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Vitamin D Levels After Kidney Transplantation and the Risk of Cytomegalovirus Infection

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Abstract

Background: Some studies reported an association between low levels of vitamin D and the risk of infections, especially viral infections. Kidney transplant patients are at risk of opportunistic infections; however, no study has been conducted on the association between vitamin D levels and the risk of CMV infection.

Objectives: The aim of this study was to compare the level of vitamin D in two groups of patients with and without CMV infection within four months after the transplantation. Moreover, we aimed to find a relation between vitamin D level, before and after transplantation in each group.

Patients and Methods: This prospective cohort study was conducted in Baqiyatallah hospital in Tehran in 2013. A total of 82 kidney transplant patients were enrolled and vitamin D levels were measured in them before transplantation. The kidney transplant patients had been followed up for four months and monitored for the presence of cytomegalovirus antigen (CMV Ag) in their blood. In patients with positive CMV Ag, vitamin D level was measured again when they became positive but in other patients it was measured at the end of follow-up; at the end, characteristics of patients and vitamin D levels were compared between the two groups.

Results: Of all, 40 patients were CMV Ag positive and 42 patients were negative. In most patients transplanted organs were taken from cadaver (66%) and the most common type of dialysis was hemodialysis (92%). Most participants did not undergo antithymocyte globulin therapy (69%) and pulse corticosteroid therapy (83%). Vitamin D level before transplantation was 17.2 ± 11.6 ng/mL. In patients with positive results or at the end of follow-up in patients without CMV Ag, vitamin D level was 16.3 ± 11.4 ng/mL. Only 11% of kidney transplant patients, within four months after transplantation, had a normal level of vitamin D (> 30 ng/mL). There was no significant difference between the two groups for patients' characteristics ($P > 0.05$). Vitamin D levels, before transplantation and at the time of detecting CMV Ag or at the end of follow-up period in patients without CMV, were not significantly different between the two groups ($P > 0.05$). However, vitamin D levels decreased in patients with CMV, while it increased in CMV Ag negative patients, which was statistically significant ($P = 0.037$).

Conclusions: Only 11% of kidney transplant patients, even with a successful transplantation of the kidney and with an acceptable performance of the transplanted kidney, had an adequate level of vitamin D. Although, we did not find any significant association between vitamin D levels and CMV infection during a 4-month follow-up after kidney transplantation. It was observed that, compared with the time before transplantation, vitamin D levels decreased in patients with CMV, while it increased in CMV negative patients.

Keywords: Kidney Transplantation, Vitamin D, Cytomegalovirus Infection

1. Background

Vitamin D is one of the necessary vitamins in body and active vitamin D plays an important role in regulation of proliferation, differentiation of cells in the immune system, insulin sensitivity and bone and cardiovascular health (1). The level of vitamin D in patients with chronic kidney disease is low, and as kidney function decreases, vitamin D level is reduced as well, so that 71% of stage III patients and 83% of stage IV patients have vitamin D deficiency. This problem can be attributed to nutritional problems, reduced mobility, reduced exposure to sunlight and increased levels of fibroblast growth factor 23 (FGF23). Disorders of mineral metabolism, which occur in chronic kidney disease, do not improve shortly after successful renal transplantation; however, it can be managed with appropriate pharmacological treatments (2). Different risk factors can lead to decreased levels of vitamin D after the transplantation such as African-American ethnicity, limited sun exposure, diets low in vitamin D, low fat mass, low serum albumin, dysfunction of liver, chronic obstructive pulmonary disease (COPD), transplant dysfunction, diabetes, malabsorption, cold seasons, smoking, female gender, use of corticosteroids (increased metabolism of 25-hydroxy vitamin D), history of transplantation, proteinuria and use of ACE inhibitors and Angiotensin receptor blockers at the time of transplantation. The prevalence of vitamin

D insufficiency after organ transplantation has been variously reported by different studies from 51% to 97% and its deficiency has been reported from 26% to 30%. It has been mainly attributed to the fact that patients are inhibited from exposure to sunlight, because they are at an increased risk of secondary skin cancer due to the use of immunosuppressive drugs (3).

