzed using the Kolmogorov-Smirnov test. Mean ± SD was used for descriptive analysis of parametric quantitative data, whereas number and percentage were used to analyze the qualitative data. The student's *t*-test was used for parametric data analysis, and the Mann-Whitney *U* test was used for non-parametric data analysis. Pearson's chi-square test was used to analyze qualitative data. The level of statistical significance was set at $P < 0.05$. Binary logistic regression analysis was used to determine the independent factors related to rejection. After excluding multicollinear variables, clinically relevant variables and parameters presenting statistical significance were subject to the binary logistic regression analysis. The odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were used to show the factors affecting the outcomes.
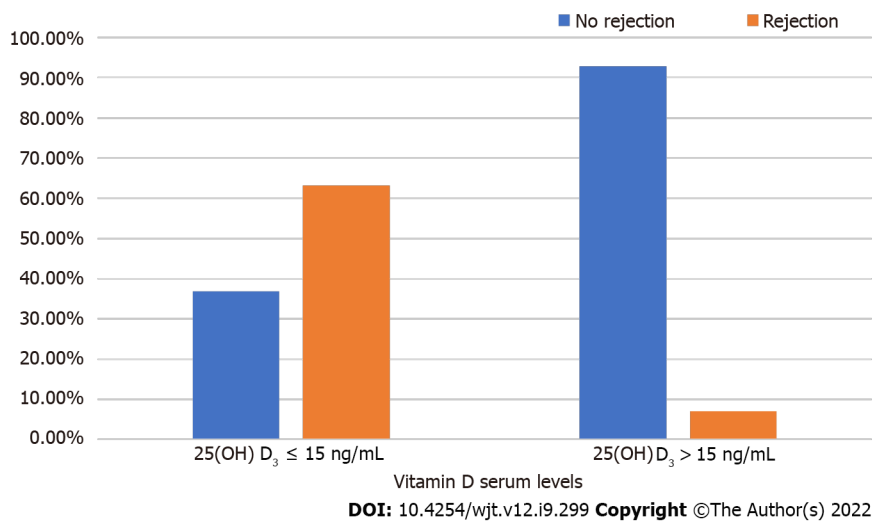
Figure 1 Baseline vitamin D levels at the time of biopsy, and the rejection rate in the low and high vitamin D level groups (*P* < 0.001).

RESULTS

Among 130 kidney transplant recipients, 52 met the study inclusion criteria. The mean age of the recipients was 41 ± 11.9 years, of which 38 (73.1%) were male and 14 (26.9%) were female. During the post-transplantation period, 25 (48.1%) patients had hypertension and 15 (28.8%) had diabetes mellitus. Pre-transplantation duration of dialysis was 5.8 ± 4.71 years, and hemodialysis was the most common therapy (82.7%). The majority (65.4%) of the study population received live donor kidney transplants, of which 3 (5.8%) were transplanted preemptively. Of the 34 live donors, 20 were spousal donations, 10 were first-degree relatives, and 4 were second-degree relatives.

The average age of the donors was 49.6 ± 9.7 years, and the majority of them were 29 (55.8%) male. The mean post-transplant duration of follow-up was 5.91 ± 1.83 years. The mean number of HLA mismatches was 3 ± 1. Delayed graft function developed in 9 (17.6%) patients. Fourteen (27.5%) patients were donor-specific antibody (DSA)-positive at the time of renal biopsy. Kidney failure had occurred due to hypertension in 25 (48.1%), diabetes mellitus in 15 (28.8%), glomerulonephritis in 7 (13.5%), post-renal kidney disease in 3 (5.8), and unknown reasons in 2 (3.8%) of the recipients (Table 1).

