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Low vitamin D levels are associated with increased rejection and infections after lung transplantation

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BACKGROUND: The prevalence of vitamin D deficiency in lung disease is greater than in the general population. Vitamin D deficiency may negatively affect immune and lung function. Accordingly, we hypothesized that lung transplant recipients with vitamin D deficiency are more susceptible to rejection and infections after transplantation.

METHODS: Transplant outcomes were reviewed in a retrospective cohort of 102 lung transplant recipients who had 25-hydroxyvitamin D [25(OH)D] levels drawn during the near-transplant period (100 days pre- or post-transplant).

RESULTS: In the near-transplant period, 80% of recipients were 25(OH)D-deficient and 20% were not 25(OH)D-deficient. Episodes of acute cellular rejection in the deficient group were more frequent than in the non-deficient group [mean 1.27 (0.99 to 1.55) vs 0.52 (0.12 to 0.93), $p = 0.006$]. The rejection rate in the deficient group was more than double that of the the non-deficient group [IRR 2.43 (1.30 to 4.52), $p = 0.005$]. Infectious episodes were also more frequent in the deficient group than in the non-deficient group [mean 4.01 (3.24 to 4.79) vs 2.71 (1.47 to 3.96), $p = 0.04$]. The mortality rate of recipients who remained 25(OH)D-deficient 1 year after transplant was almost 5-fold higher than in recipients who were not 25(OH)D-deficient [IRR 4.79 (1.06 to 21.63), $p = 0.04$].

CONCLUSIONS: Low serum 25(OH)D levels in lung transplant recipients were associated with increased incidence of acute rejection and infection. The mortality of recipients who remained deficient 1 year post-transplant was higher than that of recipients who maintained normal vitamin D levels at 1 year post-transplant.

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Vitamin D deficiency is found in over two-thirds of lung transplantation candidates.[1–3] In addition to the well-known effects on bone metabolism,[3] low serum levels of 25-hydroxyvitamin D [25(OH)D] have also been associated with a higher prevalence of infections, cancer, cardiovascular, and autoimmune disorders.[4,5] In addition, recent observational studies have raised the possibility that vitamin D can influence lung function.[6] Asthmatic patients with reduced serum 25(OH)D have greater impairment of lung function, increased airway hyperresponsiveness and reduced glucocorticoid response than asthmatic patients with normal 25(OH)D levels.[7,8] In a murine model, vitamin D deficiency was shown to negatively impact lung structure and function.[9]

Vitamin D is essential for proper development and maintenance of the immune system.[4,5,10] Active vitamin D [$1,25(OH)_2D_3$] plays an integral role in cell-mediated immunity by having an inhibitory influence on proliferation, differentiation and responsiveness of T lymphocytes.[10–14] In addi-

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tion to the inhibitory influence on cell-mediated immunity, vitamin D also enhances the innate immune response.[5,15] Respiratory epithelium and pulmonary macrophages have the capability of utilizing vitamin D to upregulate production of anti-microbial peptides.[11,15,16] Vitamin D deficiency predisposes to increased frequency of upper respiratory tract infections and tuberculosis.[17–21]

Considering the high prevalence of vitamin D deficiency in lung transplant recipients,[1–3] and given the mounting evidence for the involvement of vitamin D in normal immune response[10–16] and normal lung function,[6–9] it would appear biologically plausible to suggest a link between vitamin D deficiency and clinical outcomes in lung transplant recipients. The main objective of our study was to evaluate, for the first time, the relationship between vitamin D deficiency and clinical outcomes in lung transplant recipients. Specifically, we tested the hypothesis that lung transplant recipients with vitamin D deficiency would be more susceptible to rejection and infections than those without vitamin D deficiency.

Methods

Study design and population

The medical records were reviewed for all patients who underwent lung transplantation between January 1, 2007 and May 31, 2010 at the Loyola University Medical Center, Maywood, Illinois. Patients were included in the study cohort if a serum 25(OH)D was drawn in what we called the *near-transplant period*—that is, the period ranging from 100 days pre- to 100 days post-transplant. Patients were excluded from the study if they died within the near-transplant period. Serum 25(OH)D levels were drawn as part of routine bone health and nutrition evaluations and concentrations were determined by chemiluminescence immunoassay (DiaSorin; Italy). 25(OH)D levels were considered low if they were <30 ng/ml.[4,5] The patients were assigned to two groups based on serum 25(OH)D level, either normal or deficient in the near-transplant period. An additional analysis was performed 1 year after transplant and it was noted whether normal 25(OH)D levels were achieved or maintained 1 year post-transplant or if the recipient remained persistently deficient. All follow-up data was completed by December 31, 2010. This study was reviewed and approved by the Loyola University Chicago Health Sciences Division Institutional Review Board for the Protection of Human Subjects (LU-201877).

