The Relationship Between Serum Level of 25-hydroxy Vitamin D and Cytomegalovirus Infection in Kidney Transplant Recipients

Fatemeh Musavi-Mehdiabadi[1], Farrokhlagha Ahmadi[2], Mahboob Lesanpezeshki[2], Effat Razeghi[2]

[1]Department Of Nephrology, Kerman University Of Medical Sciences, Kerman, Iran
[2]Nephrology research Center, Tehran University Of Medical Sciences, Tehran, Iran

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Introduction. Kidney transplant recipients are at risk of opportunistic infections; previous studies demonstrated the association between low level of vitamin D and the risk of viral infections. This study was designed to evaluate the relationship between serum 25-hydroxy vitamin D level and active Cytomegalovirus infection / disease in kidney transplant recipients.

Methods. A total number of 83 kidney transplant recipients enrolled in this case-control study from June 2013 to January 2014. 38 patients had active CMV infection / disease and 45 patients had no evidence of active CMV infection. Serum level of 25-hydroxy vitamin D was measured in these two groups and classified as different levels of *sufficient* (more than 30ng/mL), *insufficient* (15-30 ng/mL), and *deficient* (less than 15 ng/mL). Data were analyzed in SPSS 21 statistical software by using statistical tests of Pearson correlation coefficient, chi-square and t-test.

Results. Mean serum 25-hydroxy vitamin D level was 14.42 ng/mL in case group and 17.52 ng/mL in control group. There was no significant difference between the groups in terms of patients' characteristics ($P > .05$). No significant statistical difference was found between mean 25-hydroxy vitamin D level in case and control groups ($P > .05$) but Vitamin D deficiency (serum 25-hydroxy vitamin D less than15 ng/mL) was noticed in 63.1% of CMV infected group versus 42.2% of control group. Thus vitamin D deficiency was seen more prevalent in the CMV infected group ($P > .05$).

Conclusion. Although we did not find a statistically significant relationship between vitamin D levels and the CMV infection, CMV infected patients had lower vitamin D level compared with non-infected recipients, hence vitamin D deficiency can be considered as a risk factor for CMV reactivation after renal transplantation.

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INTRODUCTION

Kidney transplantation is the best renal therapy for end-stage renal disease (ESRD) patients. Vitamin D is a steroid hormone with known functions in regulating bone mineralization and calcium hemostasis. Vitamin D is generally provided by sunlight and foods like fish oil or nutritional supplements. Endogenous vitamin D3 is generated from 7-dehydrocholesterol in contact with ultraviolet light in the skin.[1] Vitamin D is changed into 25-hydroxy vitamin D In the liver and 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D3$) in

the kidney.[2] Activated vitamin D acts as a calcium regulator hormone but non-classic or novel actions have been also described for it in addition to known classic actions including adjustment of genes effective in bone mineralization and calcium transfer in the intestine.[3] Vitamin D deficiency is prevalent all over the world. Previous studies in Iran and neighboring countries show intense vitamin D deficiency.[1]

Various investigations have shown the role of vitamin D in the regulation of rennin-angiotensin system[4], performance of pancreatic beta cell and insulin resistance[5] and production of inflammatory cytokines.[6] Furthermore, serum level of $1,25(OH)_2D3$ decreases rapidly in the course of kidney failure that is due to the lower production of 1α-hydroxylase in renal proximal tubule and results in the progression of secondary hyperparathyroidism. Uremic patients may also have 25-hydroxy vitamin D deficiency in addition to the low $1,25(OH)_2D3$ level.[7] Physiologic doses of vitamin D supplement have been associated with decreased mortality rate in kidney transplant recipients in RCTs.[8] Decreased incidence of acute rejection and graft loss was shown with adequate vitamin D level.[9,10] Vitamin D adequacy is correlated with lower risk of post-transplant cancers.[11]

Vitamin D adequacy affects the expression of some antimicrobial peptides associated with TLRs that have antiviral effects. Human Cathelicidin, an antimicrobial peptide with anti-viral effects is induced by TLR1/2 activation. This peptide is up regulated by vitamin D.[12]

The relationship between 25-hydroxy vitamin D deficiency and anti-cytomegalovirus antibodies was shown in patients with multiple sclerosis.[13] Another study has shown the relationship between foci polymorphism of vitamin D receptor (VDR) gene and early incidence of CMV disease in the first 3 months following kidney transplantation.[14]