Maintenance immunosuppressive regimens at the time of graft biopsy were as follows: 38 (73.4%) patients were on a combination of MMF, tacrolimus, and prednisone, whereas 11 (20.9%) were receiving a combination of MMF, cyclosporine, and prednisone. Only 3 (5.7%) of the recipients used mechanistic target of rapamycin inhibitor-based regimens. At the time of allograft biopsy, the average serum trough calcineurin level was 4.8 ± 0.8, cyclosporine serum level ng/mL was 545 ± 89, and the mean daily intake of MMF was 1.7 ± 0.3 gr/d. Within the study cohort 20 patients were receiving vitamin D treatments according to the KDIGO guidelines. Among the 52 allograft biopsies, 25 (48%) showed rejection. Acute T cell-mediated rejection, acute antibody-mediated rejection (ABMR), and chronic active ABMR were observed in 6 (11.5%), 10 (19.2%), and 9 (17.3%) of the recipients, respectively. CAN was noted in 19 (36.5%) of the recipients. Calcineurin toxicity was observed in 3 (5.8%) patients, whereas BK virus nephropathy and recurrent nephritis were noted in 4 (7.7%) and 1 (1.9%), respectively.

The study population was divided into two groups based on the serum vitamin D level (Table 2). Patients with a vitamin D level > 15 ng/mL constituted group 1, and those with a level ≤ 15 ng/mL constituted group 2. The two groups were compared concerning graft function, HLA mismatches, biochemical parameters, GFR, and rejection status. Group 1 included 14 (27%) patients, and group 2 included 38 (73%). There were no significant differences concerning age, comorbidities, or HLA mismatches between the groups (*P* > 0.05). Males were predominant in group 2 (*P* = 0.035). Four (28.6%) recipients in group 1 and 15 (39.5%) recipients in group 2 were diagnosed with CAN. There was no significant difference in the CAN rate between the two groups (*P* > 0.05). Only 1 (7.1%) recipient was diagnosed with rejection in group 1 and 24 (63.2%) recipients in group 2. The biopsy-proven rejection rate was significantly higher in group 2 compared to group 1 (*P* < 0.001) (Figure 1).

The estimated GFR (eGFR) was 38 ± 18.3 in group 1 and 41 ± 19.7 in group 2. There was no significant difference between these groups regarding eGFR (*P* > 0.05). In addition, hemoglobin, serum glucose, albumin, CRP, calcium, phosphate, uric acid, total cholesterol, triglyceride, blood urea nitrogen, and creatinine did not significantly differ between the two groups (*P* > 0.05). The mean PTH level was 205 pg/mL in group 1 and 268 pg/mL in group 2. PTH level was higher in group 2 than in group 1 (*P* = 0.007).

Table 1 Demographic characteristics of the kidney recipients at the time of graft biopsy	
Parameter	Patients, *n* = 52
Mean age, yr	41 ± 11.9
Male, *n* (%)/female, *n* (%)	38 (73.1)/14 (26.9)
DM, *n* (%)/HT, *n* (%)	15 (28.8)/25 (48.1)
Hemodialysis, *n* (%)/peritoneal dialysis, *n* (%)	43 (82.7)/6 (11.5)
Mean dialysis duration, yr	5.8 ± 4.71
Pre-emptive, *n* (%)	3 (5.8)
Donor type: Living, *n* (%)/Cadaver, *n* (%)	34 (65.4)/18 (34.6)
Donor sex: Male/female	29 (55.8)/23 (44.2)
Donor age in yr	49.6 ± 9.7
Time since transplantation, yr	5.91 ± 1.83
Number of HLA mismatches	3 ± 1
DGF, *n* (%)	9 (17.6)
DSA, *n* (%)	14 (27.5)
Cyclosporine/tacrolimus serum levels, ng/mL	545 ± 89/4.8 ± 0.8
MMF, gr/d	1.7 ± 0.3
Pre-transplant kidney failure etiology	
DM, *n* (%)	15 (28.8)
HT, *n* (%)	25 (48.1)
Glomerulonephritis, *n* (%)	7 (13.5)
Post-renal kidney failure, *n* (%)	3 (5.8)
Unknown, *n* (%)	2 (3.8)

CSA: Cyclosporine A; DM: Diabetes mellitus; DGF: Delayed graft function; DSA: Donor-specific antibody; HLA: Human leukocyte antigen; HT: Hypertension; MMF: Mofetil mycophenolate; TAC: Tacrolimus.