Taking immunosuppressive drugs puts a person at risk of opportunistic infections, so that the incidence of Cytomegalovirus (CMV) infection after the first month of transplantation, in the absence of anti-viral prophylaxis, is estimated to be 30% to 78%. Cytomegalovirus Antigen (CMV Ag) can be transferred from the donor kidney or via transfusion of blood products; it can also transfer through sexual contact. CMV may remain hidden in the body until the end of life. However, the use of immunosuppressive drugs can cause severe and fatal illness due to this virus (3). Therefore, any strategy to reduce the incidence of infection and increase the response to treatment can be helpful in survival of transplant patients.

Several studies conducted on the association between levels of vitamin D or vitamin D supplements and certain viral infections, including lower respiratory tract infections, influenza, hepatitis B and C, HIV, HSV1 and EBV. In many cases, it has been reported that low levels of this vitamin increases the risk of severe cases of disease or resistance to treatment (4-12). There is only one study investigating the association of CMV and vitamin D levels in patients with multiple sclerosis (MS); they found that a lower level of CMV antibody is associated with insufficient levels of vitamin D (13). However, no study has been yet conducted on the association of vitamin D levels and risk of CMV in kidney transplant patients. Hence, given the high prevalence of CMV infection and drug resistant cases of the infection, high costs for treatment of the problem and its complications in kidney transplant patients and increased risk of viral infection in the presence of low levels of vitamin D, this study aimed to investigate the association of vitamin D levels and CMV infection (positive CMV Ag) within the first four months after kidney transplantation.

2. Objectives

The aim of this study was to compare the level of vitamin D in two groups of patients with and without CMV infection within four months after transplantation. Moreover, we aimed to find a relation between vitamin D level before and after transplantation in each group.

3. Patients and Methods

This prospective cohort study was conducted in Baqiyatallah hospital in Tehran, Iran from June 2013 to December 2013. A total of 82 kidney transplant patients were enrolled. All patients were taking immunosuppressive drugs including triple therapy with glucocorticoids, cyclosporine and mycophenolate mofetil. In some cases, tacrolimus or azathioprine was used instead of cyclosporine and rapamycin instead of mycophenolate mofetil. Exclusion criteria were patients' non-compliance to refer regularly, not taking drugs and irregular use of medications. A written informed consent was taken from all participants and the study was ethically approved by Baqiyatallah University of Medical Sciences, Tehran, Iran.

A checklist was used to collect patients' data at the time of transplantation including demographic characteristics (age and sex), underlying disease leading to kidney failure, kidney transplant characteristics (creatinine before and after transplantation, transplant type, type of dialysis, status of transplanted kidney, antithymocyte globulin therapy or pulse corticosteroid therapy) and laboratory results (blood factors, fasting blood sugar, cholesterol (LDL, VLDL and HDL), triglycerides, BUN (Blood Urea Nitrogen), creatinine, CMV IgG, CMV IgM, blood group, Rh and serum level of 25-hydroxy vitamin D). Patients were followed up monthly for four months after the kidney transplantation and at any time blood CMV Ag became positive, 25-hydroxy vitamin D level was measured. In addition, in case of detecting symptoms such as fever, respiratory problems, digestive problems, etc., blood CMV Ag was checked again; if the result was negative and there was still a strong clinical suspicion, the suspected patient underwent CMV PCR test. Patients with CMV Ag positive received proper treatments and excluded from the study. Patients with CMV Ag negative results after four months of follow-up were selected as non-infected group and their blood 25-hydroxy vitamin D level evaluated at the end of the fourth month. Patients were classified into three groups as follows; 25-hydroxy vitamin D level higher than 30 ng/mL as normal, between 15 and 30 ng/mL as insufficiency and less than 15 ng/mL as deficiency (14). The characteristics of patients and vitamin D levels were compared between the two CMV infected and non-infected groups.