Human cytomegalovirus (CMV) is a human herpes virus-5 from Beta Herpes viridae family that is considered as the most prevalent viral pathogen after transplantation. Clinical manifestations of CMV are diverse in transplant recipients from acute CMV disease to transplanted organ dysfunction or graft loss.[15,16] Despite progression in surgical techniques and immunosuppressive drugs, long term graft survival has not been increased significantly and one of the main culprits in this field is CMV.[17,18] In the absence of preventive strategies, 40 to 100% of transplant recipients experience CMV infection and about 67% of them suffer from CMV disease.[19] Thanks to the novel preventive methods the rate of incidents in CMV has declined significantly to about 5%.[20]

CMV infection is a known risk factor for decreasing patient and graft survival in kidney transplant recipients, pleiotropic roles of Vitamin D and its derivatives in regulating of renal protective cellular process such as anti-inflammatory and anti-fibrotic pathways have been shown in kidney transplant recipients. Recent studies have demonstrated that vitamin D regulates the expression of specific endogenous antimicrobial peptides in immune cells leads to a potential role for vitamin D in modulating the immune response to various infectious diseases. Considering the supposed protective effects of vitamin D, this study was conducted with the aim of evaluating the relationship between serum level of 25 (OH) D and CMV infection in kidney transplant recipients.

MATERIALS AND METHODS

This research was a case/control study conducted from 2013 to 2014 on patients who had functional graft with active infection or cytomegalovirus disease during admission. The study was conducted on 83 transplant recipients in two groups:

- Case group: 38 patients in case group who had CMV infection /disease.
- Control group: 45 patients in control group who had no evidence of active CMV infection.

Diagnosis of cytomegalovirus infection/disease was based on suggestive clinical symptoms and laboratory abnormalities confirmed by viral antigen (Ag-PP65) or PCR tests (quantitative or qualitative). Inclusion criteria were CMV seropositive kidney recipient from CMV seropositive donor (D+/R+) who had functional kidney (with GFR according to MDRD-7 formula over 20 cc/mm) at the time of study and diagnosis of CMV infection with CMV PCR method (diagnostic sensitivity of 30 copy/mL) that was conducted in reference laboratory. CMV disease was defined as the presence of laboratory evidences of CMV infection and symptoms and signs of organs (lung, kidney, intestine, etc.) involvement. All patients received anti-thymocyte gobulin (rabbit) as induction therapy in the time of transplantation. Exclusion criteria was receiving

vitamin D supplements (oral or parenteral during 3 past months). Patient records were extracted from the information file and the documents contained in the hospitalization file. The Overall quality of the research was recited for the patients in the form of oral information. Meanwhile, the patients were assured about the confidentiality of their files.

All tests including 25-hydroxy vitamin D, calcium, phosphorus and PTH were checked in the reference laboratory. Data were analyzed in SPSS 21 statistical software by using statistical tests of Pearson correlation coefficient, chi-square, t test, and one-way ANOVA.

RESULTS

The mean age of case group was 40.8 versus 41.9 years in control group, mean age of donor was 29.5 in case group versus 28.7 years in control group ($P > .05$). Sixty percentage of enrolled recipients in control group and 62% in case group were male ($P > .05$).

The mean time passed from kidney transplantation was 35.7 months in case group and 50.8 months in control group. Mean duration of advanced renal failure (ESRD) and hemodialysis or peritoneal dialyses before transplantation was 28.6 months in case group versus 23.04 months in control group. Mean serum creatinine was 1.73 mg/dL in case group and 1.40 mg/dL in control group. The mean frequency of hospitalization due to suspicious acute rejection (with or without kidney biopsy) was 0.71 in case group and 0.24 in control group in total lifetime of the graft (Table 1). There was a significant statistical difference between the two groups in the frequency of suspicious acute rejection ($P < .05$), serum calcium level ($P < .05$), serum creatinine ($P < .05$), corticosteroid maintenance dose ($P > .05$) and serum PTH level ($P > .05$). The etiologies of ESRD is summarized in Table 2. There was no significant difference between two groups in terms of etiology ($P > .05$). This study demonstrated that 92% of the patients had been hemodialyzed, 3.5% peritoneal dialyzed, and 2.6% preemptively transplanted in case group. 84.4% of patients had been hemodialyzed, 4.4% peritoneal dialyzed, and 11.1% had been transplanted preemptively in control group. Comparing RRT modality showed no significant statistical difference in two groups ($P > .05$). There was no significant difference between the two groups in terms of graft type ($P > .05$); 26.3% of case group received graft from living non-related donor and 73.7% transplanted from cadaver, but 42.2% of control group was transplanted from living donor and 57.8% from cadaver. The immunosuppressive regimen of case group contained Tacrolimus and cyclosporine in 15.8% and 84.4%, respectively. 11.1% of patients in control group were consuming Tacrolimus, 84% Cyclosporine, and 6.7% Sirolimus. All of the patients in two groups were treating by Mycophenolate Mofetil.

