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Vitamin D Status of HIV-positive Patients with Advanced Liver Disease Enrolled in the Solid Organ Transplantation in HIV Multi-site Study

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Abstract

Optimal vitamin D status may benefit liver transplant (LT) patients. Higher levels of 25-hydroxyvitamin D [25(OH)D] mitigate steroid-induced bone loss post-LT, correlate with better HCV treatment responses, and increase graft survival. This study investigated 25(OH)D levels and assessed strategies for vitamin D deficiency prevention in HIV-positive patients with advanced liver disease enrolled in the Solid Organ Transplantation Multi-site Study. 25(OH)D was measured in banked specimens of 154 LT candidates/recipients using the Diasorin assay; deficiency was defined as 25(OH)D < 20 ng/mL. Information about vitamin D supplement use post-LT was obtained from medication logs and via survey. Logistic regression, Cox regression and linear repeated measures analyses were performed in SAS. We found that none of the 17 academic medical centers in the United States routinely recommended vitamin D supplements prior to LT, and only a minority (4/17) recommended vitamin D supplements to all patients after LT. Among 139 patients with pre-LT values, 71% had vitamin D deficiency, which was significantly associated with cirrhosis (p=0.01) and no other variable. Vitamin D status improved modestly after LT; however, 40% were deficient one year post-LT. In a multivariable linear repeated measures model, higher pre-LT 25(OH)D (p<.0001), summer season for specimen collection (p=0.0003), a routine vitamin D supplementation strategy post-LT (p=0.0004) and time elapsed post-LT (p=0.01) were significantly associated with an increase in the post-LT 25(OH)D level; black race was associated with a decreased level (p=0.02). In conclusion, the majority of patients awaiting LT were vitamin D deficient, and about half were vitamin D deficient post-LT. More extensive use of vitamin D supplements and/or more sun exposure are needed to prevent deficiency in HIV-positive LT candidates and recipients.

Keywords

25-hydroxyvitamin D; hepatitis C virus; liver transplantation; sustained virological response

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Introduction

The vitamin D axis plays an integral role in maintaining human health. Vitamin D is synthesized in the skin or acquired from dietary sources and is transported to the liver where it is hydroxylated to form 25-hydroxyvitamin D [25(OH)D], which is the single best indicator of a patient's vitamin D status. A second hydroxylation step occurs in the kidney and at multiple sites of local metabolism to produce 1,25-dihydroxyvitamin D, which acts as a steroid hormone that regulates gene expression in multiple tissues, increasing the intestinal absorption of calcium and strengthening bone (1). In addition to its classical functions in bone and calcium metabolism, vitamin D has been reported to have many additional effects that may benefit patients undergoing solid organ transplantation, including anti-inflammatory and anti-fibrotic effects (2), reducing rates of acute allograft rejection (3–5) and protecting against liver cancer (6,7).

Several studies have shown a positive correlation between higher 25(OH)D levels and antiviral treatment responses in HCV monoinfected patients (8–12); however, this relationship may be influenced by racial differences in vitamin D endocrinology (13). One study found a positive relationship between 25(OH)D levels and sustained virological response (SVR) rates in HIV/HCV co-infected patients (14), whereas another study did not find an association with SVR but did find that 25(OH)D levels were negatively correlated with liver fibrosis (15). Recent studies suggest that the relationship between 25(OH)D levels and treatment response rates may depend on genetic differences in the haplotype of the vitamin D receptor, which may account for some of the differences in the findings of various studies (16). Vitamin D supplementation has been reported to increase SVR rates in HCV monoinfected patients undergoing interferon/ribavirin treatment (17,18) and was also associated with greater SVR rates in HCV-positive patients treated post-LT (19).

Nutritional deficiencies are common among patients with advanced disease and compromise health across a spectrum of disease conditions. A recent study found that 81% of patients awaiting liver transplantation (LT) had 25-hydroxyvitamin D [25(OH)D] levels below 32 ng/mL (20), which many experts consider to be the lower limit of the optimal level (21). Adequate levels of vitamin D are particularly important for patients with advanced liver disease because these patients have a high risk of bone fractures. A study of 360 patients who underwent liver transplantation (LT) found that about 20% had evidence of bone fractures prior to LT, and the fracture rate increased following LT with 25% of patients experiencing a new fracture in the 6 months after LT (22). Vitamin D may be especially important for HIV-positive patients with end stage liver disease because HIV infection can directly contribute to bone loss, and the anti-retroviral medications used to suppress HIV infection can also cause bone loss and increased bone fractures (23). HIV-practice guidelines recommend a level above 32 ng/mL (24).