Data analysis was performed using SPSS for Windows 22 software (software package used for statistical analysis). Quantitative variables were described by mean and standard deviation and qualitative variables were described by frequency (percent). Quantitative variables were compared between the two CMV infected and non-infected groups using independent samples t-test and qualitative variables were compared using Chi-square test. To compare changes in vitamin D levels between the two groups, Mann-Whitney U test was used. The level of significance was set at $P < 0.05$.

4. Results

In this study, 45 patients (55%) were male and 37 (45%) female; the range and mean age (SD) of patients were 17 - 73 years and 48 ± 14 years, respectively. Within four months after transplantation, 40 patients became CMV

Ag positive (infected with CMV) and 42 patients remained CMV Ag negative (non-infected with CMV). Table 1 compares demographic characteristics, reasons of kidney failure and blood groups and Rh between the two groups. As shown, CMV Ag positive patients were significantly older than non-infected ones (P = 0.028). However, no significant difference was observed between the two groups for other factors (P > 0.05). Table 2 compares the results of tests conducted before transplantation between the two groups. In most patients, transplanted organs were obtained from cadaver (66%) and the most common type of dialysis was hemodialysis in 92% of patients. Most participants did not undergo antithymocyte globulin therapy (69%) and pulse corticosteroid therapy (83%). Table 3 compares creatinine levels before and after kidney transplantation and kidney transplantation characteristics between the two groups; the results showed no significant difference (P > 0.05). Table 4 compares antibodies against CMV before transplantation and as shown there was no significant difference between the two groups (P > 0.05).

Vitamin D level before transplantation was 17.2 ± 11.6 ng/mL. When patients developed positive results for CMV Ag or at the end of follow-up in non-infected patients, vitamin D level was 16.3 ± 11.4 ng/mL. After kidney transplantation, only nine patients (11%) had vitamin D levels greater than 30 ng/mL. Moreover, 25 patients (31%) had insufficient levels of vitamin D (15 - 30 ng/mL) and 48 patients (58%) had vitamin D deficiency (15 ng/mL). Table 5 compares the levels of vitamin D between the two groups. As shown, vitamin D levels, before and after transplantation (at the time of detecting CMV Ag positivity or at the end of follow-up period in non-infected patients) were not significantly different (P > 0.05); however, compared with the time before transplantation, vitamin D levels decreased in CMV Ag positive patients, while it increased in non-infected patients and it was statistically significant between the two groups (P = 0.037).

Table 1. Comparison of Demographic Characteristics, Reasons of Kidney Failure, Blood Groups and Rh Between the Two Groups of Patients With and Without CMV[a]

Demographic Data	Infected With CMV (N = 40)	Non-Infected With CMV (N = 42)	P Value
Age , year	51 ± 14	44 ± 14	.028 [b]
Gender			
Male	24 (60)	21 (50)	.363 [c]
female	16 (40)	21 (50)	
Cause of kidney failure			
Diabetes	23 (58)	12 (28)	.064 [c]
Hypertension	2 (4)	4 (10)	
Polycystic kidney disease (ADPKD)	3 (8)	2 (5)	
Nephrotic Syndrome	NA	3 (7)	
Stones	1 (2)	NA	
Pyelonephritis	NA	1 (2)	
Unknown	12 (28)	21 (48)	
Blood group			
A	16 (40)	10 (24)	.289 [c]
B	5 (12)	5 (12)	
AB	2 (5)	6 (14)	
O	17 (43)	21 (50)	
Rh			
Positive	39 (97)	37 (88)	.102 [c]
Negative	1 (3)	5 (12)	

Abbreviation: NA, not available.
[a]Data are presented as mean ± SD or No.(%).
[b]Independent sample t-test.
[c]Chi-square test.