Clinical data

Presence of acute cellular rejection (ACR) in transbronchial biopsy specimens was defined according to standard International Society for Heart and Lung Transplant (ISHLT) guidelines.[22,23] Surveillance bronchoscopies are routinely performed at our institution 1, 3, 6, 9 and 12 months after transplant with additional bronchoscopies performed if there is a change in respiratory status, including declining spirometry. A cumulative acute rejection (CAR) score in the first year post-transplant was calculated for each patient.[24] Development of chronic rejection, bronchiolitis obliterans syndrome (BOS), was determined in accordance with ISHLT criteria.[25,26] The standard maintenance immunosuppression regimen during the study period included a calcineurin inhibitor (tacrolimus), an anti-metabolite (azathioprine) and steroids. Patients routinely received induction immunosuppression with either basiliximab or daclizumab during the study period, with the exception of those patients seronegative for cytomegalovirus (CMV) receiving an allograft from a CMV-seropositive donor. Vitamin D supplementation was determined at the discretion of the treating physician. An episode of infection was defined by diagnostically confirmed evidence of infection or by each independent treatment course of anti-microbial agents.

Statistical analysis

Values are expressed as mean or median and confidence intervals. Comparisons between groups were performed using Pearson's chi-square test and odds ratio (OR). For non-normally distributed variables Wilcoxon's rank-sum test was used for comparison. Poisson regression was used to obtain incident rate ratios and to adjust for the confounding variable of induction immunosuppression for lung rejection outcomes (ACR, CAR or BOS). Survival estimates were obtained using Kaplan–Meier survival curves and assessed with a log-rank value. Statistical significance was established at $p < 0.05$. STATA (version 11.0) software (Statcorp, College Station, TX) was used for the analysis.

Results

Patients' characteristics and 25(OH)D levels

There were 102 recipients included in the study cohort (Figure 1). Characteristics and transplant outcomes of the recipients in the study cohort were similar to those of patients without 25(OH)D levels available in the near-transplant period. Patient characteristics for the near-transplant 25(OH)D and 1-year post-transplant 25(OH)D groups are summarized in Table 1. All recipients with normal serum

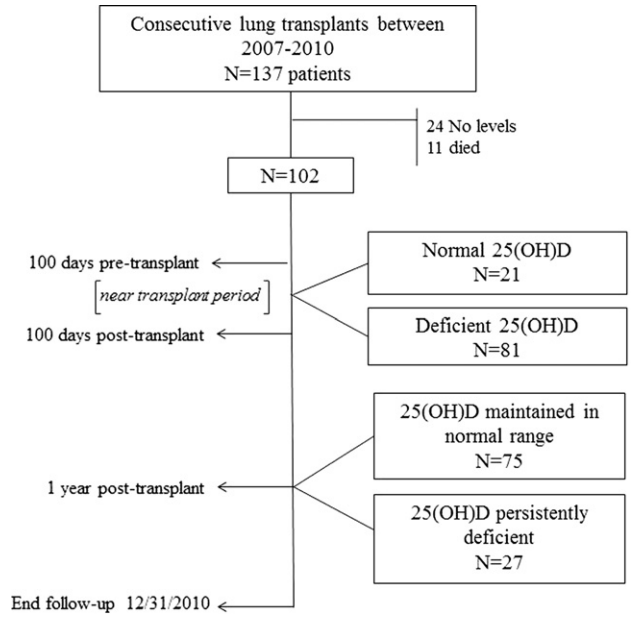

Figure 1 Flowchart of participants.