The Solid Organ Transplantation in HIV Multi-site Study was performed to assess safety and other outcomes of transplantation in HIV-positive patients following the introduction of highly active anti-retroviral therapy (HAART). This retrospective, ancillary study was undertaken to determine whether the vitamin D needs were met by the standard practices being followed at the 17 academic medical centers participating in the parent study and to assess risk factors for vitamin D deficiency post-LT.

PATIENTS AND METHODS

Subjects

This is a retrospective analysis of data and samples collected during a prospective cohort study of HIV-positive patients with advanced liver disease who participated in the Solid

Organ Transplantation in HIV Multi-site study, an investigation that was conducted at 17 centers in the United States (ClinicalTrials.gov, NCT00074386). The inclusion criteria of the main study have been described previously (25). The study group included in this investigation was comprised of 154 LT candidates/recipients who had at least one pre- or post-LT banked serum specimen available for quantitation of 25(OH)D via the Diasorin immunoassay. Specimens were collected between November 2003 and October 2010 and stored in freezers at −80 degrees C. Time-points for specimens used in the analysis included: enrollment (pre-transplant), 3 months, 6 months, 1 year and 2 years post-transplant. Forty of the 154 subjects did not undergo LT during the study, and hence had baseline samples only. Of the 114 LT patients, 83 had both pre- and post-LT samples, 15 had post-LT samples only, and 16 had pre-LT only. In LT recipients, pre-LT samples were collected at a median (interquartile range [IQR]) of 1 [0–65] day prior to LT. Vitamin D deficiency was defined as a 25(OH)D level < 20 ng/mL, severe deficiency as a level < 10 ng/mL, inadequacy as a level < 32 ng/mL, and potential toxicity as above 150 ng/mL. Centers were queried about routine vitamin D supplementation strategies post-LT. Center-specific vitamin D supplementation strategies were categorized as either prescribed on an individual basis or routinely prescribed for all patients. Post-LT, vitamin D supplement use was reported by patients on concomitant medication logs at select time points per the study protocol. Information about pre-LT supplement use was not available.

Treatment of recurrent HCV

HCV-positive patients who developed cholestatic hepatitis or had evidence of fibrosis progression were treated with pegylated interferon-α2a or α2b plus ribavirin (target dose 800 mg/day) post-LT. Recurrence was defined by the presence of cholestatic hepatitis or bridging fibrosis/cirrhosis in a liver biopsy, by the initiation of HCV therapy, or by graft loss attributed to HCV.

Statistical methods

Continuous variables were analyzed using the Wilcoxon-rank sum test, and paired continuous variables using the signed rank test. Logistic regression was used to identify baseline factors associated with vitamin D deficiency before LT (at enrollment) and vitamin D deficiency and severe vitamin D deficiency at one year after LT. The variables analyzed included the North/South location of the transplant center (Supplemental Table 1), the season when serum specimen collection was done (“season of measurement”), the laboratory-based MELD score, age, race, gender, ethnicity, cirrhosis (as the subject’s primary hepatic diagnosis, versus cholestatic, fulminant liver failure, metabolic disease, tumor or toxicity), etiology of chronic liver disease (HCV versus no HCV), non-nucleoside reverse transcriptase (NNRTI) use, tenofovir use, ritonavir use, hepatocellular carcinoma, body mass index (BMI), and nadir CD4 count. Pre-LT 25(OH)D level, post-LT routine vitamin D supplementation strategy and post-LT vitamin D supplementation use were evaluated in post-LT analyses only. Potential predictors of 25(OH)D levels over the two-year period post-transplant were examined via univariable and multivariable linear repeated measures models. In addition to the variables stated above, CD4 count, MELD score, GFR (estimated by CKD-EPI equation), HCV recurrence, time after LT, and the aforementioned antiretroviral and vitamin D supplementation use variables were all evaluated as time-dependent covariates in the repeated measures models. In all analyses, variables with $p < 0.15$ from the univariable model were included in an initial multivariable model. Subsequently, variables with $p \geq 0.10$ were excluded, the model was re-fit, and all interactions examined. The 25(OH)D level at HCV therapy initiation (both as a binary factor: vitamin D deficiency or not; and as a continuous factor) was evaluated as a predictor of End-of-Treatment (EOT) response to therapy in a univariable logistic regression model. Despite the small sample size, the impact of the 25(OH)D D level on the EOT rate was

evaluated in a multivariable model adjusted for the HCV genotype, the only factor previously shown to be marginally associated with the EOT rate in this population (25). The 25(OH)D level was also evaluated as a time-dependent covariate in univariable proportional hazards regression models for post-LT death, development of treated acute rejection, and histologic hepatitis C recurrence (in the HCV-infected subgroup only). The 25(OH)D level was examined in three different ways: as a binary factor (vitamin D deficiency or not, and severe vitamin D deficiency or not), and as a continuous variable. A p value below 0.05 was considered statistically significant; all statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Prescription of vitamin D supplements

None of the centers routinely recommended vitamin D supplements prior to LT, and only a minority (4/17) recommended vitamin D supplements to all patients after LT (Supplemental Table 2). Among the four centers that employed a strategy of routine supplementation post-LT, the most commonly reported dose was 800 IU per day (three centers). One center prescribed a vitamin D dose of 600 IU per day.