71.1% (27 patients) of case group had

Table 2. The Etiologies of ESRD in Case and Control Groups

ESRD Etiology	Case Group Frequency (%)	Control Group Frequency (%)
Diabetes Mellitus and Hypertension	15.8	11.1
Polycystic Kidney Diseases	7.9	6.7
Glomerulonephritis	15.8	11.1
Urinary Calculus and Obstruction	5.3	11.1
Uncertain	55	57.8

Table 1. Demographic Characteristics in Case and Control Groups

Variable	Non-infected				CMV-infected				*P*
	Min	Max	SD	Mean	Min	Max	SD	Mean	
Age, y	16	65	12.5	41.9	17	62	11.9	40.8	> .05
Age of donor, y	16	45	7.1	28.71	18	47	8.3	29.50	> .05
Time Passed From Transplantation, mo	3	240	20.5	50.8	2	276	11.6	35.7	> .05
Dialysis Duration Before Transplantation	0	84	20	23.04	0	96	19.8	28.6	> .05
Serum Creatinine, mg/dL	0.8	4.9	0.7	1.40	0.8	4	0.7	1.73	< .05
Suspicious Acute Rejection	0	2	0.1	0.24	0	3	0.2	0.71	< .05
Serum Calcium	7.4	10.2	0.5	9.3	6.9	10.6	0.9	8.8	< .05
Phosphor	2.3	7.5	0.8	3.6	2.8	6	0.6	3.7	> .05
Alkaline Phosphatase	102	619	98.9	237	101	380	63.9	221.1	> .05
Corticosteroid Maintenance Dose	7.5	2.5	1.4	3.9	10	2.5	1.5	4.8	< .05
PTH	27	653	75.2	93.3	36	330	86	141	< .05

asymptomatic CMV infection and 18.4% (7 patients) presented with CMV disease while 2% had history of recurrent CMV infections. Mean serum 25(OH) D level was 14.42 ng/mL in case group and 17.52 ng/mL in control group. No significant statistical difference was found between two groups ($P > .05$) (Table 3).

This study demonstrated a significant relationship between the duration of hospitalization and the level of 25(OH) D in case group ($P < .05$, r = -0.322).

In terms of relationship between serum 25(OH) D and gender, no significant difference was observed between the two groups ($P > .05$), but this difference was significant in control group ($P < .05$). The study demonstrated serum vitamin D level is significantly higher in men than women. The mean level of serum 25(OH)D in the patients with peritoneal dialysis was lower in both groups; however this difference was not statistically significant. In comparing vitamin D level by the type of received transplant (living or cadaver), duration of dialysis prior to kidney transplantation, gender of the donor, type of pathology in kidney biopsy, cause of advanced renal failure and type of immunosuppressive regimen, no significant difference was found between the two groups. Although the corticosteroid maintenance dose was higher in case group, mean level of serum 25(OH)D by maintenance corticosteroid dosage showed no significant difference in the two groups (Table 4). The study also demonstrated that 63.2% of case group versus 42.2% of patients in control group suffered from vitamin D deficiency. Although mean level of vitamin D showed no significant statistical difference between case and control groups ($P > .05$), vitamin D deficiency was more common in case group ($P > .05$) (Table 5).

Furthermore, no significant relationship was observed between vitamin D deficiency severity and GFR in case group ($P > .05$). However, significant relationship was found between them in control one ($P < .001$) (Table 6). No significant statistical relationship was found between vitamin D deficiency severity and the type of immunosuppressive drugs, corticosteroid maintenance dosage, RRT modality and dialysis duration before transplantation ($P > .05$).