Table 1 Characteristics of Study Participants

	Near-transplant period			One-year post-transplant		
	Normal 25(OH)D (n = 21)	Deficient 25(OH)D (n = 81)	p-value	Normal 25(OH)D at 1 year post-transplant (n = 75)	Persistent deficiency of 25(OH)D (n = 27)	p-value
Age	49.0 ± 14.8	52.6 ± 14.3	0.28	52.2 ± 1.5	51.1 ± 3.4	0.48
Race, n (%)			0.09			
Caucasian	17 (81)	74 (91.4)		67 (89.3)	24 (88.9)	0.91
African American	1 (4.8)	5 (6.2)				
Hispanic	3 (14.3)	2 (2.5)				
Male gender, n (%)	10 (47.6)	42 (51.9)	0.73	35 (46.7)	17 (63)	0.15
Diagnosis, n (%)						
COPD	6 (28.6)	31 (38.3)	0.42	31 (41.3)	6 (22.2)	0.33
IPF	4 (19)	23 (28.4)		15 (20)	11 (40.7)	
CF	3 (14.3)	12 (14.8)		11 (14.7)	5 (18.5)	
Sarcoid	1 (4.8)	2 (2.5)		2 (2.7)	1 (3.7)	
BOS	3 (19.0)	3 (3.7)		2 (2.7)	1 (3.7)	
Other	4 (19.0)	10 (12.3)		14 (18.7)	3 (11.1)	
Pre-transplant FEV_1 (% predicted)	29.14	30.84	0.94			
LAS	46.7 ± 17.0	45.8 ± 16.4	0.57			
BMI (kg/m^2)	24.1 ± 4.4	24.7 ± 3.9	0.77	24.8 ± 4.1	24 ± 3.7	0.35
Pancreatic insufficiency	4 (19)	12 (14.8)	0.64	11 (14.7)	5 (18.5)	0.64
Osteoporosis, n (%)	4 (19)	17 (21)	0.78	17 (22.7)	4 (14.8)	0.32
Transplant, n (%)						
Single	11 (52.4)	54 (66.7)	0.22	47 (62.6)	18 (66.7)	0.93
Bilateral	10 (47.6)	27 (33.3)	0.23	28 (37.3)	9 (33.3)	0.71
Received induction immunosuppression, n (%)	19 (90.5)	65 (80.2)	0.26	61 (81.3)	22 (81.5)	0.91
25(OH)D (ng/ml), mean	38.5 ± 7.2	17.8 ± 6.1				
25(OH)D, median days from transplant (range)	6 (−53 to 99)	7 (−2 to 35)				
Receiving vitamin D supplementation						0.157
Prior to transplant	18 (85.7)	35 (43.2)	0.0005	40 (53.3%)	13 (48.1%)	
After transplant	21 (100)	81 (100)		75 (100%)	27 (100%)	

Values are expressed as mean standard deviations, medians or absolute numbers (percentages). Values were compared using Pearson's chi-square, and for non-normally distributed variables Wilcoxon's rank-sum test was used for comparison. BMI, body mass index; BOS, bronchiolitis obliterans syndrome; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; FEV_1, forced expiratory volume in 1 second; LAS, lung allocation score; 25(OH)D, 25-hydroxyvitamin D.

25(OH)D levels in the near-transplant period continued to have normal levels 1 year after transplant. At 1 year post-transplant, 55 patients (53.9%) had normalized serum 25(OH)D levels at a mean 112 ± 69 days after transplant, and therefore 75 patients (73.5%) comprised the normal 25(OH)D group at 1 year post-transplant. The remaining 27 patients (26.5%) remained persistently deficient.

Supplementation

At the time of lung transplantation 53 patients (52%) were receiving supplementation with vitamin D analogs. Twice as many patients in the normal 25(OH)D group than in the deficient 25(OH)D group were receiving supplementation at transplant (Table 1). In the year after lung transplant, all patients received vitamin D supplementation. The vitamin D supplementation most commonly utilized included ergocalciferol or cholecalciferol, which ranged from 1,000 IU daily to 50,000 IU once or twice weekly.

Outcomes

Episodes of ACR in the first year post-transplant were more frequent among recipients who were 25(OH)D-deficient near transplant than those who were not 25(OH)D-deficient [1.27 (0.99 to 1.55) vs 0.52 (0.12 to 0.93), $p = 0.006$] (Figure 2A). Similarly, episodes of ACR beyond 1 year post-transplant were more frequent among 25(OH)D-deficient recipients compared to those with normal 25(OH)D in the near-transplant period [1.65 (1.31 to 2.00) vs 0.76 (0.30 to 1.21), $p = 0.01$]. Mean CAR scores in the 25(OH)D-deficient group were also elevated when compared to those