Vitamin D status pre-LT

Of the total of 139 candidates with baseline values, 48 (35%) had severe deficiency, 98 (71%) had deficiency and 125 (90%) had levels below 32 ng/mL. None of the patients had 25(OH)D levels above 150 ng/mL, the level associated with vitamin D toxicity. The median [IQR] 25(OH)D level was 12.6 [7.9–22.1] ng/mL, see Fig. 1. In a multivariable logistic regression model, cirrhosis (as the primary hepatic diagnosis) was the only factor significantly associated with vitamin D deficiency [odds ratio (OR) (95% CI): 3.5 (1.4–8.8); p=0.01)]; male gender was associated with a lower risk of deficiency, but the association was not statistically significant [Odd Ratio (OR) =0.3, 95% Confidence Interval (CI), 0.1–1.04, p=0.06] (Table 1).

Vitamin D status post-LT

Both pre- and post-LT samples were available for 83 patients. By 12 weeks post-LT, the first time point analyzed, 25(OH)D levels had risen modestly, but significantly, to a median of 17.5 ng/mL (Q1=12.3, Q3=22.1) (Figure 1 and Table 2). The median increase was 4.5 ng/mL (Q1= −3.6, Q3=11.8). Post-LT levels remained higher than pre-LT levels at all time points analyzed; however, 40% were vitamin D deficient at one year and 44% were deficient at two years post-LT.

The 53 subjects with both baseline and 1-year 25(OH)D levels were included in univariable/multivariable logistic regression analyses to identify baseline factors that were associated with vitamin D deficiency and severe vitamin D deficiency at one year post-LT (Supplemental Tables 3 and 4, respectively). In the univariable analysis, black race and pre-LT 25(OH)D levels were both associated with vitamin D deficiency; however, in the multivariable analysis only the pre-LT 25(OH)D level was significant (OR=0.88 per ng/mL, 95% CI=0.81–0.96, p=0.004). In the univariable and multivariable analyses of baseline factors associated with severe vitamin D deficiency, the pre-LT 25(OH)D level was the only significant factor (OR=0.87 per ng/mL, 95% CI=0.78–0.97, p=0.01).

In a multivariable linear repeated measures model of factors associated with post-LT 25(OH)D levels, a 10 ng/mL increase in pre-LT 25(OH)D level was associated with an average 6 ng/mL increase in the post-LT 25(OH)D level (p<.0001), winter and spring/fall seasons for serum specimen collection were associated with 5.5 ng/mL (p=0.0003) and 4.6

ng/mL (p=0.0004) decrease in levels relative to summer, a strategy of routine vitamin D supplementation post-LT was associated with a 9.5 ng/mL increase (p=0.0004), and every 13 weeks elapsed post-transplant with a 0.7 ng/mL increase (p=0.01); black race was associated with a 6.1ng/mL decrease in post-LT 25(OH)D level (p=0.02; Table 3).

Relationship between 25(OH)D levels and outcomes in HCV positive patients

Recurrence—The relationship between 25(OH)D levels and HCV recurrence post-LT was examined in the subset of 67 subjects with known 25(OH)D values post-LT or within 3 months pre-LT (out of 89 HCV-infected LT recipients from the main study). Of these 67 subjects, 37 experienced HCV recurrence post-LT. In univariable proportional hazards regression analysis of HCV recurrence, neither vitamin D deficiency, (HR=0.56; 95% CI: 0.28–1.12; p=0.10), severe vitamin D deficiency (HR=1.29; 95% CI: 0.63–2.66; p=0.48), nor the 25(OH)D level (HR=1.02 per ng/mL; 95% CI: 1.00–1.04; p=0.09) post-LT was significantly associated with the incidence of HCV recurrence.

Response to HCV antiviral treatment—The relationship between 25(OH)D levels and treatment outcomes was examined in 33 patients who were treated with interferon and ribavirin post-LT and who had 25(OH)D measured within 6 months of HCV therapy initiation. Information about 25(OH)D levels was not available for an additional 6 patients who received HCV treatment.