The study cohort was also divided into two groups based on the presence or absence of biopsy-proven rejection (Table 3). The mean age was 39 ± 12.9 in the rejection group and 42 ± 10.9 in the no-rejection group. In the rejection group females were predominant [22 (88%) *vs* 16 (59.3%); *P* = 0.020]. The comorbid status, previous dialysis vintage, and donor characteristics did not differ between these two groups (*P* > 0.05). Hemoglobin, glucose, CRP, calcium, uric acid, lipid profile, and the number of HLA mismatches did not differ between groups (*P* > 0.05). Nevertheless, there were significant differences in the serum albumin, phosphorus, PTH, vitamin D, and DSA levels. The albumin was 4.0 ± 0.5 g/dL in the no-rejection group *vs* 3.5 ± 0.6 g/dL in the rejection group (*P* = 0.001). Phosphorus, PTH, and vitamin D levels in the no-rejection group were 3.9 ± 1.52 mg/dL, 197 pg/mL, and 17.4 ± 7.2 ng/mL, respectively. The results of these parameters in the rejection group were 5.3 ± 1.96 mg/dL for phosphorus, 310 pg/mL for PTH, and 9.7 ± 3.4 ng/dL for vitamin D serum levels. The *P* values of these comparisons showed a statistically significant difference between the two groups (*P* = 0.009, *P* = 0.022, and *P* = 0.003, respectively). DSA positivity was present in 14 (56%) of those with rejection (56%), whereas no patients in the non-rejection group had DSA positivity (*P* < 0.001). There was no significant difference between the two groups regarding serum cutaneous neurogenic inflammation levels and daily MMF dose (*P* > 0.05). Kidney failure with a GFR < 15 mL/min was observed in 5 (18.5%) patients in the non-rejection group and 12 (48%) in the rejection group. The kidney failure rate was significantly higher in the rejection group (*P* = 0.024); patients in the rejection group had lower GFRs and higher serum creatinine levels (*P* = 0.012 and *P* = 0.016, respectively). The serum vitamin D level was significantly lower, and the PTH level was significantly higher in the rejection group than in the non-rejection group (*P* = 0.003 and *P* = 0.022). A regression analysis was performed using rejection risk factors (Table 4). In univariate regression analysis, female sex, serum vitamin D level, phosphorus, and albumin were found to be effective in the development of rejection (*P* = 0.027, *P* = 0.007, *P* = 0.023, *P* = 0.008). However, these risk factors did not demonstrate a significant effect (*P* > 0.05).

Table 2 Comparison of demographic characteristics and laboratory findings in the low and high vitamin D level groups at the time of graft biopsy

Vitamin D level	Group 1 (> 15 ng/mL), *n* = 14	Group 2 (≤ 15 ng/mL), *n* = 38	*P* value
Age, yr	40 ± 11.9	41 ± 12.0	0.856
Male, *n* (%)	7 (50)	31 (81.6)	0.035
DM/HT, n (%)	2 (14.3)/6 (42.9)	13 (34.2)/19 (50)	0.300/0.759
Hemodialysis/peritoneal dialysis	12 (92.3)/1 (7.7)	31 (86.1)/5 (13.9)	1.00
Mean dialysis duration, yr	5.9 ± 4.5	5.6 ± 3.7	0.839
Preemptive, *n* (%)	1 (7.1)	2 (5.3)	1.00
Rejection, *n* (%)	1 (7.1)	24 (63.2)	< 0.001
CAN, *n* (%)	4 (28.6)	15 (39.5)	0.534
Number of HLA mismatches	3 ± 1	3 ± 1	1.00
ESRD actual, *n* (%)	7 (58.3)	10 (27)	0.80
Hemoglobin, g/dL	11.5 ± 2.0	10.7 ± 2.4	0.266
Glucose, mg/dL	106 ± 60.7	98 ± 33.9	0.433
Albumin, g/dL	4.0 ± 0.4	3.7 ± 0.6	0.063
Uric acid, mg/dL	7.1 ± 1.8	7.7 ± 1.5	0.276
Urea, mg/dL	68 ± 35.3	77 ± 38.6	0.416
Creatinine, mg/dL	2.08 ± 0.61	2.21 ± 1.22	0.702
eGFR, mL/min/1.73 m^2	38 ± 18.3	41 ± 19.7	0.609
Proteinuria, g/d	1.0 ± 0.9	2.5 ± 3.1	0.261
Cholesterol, mg/dL	186 ± 36.9	177 ± 46.2	0.515
Triglyceride, mg/dL	178 ± 82.9	191 ± 110.1	0.877
Calcium, mg/dL	8.9 ± 0.99	8.7 ± 0.80	0.400
Phosphorus, mg/dL	4.8 ± 1.84	4.5 ± 1.86	0.657
PTH, pg/mL (range)	205 (78-927)	268 (59-955)	0.007
CRP, mg/dL	24 ± 48.2	21 ± 29.9	0.483