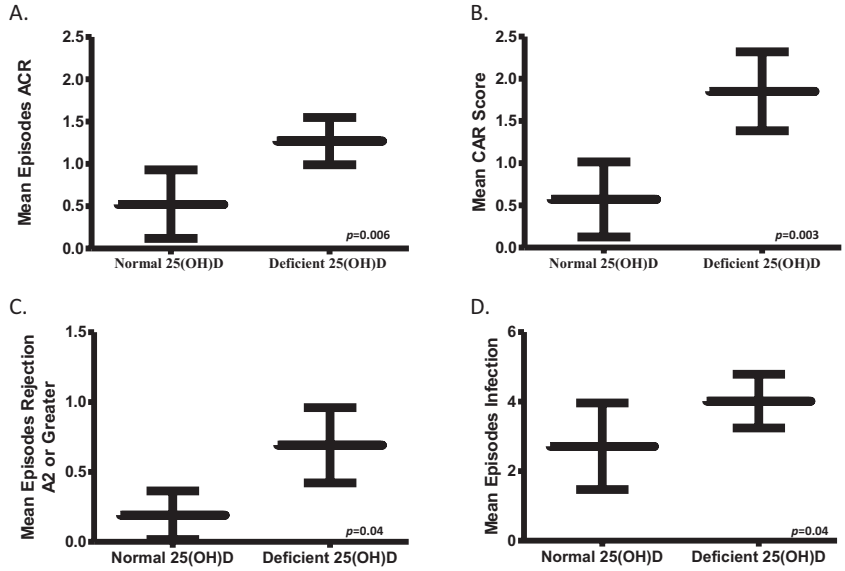

Figure 2 Comparing recipients with normal 25(OH)D and deficient 25(OH)D in the near-transplant period. (A) Comparison of episodes of acute cellular rejection in the first year after lung transplantation. (B) Mean cumulative acute rejection (CAR) scores in the first year after transplant. (C) Mean episodes of acute cellular rejection of Grade A2 to A4 in the first year after transplant. (D) Mean episodes of infection in the first year after transplant.

with normal 25(OH)D in the near-transplant period [1.85 (1.38 to 2.32) vs 0.57 (0.13 to 1.02), $p = 0.003$] (Figure 2B). In addition, episodes of moderate to high grade rejection were more frequent in the 25(OH)D-deficient group than in those recipients who were not 25(OH)D-deficient in the near-transplant period [0.69 (0.42 to 0.96) vs 0.19 (0.02 to 0.36), $p = 0.04$] (Figure 2C). Finally, mean frequency of lymphocytic bronchiolitis (LB) was 0.26 (0.16 to 0.36) in the 25(OH)D-deficient group compared to 0.09 (0 to 0.23) in those with normal 25(OH)D in the near-transplant period ($p = 0.11$). The numbers of transbronchial biopsies in the normal 25(OH)D group and in the 25(OH)D-deficient group were equivalent: 5.67 ± 1.88 and 5.94 ± 2.16, respectively ($p = 0.60$). The rejection rate in the first year after transplant in 25(OH)D-deficient recipients in the near-transplant period was more than double that of those with normal 25(OH)D levels in the near-transplant period. The risk of developing moderate- to high-grade rejection was more than 3-fold higher in those who were 25(OH)D-deficient in the near-transplant period (Table 2).

The number of ACRs in the first year post-transplant was 1.33 (0.90 to 1.77) among recipients who remained persistently 25(OH)D-deficient during the first year post-transplant and 1.04 (0.75 to 1.33, $p = 0.13$) among recipients with normal 25(OH)D levels 1 year post-transplant. Beyond 1 year, the total number of ACRs tended to be greater among recipients who remained persistently 25(OH)D-deficient during the first year post-transplant than among recipients with normal 25(OH)D levels at 1 year post-transplant [1.81 (1.25 to 2.38) vs 1.35 (1.00 to 1.69), $p = 0.07$]. The rejection rate in the first year after transplant in recipients with persistently deficient 25(OH)D levels was over double that of those with normal 25(OH)D in the near-transplant period (Table 2).