Among the 33 patients, 28 were infected with genotype 1 HCV and 5 were infected with other genotypes. Seven of the 33 patients (21%) had an EOT response measured at week 48 of treatment. The median (IQR) 25(OH)D level at treatment initiation was 30.3 ng/mL (20.8–48.2) for those who achieved an EOT response and 17.8 ng/mL (8.1–25.7) for those who did not (Figure 2). A higher baseline 25(OH)D level was the only variable significantly associated with a higher EOT response rate in multivariable logistic regression analysis [OR (95% CI): 1.13 (1.004–1.27) per ng/mL; p=0.04]; HCV genotype 1 was marginally associated with a lower EOT response rate [OR (95% CI): 0.08 (0.01–1.08); p=0.06] (Table 4).

Four of the 33 patients achieved an SVR. The median (IQR) 25(OH)D level at baseline was 39.3 ng/mL (24.8–54.4) for those patients and 20.2 ng/mL (9.8–25.7) for patients who did not have an SVR (Wilcoxon rank-sum test; p=0.04). Among the four patients with an SVR, the baseline 25(OH)D levels were 30.3 ng/mL and 48.2 ng/mL for the two with genotype 1 HCV, and 19.2 ng/mL and 60.6 ng/mL for the two with genotype 2 HCV.

Relationship between 25(OH)D levels, acute rejection, and survival

There were 34 subjects with a treated acute rejection episode and 35 deaths in the sub-group of 95 LT recipients for whom 25(OH)D levels were known post-LT or within 3 months pre-LT. In univariate proportional hazards regression models of mortality, neither the 25(OH)D level, nor vitamin D status was significantly associated with death. In univariable models of treated acute rejection, neither the 25(OH) level nor vitamin D status was significantly associated with the incidence of rejection episodes.

DISCUSSION

This study of patients enrolled in the Solid Organ Transplantation Multi-site Study is the first to examine 25(OH)D levels in HIV-positive patients pre-LT and post-LT. The samples analyzed in this study were collected between November 2003 and October 2010 at 17 academic medical centers in the United States. We found that most of the patients had vitamin D deficiency pre-LT and almost half had vitamin D deficiency post-LT. Vitamin D

deficiency was defined using a cutoff of 20 ng/mL of 25(OH)D in keeping with the Institute of Medicine's determination that the health risks of vitamin D deficiency increase when 25(OH)D levels fall below this threshold (26). The high prevalence of vitamin D deficiency is striking because HIV practice guidelines recommend a 25(OH)D level over 32 ng/mL for HIV-positive patients (24), and higher 25(OH)D levels have been found to be predictive of post transplant bone gain (27). Only 10% of the patients in our study had pre-LT 25(OH)D levels above 32 ng/mL. Of the variables we examined, cirrhosis was the only factor significantly associated with an increased risk of vitamin D deficiency. This association between vitamin D deficiency and cirrhosis accords with previous findings (20); however, when Venu and colleagues used a cut-off of 32 ng/mL to define vitamin D deficiency, they did not find an association with cirrhosis. We also observed a non-significant trend toward more vitamin D deficiency among women, which is consistent with the lower 25(OH)D levels found in women in other studies (28). Our findings highlight the need to pay particular attention to the vitamin D requirements of cirrhotic patients and women when evaluating HIV-positive LT candidates and patients.

The variables that were not significantly associated with vitamin D deficiency pre-LT in this study included race, HCV as the etiology of liver disease, and NNRTI use. All the patients in the study were HIV positive, precluding an analysis of HIV as a factor predisposing to vitamin D deficiency; however, other studies have not found an association between HIV infection and low 25(OH)D levels (29–31). A number of previous cross-sectional studies have reported an association between NNRTIs and vitamin D deficiency (30,32–35), although this was not found in all studies (36). Some studies have specifically reported an association with efavirenz but not other NNRTIs, suggesting that this may be a drug-specific effect rather than a class effect (32,37,38); however the limited number of patients in this study did not allow for a stratification based on specific NNRTIs. Our study did not find a significant association between ritonavir use and vitamin D deficiency. Ritonavir has previously been associated with higher levels of 25(OH)D in patients (30,33) and impairments of vitamin D metabolism in vitro (39). HIV-positive patients may have an increased susceptibility to the ill effects of vitamin D deficiency if they are taking certain commonly-used antiretroviral drugs; parathyroid hormone elevations occur in tenofovir users who have 25(OH)D levels < 30 ng/mL, likely increasing their risk of bone loss and bone fracture even when 25(OH)D levels remain above 20 ng/m, the usual cutoff for vitamin D deficiency (40). Vitamin D supplements may still be especially important for HIV-positive patients taking tenofovir, as noted in the package insert.