Among CMV positive patients, 27 cases suffered from CMV infection, 7 cases had CMV disease and 2 cases experienced recurrent CMV infections. The evaluation of relationship between serum 25(OH)

Table 3. Comparing Mean Serum Vitamin D Level in Case and Control Groups

Group	Vitamin level			*P*
	Frequency	Mean	SD	
Case	38	14.4	8.3	> .05
Control	45	17.5	11.4	

Table 4. The Relationship Between Vitamin D Level and Demographic Variables in Case and Control Groups

Variable	Control		Case	
	P	Correlation Coefficient (r)	*P*	Correlation Coefficient (r)
Age	> .05	-0.019	> .05	-0.219
Time Passed From Transplant	> .05	-0.042	> .05	-0.053
Dialysis Duration Before Transplantation	> .05	0.006	> .05	-0.036
Serum Creatinine	> .05	-0.166	> .05	-0.166
Suspicious Acute Rejection	> .05	-0.234	< .05	-0.322
Serum Calcium	> .05	0.215	> .05	0.267
Phosphorus	> .05	-0.208	> .05	0.182
Alkaline Phosphatase	> .05	-0.149	> .05	-0.055
Corticosteroid Maintenance Dose	> .05	0.009	> .05	-0.055
PTH	> .05	-0.138	> .05	-0.1

Table 5. Comparing Case and Control Groups by Vitamin D Deficiency Severity

Group	Vitamin deficiency				*P*
	Deficiency		Insufficiency		
	Frequency	Percentage	Frequency	Percentage	
Case	24	63.2	14	36.8	> .05
Control	19	42.2	26	57.8	

Table 6. The Relationship Between Vitamin D Level and GFR by Vitamin D Deficiency Severity

Vitamin D	GFR				
	< 30 cc/min	30-60 cc/min	> 60 cc/min	Total	*P*
Case					
Deficiency	8	10	6	24	
Insufficiency	1	7	6	14	> .05
Total	9	17	12	38	
Control					
Deficiency	3	9	7	19	
Insufficiency	0	2	24	26	< .001
Total	3	11	31	45	

Table 7. Results of Variance Analysis Comparing Vitamin D Serum Level According to CMV Infection

CMV Infection	Frequency	Mean	SD	F	*P*
Without Infection	2	11.8	1.2	0.756	> .05
Infection	27	15.4	9.3		
Disease	7	13.1	3.8		
Repeated Infection	2	7.2	6.0		

D level and CMV infection showed that although mean vitamin D level was 15.4 ng/ml in CMV infected group and 13.1 ng/ml in CMV disease group and 7.2 ng/ml in CMV recurrent infected, this difference was not statistically significant (p = 0.526) (Table 7).

DISCUSSION

CMV infection has ominous effects on clinical outcomes of the immune compromised patients including organ transplant recipients. Depending on the host immune status and the degree of immune suppression, CMV infection induces different clinical symptoms from asymptomatic infection to severe and lethal disease. Mowry et al conducted a study on children with multiple sclerosis, the results showed that lower level of CMV antibodies were associated with insufficient level of vitamin D; in contrast, adequacy of vitamin D was associated with higher levels of CMV antibodies.[13] The relationship between VDR gene polymorphism and CMV reactivation was investigated in one study. Phenotype F in VDR gene plays an important role in maintaining VDR-mRNA stability and avidity of VDR complex to VDR ligand and causes VDR immunologic tolerance. The relationship between ff Genotype of VDR and early CMV infection / disease was shown in kidney transplant recipients in a study in 2012.[14] Whether the vitamin D deficiency has such a relationship with increased CMV reactivation risk in transplanted population was our study's subject. 25(OH)D deficiency was reported in 38.7% of patients with the mean level of 13.1 ng/mL in the study of Kim et al, serum vitamin D level was reported higher in men than women.[11] These results were concordant with our results, in which more than 95% of patients showed vitamin D insufficiency and mean serum vitamin D level in men was more than the studied women. In previous studies, peritoneal dialysis patients had less 25(OH)D levels than hemodialyzed patients in post-kidney transplant period that this difference is to some extent justifiable by the essential loss of vitamin-D binding protein through peritoneal membrane and direct loss of 25(OH)D from the peritoneum into the dialysate solution during peritoneal dialysis; while the inability of protein molecules to transport through membrane because of molecule size limitation is the justification of this subject in hemodialysis.[21] Vitamin D level was correspondingly lower in peritoneal dialysis patients than hemodialysis patients in our study, even though this difference did not reach significance according to the low number of PD patients. In previous studies, lower vitamin D level at the time of kidney transplantation was associated with serious effects on the graft function, pathways including podocyte hypertrophy, albuminuria, mesangial cell proliferation, and renin-angiotensin-aldosterone system activation have been prevented by treating with analogues of vitamin D through the suppression of the TGF-β-dependent pathways.[22] In previous studies, vitamin D analogue supplements decreased transplant acute rejection in renal graft recipients.[23]