CAN: Chronic allograft nephropathy; CRP: C-reactive protein; DM: Diabetes mellitus; eGFR: Estimation glomerular filtration rate; ESRD: End-stage renal disease; HLA: Human leukocyte antigen; HT: Hypertension; PTH: Parathyroid hormone.

DISCUSSION

Vitamin D deficiency is associated with a broad spectrum of diseases, including autoimmune conditions such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, and type 1 diabetes. In addition, vitamin D deficiency is associated with a severe decrease in the GFR and shorter life expectancy in patients with chronic kidney diseases[14-16].

Epidemiological studies conducted with kidney transplant recipients reported that the prevalence of vitamin D deficiency is as high as 90%, possibly due to the side effects of immunosuppressive regimens and a reduction in sun exposure related to the recommendation that these patients avoid sunlight[2,3,17, 18]. Falkiewicz *et al*[19] reported severe 1.25-dihydroxyvitamin D deficiency in 83% of kidney transplant recipients and that these patients had a high graft failure rate, which is in agreement with the present finding that the mean serum vitamin D level was 12.3 ± 6.2 ng/mL, indicating severe vitamin D deficiency. Findings regarding the relationship between vitamin D and organ rejection are inconsistent. For example, Zimmerman *et al*[5] reported no relationship between the vitamin D level and acute allograft rejection. By contrast, Kim *et al*[20] who conducted a prospective clinical trial that considered 25 nmol/L as the threshold for vitamin D deficiency, observed a correlation between a low vitamin D level and the acute rejection rate. Similarly, Lee *et al*[21] reported that kidney transplant recipients with a vitamin D level < 50 nmol/L within 30 d of transplantation had a higher risk of acute rejection during the 1st year post-transplant. Additionally, Bienaimé *et al*[22] showed that vitamin D deficiency led to interstitial fibrosis and tubular atrophy within the kidney parenchyma in kidney transplant recipients.

Table 3 Demographic characteristics and laboratory findings according to rejection status at the time of graft biopsy

Rejection	No	Yes	*P* value
Patients, *n*	27	25	
Mean age, yr	42 ± 10.9	39 ± 12.9	0.316
Female, *n* (%)	16 (59.3)	22 (88.0)	0.020
DM, *n* (%)/HT, *n* (%)	7 (25.9)/13 (48)	8 (32.0)/12 (48)	0.629/0.991
Donor type Cadaver, *n* (%)	7 (25.9)	11 (44.0)	0.171
Donor age, yr	47.7 ± 9.6	51.8 ± 9.6	0.133
Time since transplantation, yr	4.4 ± 1.4	5.3 ± 3.1	0.236
Number of HLA mismatches	2.2 ± 1.2	2.6 ± 1.2	0.263
DSA, *n* (%)	0	14 (56.0)	< 0.001
Cyclosporine/tacrolimus serum levels, ng/mL	576 ± 98/4.7 ± 0.9	490 ± 29/4.9 ± 0.7	0.063/0.352
MMF, gr/d	1.7 ± 0.3	1.7 ± 0.3	0.601
ESRD actual, *n* (%)	5 (18.5)	12 (48)	0.024
Hemoglobin, g/dL	11.5 ± 2.2	10.4 ± 2.3	0.095
Glucose, mg/dL	95 ± 37.7	107 ± 46.7	0.399
Albumin, g/dL	4.0 ± 0.5	3.5 ± 0.6	0.001
Uric acid, mg/dL	7.3 ± 1.6	7.7 ± 1.6	0.364
Creatinine, mg/dL	1.78 ± 0.44	2.59 ± 1.40	0.016
eGFR, mL/min/1.73 m²	45 ± 19.3	36 ± 18.3	0.012
Cholesterol, mg/dL	177 ± 37.2	181 ± 49.8	0.810
Triglyceride, mg/dL	180 ± 103.4	196 ± 104.1	0.379
Calcium, mg/dL	8.8 ± 0.79	8.7 ± 0.92	0.562
Phosphorus, mg/dL	3.9 ± 1.51	5.3 ± 1.96	0.009
PTH, pg/mL (range)	197 (59-440)	310 (106-955)	0.022
Vitamin D, ng/mL	14.7 ± 7.2	9.7 ± 3.4	0.003
CRP, mg/mL	20 ± 24.9	23 ± 43.2	0.05