Episodes of infection in the first year post-transplant were more frequent in recipients who were 25(OH)D-deficient compared to recipients with normal 25(OH)D in the near-transplant period (Figure 2D and Table 3). Frequency of infection data are detailed in Table 3. The infection rate in the first year after transplant was greater in recipients who were 25(OH)D-deficient in the near-transplant period than in recipients with normal 25(OH)D (Table 2). Episodes of infection were also more frequent in recipients who were persistently 25(OH)D-deficient 1 year after transplant than

Table 2 Incidence Rate Ratios and Confidence Intervals

	IRR	CI	*p*-value
Deficient near transplant vs normal			
Rejection	2.43	1.30–4.52	0.005
Moderate–severe rejection	3.30	1.19–9.13	0.02
Lymphocytic bronchiolitis	2.71	0.63–11.60	0.18
BOS	1.39	0.40–4.76	0.60
Infection	1.47	1.12–1.96	0.006
Death	2.21	0.51–9.63	0.29
Persistently deficient 1 year post-transplant vs normal			
Rejection	2.54	1.30–5.00	0.007
Moderate–severe rejection	1.73	1.03–2.93	0.04
Lymphocytic bronchiolitis	1.76	0.76–4.06	0.19
BOS	0.57	0.10–3.42	0.54
Infection	1.99	1.47–2.71	<0.0005
Death	4.79	1.06–21.62	0.04

BOS, bronchiolitis obliterans syndrome; CI, confidence interval; IRR, incidence rate ratio.

Table 3 Infections in the First Year Post-transplant

	Near-transplant period			One year post-transplant		
	Normal 25(OH)D (n = 21)	Deficient 25(OH)D (n = 81)	p-value	Normal 25(OH)D at 1 year after transplant (n = 75)	Persistent deficiency of 25(OH)D (n = 27)	p-value
Total infections mean 1 year post-transplant	2.71 (1.47–3.96)	4.01 (3.24–4.79)	0.040	3.15 (2.46–3.84)	5.41 (3.89–6.92)	0.0009
Bacterial, mean	2.57 (1.34–3.80)	3.59 (2.86–4.33)	0.047	2.87 (2.19–3.54)	4.81 (3.41–6.22)	0.0017
Viral, *n* (%)	0	6 (7.4)	0.20	4 (5.3)	2 (7.4)	0.69
CMV status negative at transplant	9 (42.9)	33 (40.7)		29 (38.7)	13 (48.1)	
CMV primary, *n* (%)	2 (22.2)	11 (33.3)	0.52	5 (17.2)	8 (61.5)	0.004
CMV reactivation, *n* (%)	3 (14.3)	13 (16.0)	0.91	9 (12.0)	7 (25.9)	0.09
Fungal, *n* (%)	3 (14.3)	15 (18.5)	0.90	9 (12.0)	9 (33.3)	0.05
NTM, *n* (%)	1 (4.8)	8 (9.9)	0.46	4 (5.3)	5 (18.5)	0.038
TB, *n* (%)	0	1 (1.2)	0.61	1 (1.3)	0	0.55

Values are expressed as mean ± confidence intervals, or absolute numbers (percentages). Values compared using Pearson's chi-square, and for non-normally distributed variables Wilcoxon's rank-sum test was used for comparison. CMV, cytomegalovirus; NTM, non-tuberculous mycobacterium; TB, tuberculosis; 25(OH)D, 25-hydroxyvitamin D.

in those with normal 25(OH)D at 1 year post-transplant (Table 3). Those recipients with persistently deficient levels of 25(OH)D more frequently developed infections from bacteria, CMV, fungal and non-tuberculosis mycobacterial infections compared to those with normal 25(OH)D levels (Table 3). Similarly, the infection rate in those persistently 25(OH)D-deficient 1 year after transplant was almost double the rate of those with normal 25(OH)D levels (Table 2).

The incidence of BOS was 22.9% in those with deficient 25(OH)D in the near-transplant period, compared with 16.7% in the normal 25(OH)D group [OR = 1.37 (0.45 to 4.20), p = 0.56]. In those persistently 25(OH)D-deficient, the incidence of BOS was 25%, compared with 10% in those with normal 25(OH)D at 1 year after transplant [OR 2.5 (0.63 to 9.91), p = 0.15]. Duration of hospitalization after transplant tended to be longer in the near-transplant 25(OH)D-deficient group compared with the normal 25(OH)D group: 20.2 ± 15.3 vs 16.5 ± 12.8 days (p = 0.14), respectively.