Table 2. Comparison of the Results of the Laboratory Tests Before Transplantation Between the Two Groups of Patients With and Without CMV[a]

Laboratory Data	Infected With CMV (N = 40)	Non-Infected With CMV (N = 42)	P Value[b]
Hemoglobin, g/dL	11.3 ± 1.8	11.4 ± 1.9	.824
White blood cells, × 1000/μL	7.8 ± 1.7	7.4 ± 2.0	.352
Fasting blood sugar, mg/dL	127.9 ± 76.7	91.3 ± 17.9	.005
BUN, mg/dL	62.6 ± 32.2	54.7 ± 19.6	.177
Ca, mg/dL	9.2 ± 0.9	9.1 ± 0.7	.596
P, mg/dL	5.5 ± 1.4	5.5 ± 1.6	.992
Albumin, g/dL	4.2 ± 0.3	4.2 ± 0.3	.272
Uric acid, mg/dL	6.7 ± 1.5	6.3 ± 1.4	.278
Cholesterol, mg/dL	160.8 ± 40.8	141.4 ± 26.7	.013
Triglycerides, mg/dL	160.6 ± 74.6	133.7 ± 52.6	.062
LDL, mg/dL	94.3 ± 35.7	87.4 ± 22.0	.296
HDL, mg/dL	37.6 ± 9.1	37.0 ± 7.7	.741
AST, IU/L	16.9 ± 5.8	16.7 ± 4.7	.872
ALT, IU/L	20.2 ± 10.3	19.8 ± 8.2	.868
ALP, U/L	304.0 ± 184.2	255.8 ± 162.1	.212

[a]Data are presented as mean ± SD.
[b]Independent sample t-test.

Table 3. Comparison of Characteristics of Kidney Transplant Between the Two Groups of Patients With and Without CMV[a]

Variables	Infected With CMV (N = 40)	Non-Infected With CMV (N = 42)	P Value
Creatinine before transplantation, mg/dL	7.8 ± 2.5	7.4 ± 2.7	.588[b]
Creatinine after transplantation, mg/dL	1.8 ± 1.1	1.2 ± 1.9	.291[b]
Type of transplant			.507[c]
From family members	0 (0)	1 (2)	
From nonfamily members	12 (30)	15 (36)	
From dead bodies	28 (70)	26 (62)	
Type of dialysis			.506[c]
Hemodialysis	29 (97)	36 (86)	
Preemptive	1 (3)	6 (14)	
The status of transplanted kidney			
Normal	27 (68)	28 (67)	
SGF (Slow Transplant Function)			.639[c]
	8 (20)	6 (13)	
DGF (Delayed Transplant Function)	4 (10)	4 (10)	
Loss of transplant	1 (2)	4 (10)	
Antithymocyte globulin therapy	13 (33)	12 (29)	.699[c]
Pulse corticosteroid therapy	5 (13)	9 (21)	.283[c]

[a]Data are presented as mean ± SD or No.(%).
[b]Independent sample t-test.
[c]Chi-square test.

Table 4. Comparison of CMV Antibodies Before Transplantation Between the Two Groups of Patients With and Without CMV[a]

CMV Infection	Infected With CMV (N = 40)	Non-Infected With CMV (N = 42)	P Value
CMV IgG, U/mL	12.5 ± 3.5	12.3 ± 3.7	.795[b]
CMV IgM, U/mL	2.9 ± 1.5	2.8 ± 1.6	.963[b]
CMV IgG			
Positive	25 (63)	30 (71)	.390[c]
Negative	15 (37)	12 (29)	

[a]Data are presented as mean ± SD or No.(%).
[b]Independent sample t-test.
[c]Chi-square test.