Vitamin D deficiency has been also associated with higher incidence of acute kidney rejection in Kim et al study.[11] These results were also obtained in our study in which the frequency of hospitalization due to acute rejection was significantly and negatively correlated with lower 25(OH)D level although our groups were comparable in terms of induction and maintenance immunosuppressive regimen, CMV prophylactic protocol and duration of graft reception.

In previous studies, insufficient 25(OH)D level was associated with adverse effects on graft function for several months after transplantation.[24,25] Our study found significant relationship between severity of serum vitamin D deficiency and estimated GFR of patients in both groups of case and control. In our study, no significant relationship was obtained between serum vitamin D deficiency and calcium, phosphor or intact PTH that was coincided with some previous studies.[26]

This study had some limitations; our results could be affected by the lack of serial measurement of 25(OH)D levels which may have fluctuated during the first year of transplantation. 25(OH)D serum level has been checked only once at the time of the study; possibly basic serum 25(OH)D measurement at the time of kidney transplantation and the next follow-up of patients in the post-transplant course in terms of CMV reactivation and/or an increase in anti-CMV IgG titer and/or the emergence of de novo infection by this virus could provide more reliable results.

The half-life of circulating 25(OH)D is 2 weeks while the half-life of its active metabolite $1,25(OH)_2D3$ is less than 4 hours; in normal condition, the concentration of $1,25(OH)_2D3$ is 1000 times less than serum concentration of 25(OH)D. Measurement of 25(OH)D level in serum provides more accurate results than checking active metabolite of $1,25(OH)_2D3$ in serum. However reviewing the tissue level of 25(OH)D and its active metabolite might be more accurate but is not available easily. In previous studies there was a positive correlation between serum 25(OH)D and serum $1,25(OH)_2D3$ level in transplanted patients with near normal renal function hence serum 25(OH)D can be considered as an estimation of $1,25(OH)_2D3$ level.[27] We couldn't find significant relationship between mean level of 25(OH)D and CMV infection/disease, however the vitamin D deficiency i.e. serum level less than 15ng/ml was to some extent more severe in patient group ($P > .05$).

In this study, all hospitalization due to suspicious acute rejection didn't lead to kidney biopsy that was another limitation of our study. Nevertheless, a significant statistical correlation was observed between the frequency of hospitalization due to suspicious acute rejection and severity of vitamin D deficiency. Several factors such as exposure to sunlight on the basis of geographical location of residence, racial differences and the time of checking 25(OH)D level in terms of season and consumption of dairy products enriched with vitamin D contributed to bias in our results which should be considered in the next studies. Finally the limited sample size was the other limitation of this study.

CONCLUSION

Vitamin D deficiency is associated with ominous effect on the graft function in kidney transplant recipients. Vitamin D and its metabolites not only have known effects on musculoskeletal system but also maintain the graft function and induce immunological tolerance due to their immuno-medullatory roles. According to the importance of CMV infection/disease in kidney transplant recipients in terms of graft function and mortality, the presence of association between vitamin D deficiency and CMV reactivation and reviewing of the causality of this relationship, will be mentioned as another importance of vitamin D in this dimension. Obviously future studies must be designed in order to determine the effective and safe dose of vitamin D supplementation in transplant patients.

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Correspondence to:
Fatemeh Musavi-Mehdiabadi, MD
Department of Nephrology, Kerman University of Medical Sciences, Kerman, Iran

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