None of the centers routinely recommended vitamin D supplements to all patients prior to LT and only 4/17 (24%) made this recommendation post-LT. More extensive use of vitamin D supplements would almost certainly raise 25(OH)D levels in this population because implementation of a routine supplementation strategy post-LT increased 25(OH)D levels by an average of 9.5 ng/mL. A recent study found that among patients awaiting LT, the median increase in 25(OH)D was 6.0 ng/mL/1000 IU of vitamin D3/day (41).

An interesting finding in our study was the positive association between 25(OH)D levels and EOT responses among 33 HCV-positive patients who received peglyated-interferon/ribavirin for recurrent HCV. The four patients who achieved an SVR had significantly higher 25(OH)D levels at the initiation of treatment as compared to patients who did not. These results are consistent with published data showing that vitamin D supplements increased SVR post-LT (19). A prospective trial is needed to draw definitive conclusions about the impact of vitamin D supplements on HCV treatment responses in the LT population.

The strengths of our study include the analysis of data about HIV-positive patients undergoing LT at 17 academic medical centers throughout the United States, and the ability to follow patients up to two years post-LT with information about both clinical outcomes and 25(OH)D levels. The limitations include the lack of complete data about 25(OH)D levels and the lack of information about other indicators of vitamin D and bone status, such as the level of parathyroid hormone and bone density.

In summary, our study indicates that vitamin D deficiency is highly prevalent among HIV-positive patients who are candidates for LT and who undergo LT. Cirrhosis was strongly associated with vitamin D deficiency pre-LT. Many centers advised use of vitamin D supplements post-LT as indicated, but not usually on a routine basis. A routine supplementation strategy was associated with a large increase (over 9 ng/mL) in 25(OH)D levels, indicating that supplements can be effective in this population. Clinical trials of vitamin D (and calcium) supplements are needed to determine the optimal doses of vitamin D supplements and their impact on clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

25(OH)D	25-hydroxyvitamin D
LT	liver transplantation
NNRTI	non-nucleoside reverse transcriptase

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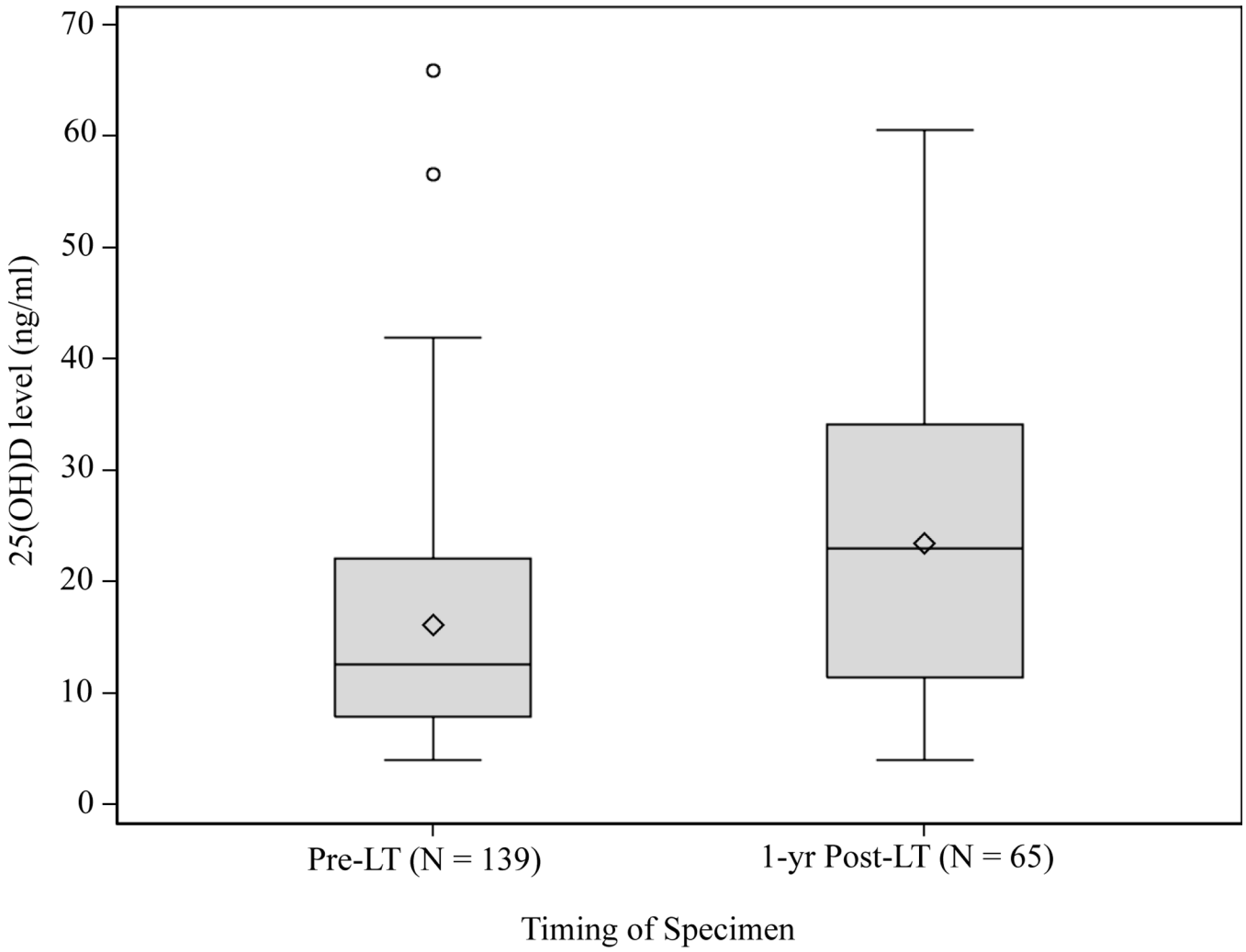