CRP: C-reactive protein; DM: Diabetes mellitus; DSA: Donor-specific antibody; eGFR: Estimation glomerular filtration rate; ESRD: End-stage renal disease; HLA: Human leukocyte antigen; HT: Hypertension; MMF: Mofetil mycophenolate; PTH: Parathyroid hormone.

Vitamin D deficiency is associated with glomerular disease in native and transplanted kidneys, and this finding has been attributed to endothelial cell dysfunction. Therefore, it was proposed that a low serum vitamin D level and an elevated fibroblast growth factor-23 level hinder endothelial cell function and lead to endothelial injury[23-25]. Although normal endothelium expresses major histocompatibility complex (MHC) class I antigens only, in endothelial injury and inflammation cases, MHC class II antigens are also expressed on the cell surface. These MHC class II antigens increase the recruitment and adhesion of CD4+ T cells and initiate allorecognition. Alloantigen recognition subsequently triggers the production of inflammatory mediators and activates the complement cascade[26-28]. The present study could not evaluate endothelial dysfunction or MHC class II antigen expression due to its retrospective design; however, a correlation between a low serum vitamin D level and the kidney rejection rate was observed (*P* < 0.001).

On the other hand, as graft rejection and CAN share some immunological pathways, we suggest that the serum vitamin D level might play a role in CAN risk[29]. To the best of our knowledge, the present study is the first to examine the relationship between vitamin D deficiency and CAN. In the present study, the CAN rate did not differ according to the vitamin D level (*P* = 0.534).

The present findings indicate that the long-term graft survival rate remains moderate, even with meticulous management of risk factors, including vitamin D replacement. In this study, patients with rejection had higher phosphorus and PTH measurements at the time of graft biopsy (*P* = 0.009, *P* = 0.022), and vitamin D and albumin levels were significantly lower in this group (*P* = 0.003, *P* = 0.001). Univariate regression analysis elucidated that female sex, serum vitamin D, phosphorus, and albumin

Table 4 Univariate and multivariate regression analyses for rejection

	Univariate regressions				Multivariate regression			
	B	OR	95%CI	*P* value	B	OR	95%CI	*P* value
Age	-0.02	0.97	0.93-1.02	0.381	-0.04	0.95	0.87-1.03	0.265
Sex, female	1.61	5.04	1.20-21.06	0.027	1.12	3.08	0.31-30.45	0.336
Donor type Cadaver, *n* (%)	0.46	1.58	0.50-5.00	0.434	1.52	4.60	0.71-29.77	0.109
Donor sex, female, *n* (%)	-0.33	0.71	0.23-2.15	0.555	0.40	1.50	0.26-8.38	0.643
Donor age, yr	0.03	1.04	0.98-1.10	0.192	0.40	1.04	0.95-1.13	0.340
DGF, *n* (%)	-0.22	0.80	0.18-3.40	0.763	-1.41	0.24	0.01-4.36	0.337
MMF, gr/d	0.78	2.19	0.69-6.97	0.183	0.84	2.32	0.33-16.37	0.397
Serum fosfor (mg/dL)	0.43	1.53	1.06-2.22	0.023	0.63	1.87	1.01-3.48	0.05
Vitamin D, ng/mL	-0.153	0.85	0.76-0.96	0.007	-0.12	0.88	0.72-1.06	0.196
PTH	0.01	1.00	1.00-1.01	0.052	0.01	1.00	0.99-1.00	0.516
Albumin (g/dL)	-1.49	0.22	0.07-0.68	0.008	-1.17	0.30	0.05-1.69	0.177
CSA serum level, ng/mL	-0.01	0.99	0.99-1.00	0.265	0.01	1.00	0.99-1.00	0.983
TAC serum level, ng/mL	0.167	1.18	0.92-1.51	0.189	0.02	1.01	0.54-1.89	0.955