Survival data

Survival was similar among recipients with deficient 25(OH)D in the near-transplant period and in those with normal 25(OH)D levels (Figure 3A). In contrast, survival among recipients who were persistently 25(OH)D-deficient 1 year after transplant was poorer than in recipients with normal 25(OH)D at 1 year after transplant (p = 0.0004) (Figure 3B). The mortality rate was almost 5-fold higher in

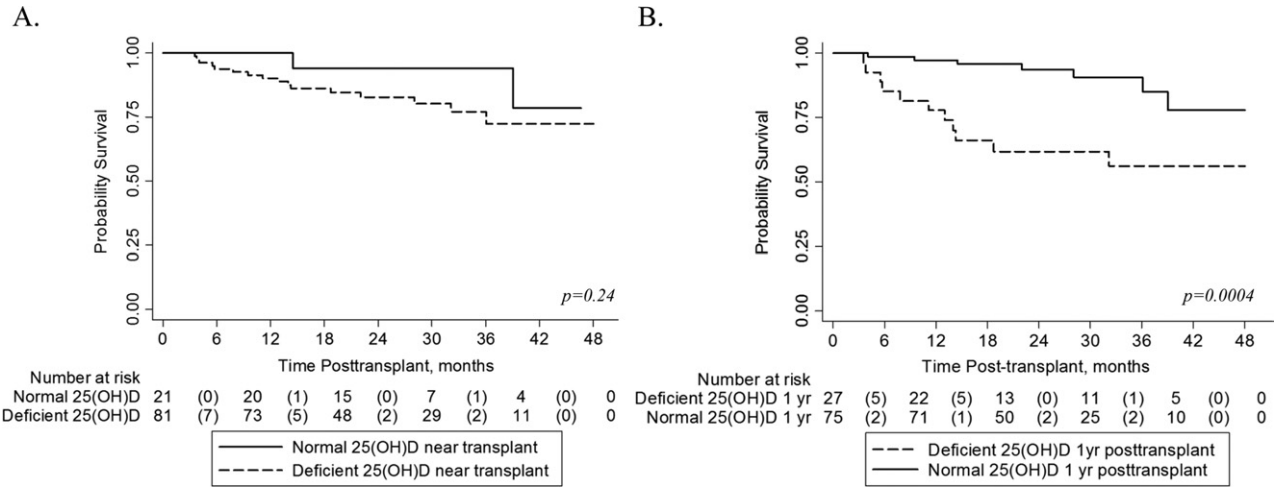

Figure 3 Kaplan–Meier survival estimates. (A) Comparison of those with normal 25(OH)D to those who were 25(OH)D-deficient in the near-transplant period. (B) Comparison of those with normal 25(OH)D in the first year after transplant to those who remained persistently 25(OH)D-deficient.

recipients who remained persistently deficient compared to those with normal levels (Table 2).

Discussion

This is the first study to explore the impact of 25(OH)D deficiency on the clinical course of lung transplant recipients. This study has three major findings. First, 25(OH)D deficiency near the time of lung transplant was associated with increased risk of acute rejection and infection. Second, the negative impact of 25(OH)D deficiency on rejection and infection continued if the deficiency was not corrected in the year after lung transplantation. Finally, persistent 25(OH)D deficiency after transplant was associated with poorer survival.

Nearly 80% of patients in this cohort were 25(OH)D-deficient near the time of lung transplant. This highly prevalent problem has been reported consistently among patients with end-stage lung disease[2,3] and in patients awaiting other solid-organ transplants.[27–30] Several factors may have contributed to 25(OH)D deficiency in our patients. Adipose and skeletal muscle tissues necessary for storage of vitamin D are commonly decreased in patients with chronic lung disease.[1,30] Malabsorption of vitamin D in recipients with cystic fibrosis and inadequate intake of 25(OH)D may also contribute. Finally, near the time of lung transplant, patients do not engage in outdoor physical activity,[3] and after transplant they deliberately avoid sunlight exposure due to the risk of skin cancer while on immunosuppression.[3]

The presence of 25(OH)D deficiency near the time of lung transplantation was associated with over double the risk of acute rejection in the first year after transplant. An association between 25(OH)D deficiency and organ rejection has also been reported in liver, kidney and heart transplant recipients.[27–29] Allograft rejection is initiated when antigen-presenting cells, such as dendritic cells, present T lymphocytes with foreign antigen from the allograft. This leads to recruitment and activation of effector T cells to the allograft, which consequently results in loss of function and allograft injury.[31] There are several mechanisms through which 25(OH)D deficiency could increase the risk of rejection. First, the active form of vitamin D [$1,25(OH)_2D_3$] can slow the maturation of antigen-presenting cells—including dendritic cells—when administered in vitro.[32] This implies that, in the presence of $1,25(OH)_2D_3$, the ability of dendritic cells to activate T lymphocytes is diminished.[1] Second, vitamin D also induces dendritic cells to acquire tolerance that favors activation of regulatory rather than effector T cells.[33,34] Finally, a synergistic effect between vitamin D analogs and classical immunosuppressants has been observed.[34,35]