Figure 1.
Distribution of 25(OH)D levels before and one year after liver transplantation. In the box and whisker plot, the line inside the box indicates the median value whereas the bottom and top edges of the box indicate the intra-quartile range. Outlier values are shown in circles; means are indicated by diamonds.

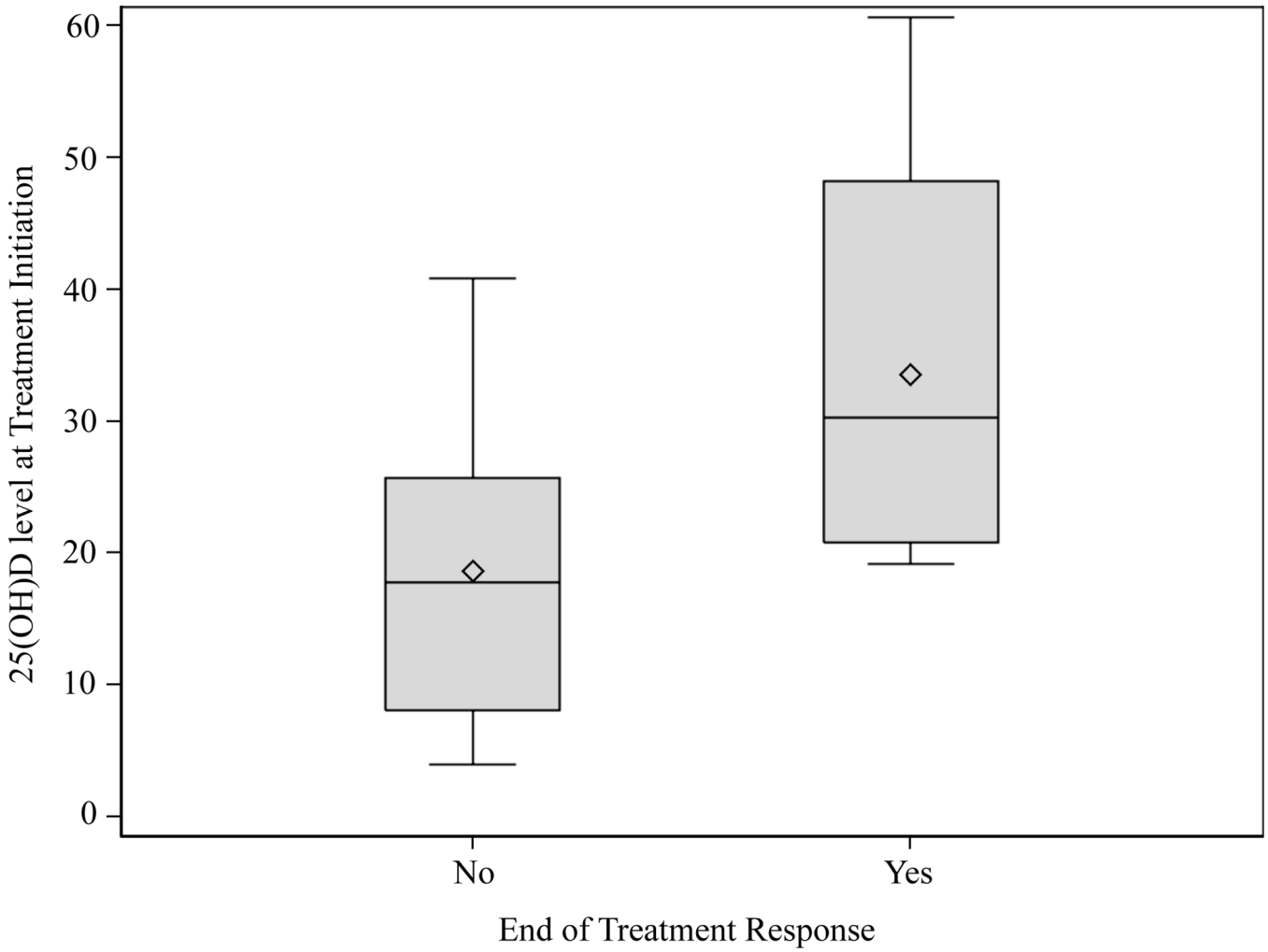

Figure 2.
Box and whisker plots of 25(OH)D levels of patients who did not have an end of treatment response to HCV therapy (left) and those who did (right). The line inside the box indicates the median value whereas the bottom and top edges of the box indicate the intra-quartile range. Outlier values are shown in circles; means are indicated by diamonds.

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Table 1

Factors associated with vitamin D deficiency prior to LT

		Total (N=139)	25(OH)D < 20 ng/mL (N=98)	25(OH)D ≥ 20 ng/mL (N=41)	OR (95% CI) for Vitamin D Deficiency*	P-Value*
Gender	Male	115	77 (67%)	38 (33%)	0.3 (0.1, 1.03)	0.06
	Female	24	21 (88%)	3 (13%)	Reference	
Race†	Black	28	22 (79%)	6 (21%)	1.7 (0.6, 4.6)	0.29
	Non-black	110	75 (68%)	35 (32%)	Reference	
Ethnicity#	Hispanic	18	16 (89%)	2 (11%)	3.6 (0.8, 16.5)	0.10
	Non-Hispanic	113	78 (69%)	35 (31%)	Reference	