CI: Confidence interval; CSA: Cyclosporine A; DGF: Delayed graft function; MMF: Mofetil mycophenolate; OR: Odds ratio; PTH: Parathyroid hormone; TAC: Tacrolimus.

were significant risk factors affecting rejection. However, in the multivariate regression analysis, these risk factors did not affect the rejection status (*P* > 0.05).

The present study had some limitations, including a retrospective single-center design; the retrospective design might have led to selection and recall biases, and its single-center nature precludes generalization of the findings. In addition, the study population was small and might have been insufficient for establishing the existence of cause and effect relations.

CONCLUSION

In conclusion, the serum 25 (OH) vitamin D level of kidney transplant recipients remained low despite vitamin D replacement recommended by KDIGO guidelines. However, the multivariate regression analysis did not find the same variables effective on rejection. Nonetheless, diagnostic and predictive accuracy is limited when a single test is used, and larger-scale prospective clinical studies are needed to more clearly discern the effects of the serum vitamin D level on the renal allograft rejection rate.

ARTICLE HIGHLIGHTS

Research background
Vitamin D deficiency is commonly diagnosed in patients with kidney transplantation. Deficiency rate remains high despite replacement therapies as per the Kidney Disease Improving Global Outcomes guidelines.

Research motivation
Vitamin D has immunomodulatory effects and vitamin D receptors can be found in various types of cells including T cells and dendritic cells. Its deficiency may predispose transplant recipients to rejection and chronic allograft nephropathy (CAN).

Research objectives
This study determined the association between the serum 25 (OH) vitamin D, biopsy-proven allograft rejection, and CAN rates.

Research methods

Retrospective clinical study involving adult kidney transplant recipients requiring graft biopsy due to declined function, hematuria, and proteinuria.

Research results

Vitamin D level was 9.7 ± 3.4 ng/mL in the rejection group *vs* 14.7 ± 7.2 in the non-rejection group; this difference was statistically significant (P = 0.003). In univariate regression analysis of risk factors affecting rejection, sex, serum vitamin D, phosphorus and albumin were found to have impact (P = 0.027, P = 0.007, P = 0.023, P = 0.008). In multivariate regression analysis, the same factors did not affect rejection.

Research conclusions

The serum 25 (OH) vitamin D level in kidney transplant recipients remained low. Although low serum vitamin D level emerged as a risk factor for rejection in univariate analysis, this finding was not confirmed by multivariate analysis. Prospective studies are required to appreciate the effect of serum vitamin D levels on allograft rejection.

Research perspectives

Kidney transplantation is the best treatment option for patients with terminal kidney failure. Successful transplantation prolongs longevity and significantly improves the quality of life. However, the long term success of kidney transplantation depends on preventing the chronic allograft dysfunction. Chronic allograft dysfunction is secondary to various immunological, infectious and drug related insults to the graft. Its prevention depends on close clinical follow-up and optimization of controllable variables, such as serum vitamin D levels.

FOOTNOTES

ORCID number: Semih Buyukdemirci 0000-0002-0384-3877; Ebru Gok Oguz 0000-0002-2606-3865; Sanem Guler Cimen 0000-0002-5266-9529; Hatice Sahin 0000-0002-7146-4828; Sertac Cimen 0000-0002-0252-8840; Mehmet Deniz Ayli 0000-0003-3145-1595.