The increase in episodes of acute cellar rejection after transplant is a major risk factor for the subsequent development of BOS.[36] Surprisingly, we observed no association between low 25(OH)D and the development of BOS. Perhaps a longer follow-up period is necessary to clearly delineate whether there is a detrimental effect on BOS development in patients with deficient 25(OH)D. The median follow-up among all patients in our cohort was 25.4 months. According to ISHLT data, 78% of lung transplant recipients are free from BOS at this time-point, but by 5 years post-transplant 49% of recipients have developed BOS.[36,37]

In contrast to the inhibitory role of vitamin D in cell-mediated immunity, vitamin D enhances the innate immune response.[11,14,38] The National Health and Nutrition Examination Survey (NHANES) and others studies have observed that vitamin D deficiency predisposes to upper respiratory tract infections and higher rates of active tuberculosis.[17–21] Our data support an association between increased susceptibility to infection in patients with low 25(OH)D. The innate immune response in the lung leads to upregulation of vitamin D–responsive genes, increasing hydroxylation of 25(OH)D to active $1,25(OH)_2D_3$, resulting in increased production of cathelicidin, an anti-microbial peptide.[15] This may account for our observation that those with persistent vitamin D deficiency had an almost 2-fold higher risk of developing an infection requiring anti-microbial agents in the year after transplant compared to those with normal vitamin D levels.

Finally, our study has revealed a significant survival benefit in those patients who achieved optimal vitamin D levels in the year after transplantation. We hypothesize that the increased mortality rate in those who remain persistently vitamin D-deficient may be a detrimental consequence of increases in acute rejection and infections. An alternative hypothesis is that recipients with persistent vitamin D deficiency may suffer from a greater severity of illness after transplant. At the time of transplant, however, indicators of severity of illness, such as lung allocation score (LAS), were not significantly different between groups. Even so, 25(OH)D deficiency may be an indicator of a more turbulent post-transplant course.

There are several limitations to our study. The definition of optimal serum 25(OH)D remains controversial.[4,5] Our choice of the 30-ng/ml threshold of 25(OH)D, below which we classified our patients as 25(OH)D-deficient, was based on a decrease in active calcium intestinal absorption and an increase in parathyroid hormone (PTH) production seen with 25(OH)D <30 ng/ml.[4,5] Vitamin D levels in our cohort were drawn both before and after transplantation, and therefore we cannot comment on the independent contribution of pre- vs post-transplant levels on clinical outcomes. It is unlikely, however, that 25(OH)D levels change quickly within 100 days.[39] Further investigations done prospectively could clarify this limitation. Although every patient in our cohort was prescribed a vitamin D analog after transplant, inadequate 25(OH)D levels were still observed. Inability to reach adequate 25(OH)D levels could be due to inadequate supplementation. Patients on long-term glucocorticoids, such as lung transplant recipients, require higher doses of vitamin D to achieve normal serum levels.[2] Inadequate serum vitamin D levels may also be due to patient non-compliance. Attention should be given to additional oral vitamin D replacement with step-up protocols to correct

deficient 25(OH)D levels in the post-transplant period because this patient population cannot increase their exposure to sunlight given the high risk of skin cancer.

Our findings have implications both for recipients of lung transplantation as well as those patients with end-stage lung disease who are considering lung transplantation. Attentive treatment of 25(OH)D deficiency is necessary both before and after transplant. No prospective trials of vitamin D analogs in transplant recipients have been conducted, although it clearly remains challenging to achieve optimal serum vitamin D levels in this patient population. Examining the effect of vitamin D supplementation in lung transplant recipients in a prospective manner would be beneficial to assess more accurately overall supplementation and transplant outcomes in this medically complex patient population. Further research into the interactions between vitamin D, the immune system and immunosuppressive therapy are needed to clarify the impact that vitamin D has on rejection and infections in lung transplant recipients.

In conclusion, we assert that there are multiple benefits to maintaining normal serum vitamin D levels in the lung transplant population, such as decreased frequency of acute rejection and infection and an overall survival benefit.

Disclosure statement

The authors have no conflicts of interest to disclose.

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