Cirrhosis	Yes	48	41 (85%)	7 (15%)	3.5 (1.4, 8.7)	0.01
	No	91	57 (63%)	34 (37%)	Reference	
HCC	Yes	41	26 (63%)	15 (37%)	0.6 (0.3, 1.4)	0.24
	No	98	72 (73%)	26 (27%)	Reference	
HCV	Yes	89	60 (67%)	29 (33%)	0.7 (0.3, 1.4)	0.29
	No	50	38 (76%)	12 (24%)	Reference	
Region	North	110	78 (71%)	32 (29%)	1.1 (0.5, 2.7)	0.84
	South	29	20 (69%)	9 (31%)	Reference	
Season of measurement	Winter	28	23 (82%)	5 (18%)	2.8 (0.9, 8.8)	0.09
	Spring/Fall	71	50 (70%)	21 (30%)	1.4 (0.6, 3.2)	0.39
	Summer	40	25 (63%)	15 (38%)	Reference	N/A
Age (years)	Median [IQR]	N/A	49 [44–52]	49 [42–53]	1.02 (0.97, 1.07)	0.42
MELD	Median [IQR]	N/A	17 [12–26]	15 [11–32]	0.98 (0.94, 1.03)	0.43
BMI (kg/m^2)	Median [IQR]	N/A	25 [22–28]	25 [22–27]	1.03 (0.96, 1.10)	0.39
Nadir CD4 Count (/μL)	Median [IQR]	N/A	202 [133–327]	165 [79–220]	1.002 (1.000, 1.005)	0.08

		Total (N=139)	25(OH)D < 20 ng/mL (N=98)	25(OH)D ≥ 20 ng/mL (N=41)	OR (95% CI) for Vitamin D Deficiency*	P-Value*
Antiretroviral medications	NNRTI	31	25 (81%)	6 (19%)	2.0 (0.8, 5.3)	0.17
	No NNRTI	108	73 (68%)	35 (32%)	Reference	
	Ritonavir	52	36 (69%)	16 (31%)	0.9 (0.4, 1.9)	0.80
	No Ritonavir	87	62 (71%)	25 (29%)	Reference	
	Tenofovir	81	59 (73%)	22 (27%)	1.3 (0.6, 2.7)	0.48
	No Tenofovir	58	39 (67%)	19 (33%)	Reference	