REFERENCES

1   **van Walraven C**, Austin PC, Knoll G. Predicting potential survival benefit of renal transplantation in patients with chronic kidney disease. *CMAJ* 2010; **182**: 666-672 [PMID: 20351122 DOI: 10.1503/cmaj.091661]

2   **Querings K**, Girndt M, Geisel J, Georg T, Tilgen W, Reichrath J. 25-hydroxyvitamin D deficiency in renal transplant recipients. *J Clin Endocrinol Metab* 2006; **91**: 526-529 [PMID: 16303843 DOI: 10.1210/jc.2005-0547]

3   **Stavroulopoulos A**, Cassidy MJ, Porter CJ, Hosking DJ, Roe SD. Vitamin D status in renal transplant recipients. *Am J Transplant* 2007; **7**: 2546-2552 [PMID: 17908281 DOI: 10.1111/j.1600-6143.2007.01978.x]

4   **Keyzer CA**, Riphagen IJ, Joosten MM, Navis G, Muller Kobold AC, Kema IP, Bakker SJ, de Borst MH; NIGRAM consortium. Associations of 25(OH) and 1,25(OH)2 vitamin D with long-term outcomes in stable renal transplant recipients. *J Clin Endocrinol Metab* 2015; **100**: 81-89 [PMID: 25361179 DOI: 10.1210/jc.2014-3012]

5   **Zimmerman D**, House AA, Kim SJ, Booth RA, Zhang T, Ramsay T, Knoll G. The Risk of Acute Rejection Following Kidney Transplant by 25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D Status: A Prospective Cohort Study. *Can J Kidney Health Dis* 2017; **4**: 2054358117699822 [PMID: 28491335 DOI: 10.1177/2054358117699822]

6   **Holick MF**. Vitamin D deficiency. *N Engl J Med* 2007; **357**: 266-281 [PMID: 17634462 DOI: 10.1056/NEJMra070553]

7   **Rech MA**, Fleming JN, Moore CL. 25-hydroxyvitamin D deficiency and opportunistic viral infections after kidney transplant. *Exp Clin Transplant* 2014; **12**: 95-100 [PMID: 24702139]

8   **Adorini L**, Penna G. Dendritic cell tolerogenicity: a key mechanism in immunomodulation by vitamin D receptor agonists. *Hum Immunol* 2009; **70**: 345-352 [PMID: 19405173 DOI: 10.1016/j.humimm.2009.01.016]

9   **Redaelli CA**, Wagner M, Günter-Duwe D, Tian YH, Stahel PF, Mazzucchelli L, Schmid RA, Schilling MK. 1α,25-Dihydroxyvitamin D3 shows strong and additive immunomodulatory effects with cyclosporine A in rat renal allotransplants. *Kidney Int* 2002; **61**: 288-296 [DOI: 10.1046/j.1523-1755.2002.00101.x]

10 **Li F**, Liu P, Zhang X, Zhang Q, Tang S, Zhu M, Qiu M. 1,25(OH)2D3-mediated amelioration of aortic injury in streptozotocin-induced diabetic rats. *Inflammation* 2013; **36**: 1334-1343 [PMID: 23813327 DOI: 10.1007/s10753-013-9672-5]

11 **Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group**. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9** Suppl 3: S1-155 [PMID: 19845597 DOI: 10.1111/j.1600-6143.2009.02834.x]

12 **Cimen S**, Geldenhuys L, Guler S, Imamoglu A, Molinari M. Impact of specimen adequacy on the assessment of renal allograft biopsy specimens. *Braz J Med Biol Res* 2016; **49**: e5301 [PMID: 27119314 DOI: 10.1590/1414-431X20165301]

13 **Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group**. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009; S1-130 [PMID: 19644521 DOI: 10.1038/ki.2009.188]

14 **Wöbke TK**, Sorg BL, Steinhilber D. Vitamin D in inflammatory diseases. *Front Physiol* 2014; **5**: 244 [PMID: 25071589 DOI: 10.3389/fphys.2014.00244]

15 **Munger KL**, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; **296**: 2832-2838 [PMID: 17179460 DOI: 10.1001/jama.296.23.2832]

16 **González EA**, Sachdeva A, Oliver DA, Martin KJ. Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. *Am J Nephrol* 2004; **24**: 503-510 [PMID: 15452403 DOI: 10.1159/000081023]

17 **Canalis E**, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int* 2007; **18**: 1319-1328 [PMID: 17566815 DOI: 10.1007/s00198-007-0394-0]

18 **Euvrard S**, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med* 2003; **348**: 1681-1691 [PMID: 12711744 DOI: 10.1056/NEJMra022137]