Table 5. Comparison of Vitamin D Levels Between the Two Groups of Patients With and Without CMV[a]

	Infected With CMV (N = 40)	Non-Infected With CMV (N = 42)	P Value
Before the transplantation, ng/mL	19.5 ± 11.8	15.0 ± 11.1	.077[b]
At the time of diagnosis of CMV Ag or at the end of the follow-up period, ng/mL	16.1 ± 12.9	16.5 ± 9.9	.885[b]
Rate of change compared with the time before transplantation	(-3.4) ± 14.0	1.4 ± 9.9	.037[c]
Before transplantation			.085[d]
≤ 15, ng/mL	15 (38)	26 (62)	
15 - 30, ng/mL	18 (45)	11 (26)	
> 30, ng/mL	7 (17)	5 (12)	
At the time of diagnosis of CMV Ag or at the end of follow-up period			.776[d]
≤ 15, ng/mL	25 (63)	23 (55)	
15 - 30, ng/mL	11 (27)	14 (33)	
> 30, ng/mL	4 (10)	5 (12)	

[a]Data are presented as mean ±SD or No.(%).
[b]Independent sample t-test.
[c]Mann-Whitney U test.
[d]Chi-square test.

5. Discussion

This study showed that during the four-month study period after transplantation, 49% of kidney transplant patients were infected with CMV. In addition, during this period, only 11% of kidney transplant patients had normal vitamin D level (above 30 ng/mL). Moreover, 31% had insufficient level of vitamin D (15 to 30 ng/mL) and 58% had vitamin D deficiency (less than 15 ng/mL). This means that in 89% of kidney transplant patients, vitamin D level was lower than normal after transplantation. Although a statistically significant association between vitamin D levels and the risk of CMV was not found in kidney transplant patients, compared with the time before transplantation, vitamin D levels decreased in CMV infected patients, while it increased in non-infected patients.

The incidence of active CMV infection has been reported in different studies from 30% to 56%. The incidence of CMV may be affected by many factors such as serologic status of donor and recipient regarding CMV, transplant type, type and intensity of immunosuppressive therapy and method of detecting CMV (15, 16). In addition, the use of some therapeutic agents such as anti-lymphocyte is assumed a risk factor for CMV infection (17). The use of prophylactic antiretroviral therapy to prevent reactivation of latent virus has been reported by several studies and shown that prophylactic therapy can significantly reduce the incidence of cytomegalovirus infection after transplantation (15). Moreover, it has been found that the use of hyperimmune globulin products for treating CMV resulted in decreased incidence, severity and mortality of CMV infection (18). However, it has been shown that the use of inactive immunization by immunoglobulin (IgG) did not guarantee a safe protection against disease, especially in high risk patients (19). As a result, although the use of prophylactic therapy against CMV is clearly recommended, still there is a lot of controversy about the duration of treatment (15). The mentioned factors can justify the differences between the results of different studies on the incidence of CMV infection in kidney transplant patients.

Nowadays, transplantation is recognized as the main treatment for end-stage renal disease, which can improve many metabolic disorders leading to renal osteodystrophy. However, these disorders remain in many of kidney trans-

plant patients (20). In a study conducted by Taziki et al. in 2011 (21), only 6.5% of renal transplant patients had normal blood level of vitamin D and in 93.5% of patients serum level of vitamin D was low (58.7% had insufficiency and 34.8% had deficiency). These findings suggest that vitamin D deficiency in kidney transplant patients is significantly high. However, in the control group of the same study there was a high incidence of vitamin D deficiency. It is likely that decrease in vitamin D level after transplantation, compared with the time before transplantation, would be involved in viral infections. In a study conducted by Gonzalez et al., 97% of dialysis patients, compared with 86% of kidney transplant patients, were affected by 25-hydroxy vitamin D deficiency (22). In Boudville et al. study in 2006, 27.3% of kidney transplant patients had vitamin D deficiency and 75.5% had vitamin D level insufficiency. In that study, vitamin D level less than 30 ng/mL considered as insufficient and the levels less than 16 ng/mL was considered as deficient (23). Reinhardt et al. studied 129 renal transplant patients in 1998, and reported severe vitamin D deficiency in 63 cases. However, vitamin D levels were increased after transplantation, but still remained below the normal level (24).