*From univariate logistic regression analysis

†Race was unknown/not reported for 1 subject

#Ethnicity was unknown/not reported for 8 subjects

Table 2

Change in 25(OH)D levels post-LT

Time	N	Median [IQR] (ng/mL)	Deficient† (%)	Median [IQR] change in 25(OH)D	P Value*
Pre-LT	83	14.8 [7.6–22.1]	66	N/A	N/A
Post-LT Week 12	62	17.5 [12.3–22.1]	65	4.5 [−3.6, 11.8]	0.01
Post-LT Month 6	55	20.2 [14.9–30.4]	49	7.8 [−1.4, 14.4]	<.0001
Post-LT Year 1	53	23.1 [11.1–31.7]	40	4.3 [−3.0, 15.4]	0.002
Post-LT Year 2	39	22.3 [11.3–33.6]	44	5.8 [−0.2, 17.1]	0.0002

*Signed rank test

†Deficient=25(OH)D < 20 ng/mL

Table 3

Univariable and multivariable linear repeated measures analysis of factors associated with 25(OH)D levels post-LT

Univariable Analysis	Estimate (95% CI)	P Value
Gender (Female)	−4.2 (−10.9, 2.5)	0.21
Race (Black)	−9.8 (−15.9, −3, 7)	0.002
Ethnicity (Hispanic)	5.7 (−4.7, 16.1)	0.28
Cirrhosis as Indication for LT	1.8 (−4.1, 7.7)	0.54
HCC	2.1 (−3.4, 7.6)	0.46
HCV Infection	−1.1 (−6.7, 4.6)	0.71
Region (North)	0.5 (−6.5, 7.4)	0.90
Age at LT (per year)	−0.1 (−0.4, 0.2)	0.69
MELD Score at LT	0.02 (−0.2, 0.3)	0.87
Pre-LT BMI (per kg/m^2)	−0.1 (−0.5, 0.3)	0.53
Pre-LT Nadir CD4 Count (per 50 cells/μL)	0.3 (−0.6, 1.2)	0.52
Pre-LT 25(OH)D Level (per ng/mL)	0.6 (0.3, 0.8)	<.0001
Routine Vitamin D Supplementation Strategy Post-LT	9.1 (2.7, 15.4)	0.01
CD4 Count (per 50 cells/μL)*	0.3 (−0.1, 0.8)	0.16
MELD Score*	−0.04 (−0.5, 0.4)	0.86
eGFR < 60 ml/min/1.73 m^2 (CKD-EPI)*	1.8 (−2.0, 5.6)	0.33
Vitamin D Supplementation*¶	4.1 (−1.2, 9.4)	0.11
NNRTI use*	1.7 (−3.8, 7.2)	0.48
Ritonavir use*	2.3 (−2.8, 7.3)	0.34
TDF use*	2.5 (−1.8, 6.9)	0.23
HCV recurrence*	−0.7 (−5.8, 4.4)	0.77
Season of measurement*		0.0003
Winter	−5.3 (−8.1, −2.4)	0.0005
Spring/Fall	−5.0 (−7.4, −2.5)	0.0002
Summer	Reference	N/A
Time (per 13 weeks)*	0.75 (0.1, 1.4)	0.02
Multivariable Predictors	**Estimate (95% CI)**	**P Value**
Pre-LT 25(OH)D Level (per ng/mL)	0.6 (0.4, 0.8)	<0.0001
Season of Measurement*		0.0003
Winter	−5.5 (−8.3, −2.6)	0.0003
Spring/Fall	−4.6 (−7.1, −2.2)	0.0004
Summer	Reference	N/A
Routine Vitamin D Supplementation Strategy Post-LT	9.5 (4.4, 14.6)	0.0004
Time (per 13 weeks)*	0.7 (0.2, 1.3)	0.01
Race (Black)	−6.1 (−11.1, −1.0)	0.02

Vitamin D Supplementation*¶	3.9 (−0.6, 8.4)	0.08

*Time-varying covariate

¶Patient-reported data from concomitant medication logs

Table 4

Logistic regression analysis of end-of-treatment response to HCV therapy

Univariable Predictors	Odds Ratio (95% CI)	P Value
25(OH)D Level at Treatment Initiation (per ng/mL)	1.10 (1.01–1.20)	0.03
Vitamin D Deficiency at Treatment Initiation	0.14 (0.02–1.36)	0.09
HCV Genotype 1	0.11 (0.01–0.89)	0.04
Multivariable Predictors	**Odds Ratio (95% CI)**	**P Value**
25(OH)D Level at Treatment Initiation (per ng/mL)	1.13 (1.004–1.27)	0.04
HCV Genotype 1	0.08 (0.01–1.08)	0.06