19 **Falkiewicz K**, Boratynska M, Speichert-Bidzińska B, Magott-Procelewska M, Biecek P, Patrzalek D, Klinger M. 1,25 Dihydroxyvitamin D deficiency posttransplant predicts poorer outcome after renal transplantation. *Transplant Proc* 2009; **41**: 3002-3005 [DOI: 10.1016/j.transproceed.2009.07.087]

20 **Kim H**, Kang SW, Yoo TH, Kim MS, Kim SI, Kim YS, Choi KH. The impact of pretransplant 25-hydroxy vitamin D deficiency on subsequent graft function: an observational study. *BMC Nephrol* 2012; **13**: 22 [PMID: 22533967 DOI: 10.1186/1471-2369-13-22]

21 **Lee JR**, Dadhania D, August P, Lee JB, Suthanthiran M, Muthukumar T. Circulating levels of 25-hydroxyvitamin D and acute cellular rejection in kidney allograft recipients. *Transplantation* 2014; **98**: 292-299 [PMID: 24699398 DOI: 10.1097/TP.0000000000000055]

22 **Bienaimé F**, Girard D, Anglicheau D, Canaud G, Souberbielle JC, Kreis H, Noël LH, Friedlander G, Elie C, Legendre C, Prié D. Vitamin D status and outcomes after renal transplantation. *J Am Soc Nephrol* 2013; **24**: 831-841 [PMID: 23539758 DOI: 10.1681/ASN.2012060614]

23 **Al-Ishaq RK**, Kubatka P, Brozmanova M, Gazdikova K, Caprnda M, Büsselberg D. Health implication of vitamin D on the cardiovascular and the renal system. *Arch Physiol Biochem* 2021; **127**: 195-209 [PMID: 31291127 DOI: 10.1080/13813455.2019.1628064]

24 **Yildirim T**, Yilmaz R, Altindal M, Turkmen E, Arici M, Altun B, Erdem Y. Endothelial dysfunction in renal transplant recipients: role of vitamin D and fibroblast growth factor-23. *Transplant Proc* 2015; **47**: 343-347 [PMID: 25769570 DOI: 10.1016/j.transproceed.2014.12.023]

25 **Silswal N**, Touchberry CD, Daniel DR, McCarthy DL, Zhang S, Andresen J, Stubbs JR, Wacker MJ. FGF23 directly impairs endothelium-dependent vasorelaxation by increasing superoxide levels and reducing nitric oxide bioavailability. *Am J Physiol Endocrinol Metab* 2014; **307**: E426-E436 [PMID: 25053401 DOI: 10.1152/ajpendo.00264.2014]

26 **Sudfeld CR**, Giovannucci EL, Isanaka S, Aboud S, Mugusi FM, Wang M, Chalamilla G, Fawzi WW. Vitamin D status and incidence of pulmonary tuberculosis, opportunistic infections, and wasting among HIV-infected Tanzanian adults initiating antiretroviral therapy. *J Infect Dis* 2013; **207**: 378-385 [PMID: 23162137 DOI: 10.1093/infdis/jis693]

27 **Ban TH**, Kim JH, Jang HB, Lee YS, Choi BS, Park CW, Yang CW, Kim YS, Chung BH. Clinical effects of pre-transplant serum 25-hydroxyvitamin D level on post-transplant immunologic and non-immunologic outcomes in kidney transplant

recipients. *Transpl Immunol* 2017; **40**: 51-56 [PMID: 27871893 DOI: 10.1016/j.trim.2016.11.003]

28   **Westhorpe CLV**, Norman MU, Hall P, Snelgrove SL, Finsterbusch M, Li A, Lo C, Tan ZH, Li S, Nilsson SK, Kitching AR, Hickey MJ. Effector CD4^{+} T cells recognize intravascular antigen presented by patrolling monocytes. *Nat Commun* 2018; **9**: 747 [PMID: 29467472 DOI: 10.1038/s41467-018-03181-4]

29   **Nankivell BJ**, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. *N Engl J Med* 2003; **349**: 2326-2333 [PMID: 14668458 DOI: 10.1056/NEJMoa020009]

Published by Baishideng Publishing Group Inc

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: https://www.f6publishing.com/helpdesk

https://www.wjgnet.com