This indicates that renal transplant patients with a normal kidney function still face low levels of 25-hydroxy vitamin D. In Fleseriu et al. study in 2007, mean blood 25-hydroxyvitamin D level of kidney transplant patients was 19.5 ng/mL (25). However, in our study vitamin D level during the first four months after transplantation, compared with the time before transplantation, in patients with CMV continued to decline, while in non-infected group was slightly increased. It seems that differences among the results of various studies is attributable to differences in time intervals for measuring vitamin D level after transplantation and consideration of different levels for detection of vitamin D insufficiency or deficiency. However, it is clear that there is a significant prevalence of vitamin D level insufficiency, even after successful kidney transplant. In Iran, studies on general population have shown the high prevalence of vitamin D deficiency in 81% of people living in Tehran aged 20 to 64 years old (26) and 90% of people living in Mazandaran province (27). Thus, studies comparing vitamin D levels between general population and kidney transplant patients have not found statistically significant differences in mean serum 25-hydroxy vitamin D levels between the two groups. Lack of significant difference between the mentioned groups can be due to high incidence of low vitamin D levels in the general population (21).

We did not find any study on the association between vitamin D levels and CMV in kidney transplant patients. However, the association between vitamin D and other viral infections in different populations has been discussed in some studies. Only one study on the association between vitamin D level and CMV was found; the study was conducted on children diagnosed with multiple sclerosis. The results of that study 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. Moreover, in the control group, sufficient vitamin D was associated with lower levels of CMV antibodies (13).

The observational studies evaluating the association between serum 25-hydroxy vitamin D and respiratory infections had different results. Some studies reported an increased incidence of acute respiratory tract infections and low serum 25-hydroxy vitamin D (5, 28, 29). Retrospective analyses of the Third National Health and Nutrition Examination Survey conducted on 18883 patients showed that 25-hydroxy vitamin D levels less than 30 ng/mL was associated with increased risk of upper respiratory tract infection. In contrast, the risk of infection in patients with blood levels less than 10 ng/mL was 55% more than the control group (7). However, some of the studies did not report any association between serum 25-hydroxy vitamin D levels and respiratory tract infections (6, 30). Some studies found an association between vitamin D levels and influenza (8)), while others did not find such an association (10). Studies on vitamin D levels in HIV patients showed lower levels of the vitamin in patients compared to the control group (9, 31). A limited number of studies conducted on the association between vitamin D levels and Hepatitis B, Hepatitis C, EBV, HSV1, dengue fever and tuberculosis and suggested that low levels of vitamin D can be associated with more severe form of disease and/or resistance against related treatment (4, 11, 12)

5.1. Limitations

The present study is unique because it investigated the association between vitamin D levels and risk of CMV infection in kidney transplant patients, however had also some limitations. One of the limitations was the sample size. Moreover, some factors such as uncertainty about the use of different drugs by patients after transplantation, nutritional differences between patients and different levels of exposure to sunlight are among the factors that significantly influence the level of vitamin D in these patients. Moreover, a simultaneous study of a control group consisting of patients' relatives can remove some of the confounding factors such as diet and can show the differences or lack of differences between study population and general population. Measuring vitamin D levels and assessing their association with CMV infection in a longer period of time can result in more reliable results.

5.2. Conclusions

This study showed that compared with the time before transplantation, vitamin D levels decreased in patients with CMV, while it increased in non-infected patients. Given the high prevalence of low vitamin D levels in kidney transplant patients, further studies with a larger sample size and with a control of confounding factors can confirm the role of vitamin D as a factor affecting innate immunity and preventing aggravation of CMV infection.

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Footnotes

Authors' Contribution: Azadeh Saber: data collection, scientific writing, data analysis. Farzaneh Fotuhi: data collection. Zohre Rostami: correspondence, data collection, writing, study design. Behzad Einollahi: data collection. Eghlim Nemati: data collection.

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