Bone Mineral Density and Fat-Soluble Vitamin Status in Adults with Cystic Fibrosis Undergoing Lung Transplantation: A Pilot Study

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ABSTRACT

Purpose: Patients with cystic fibrosis (CF) often experience low bone mineral density (BMD) pre- and post-lung transplantation (LTX). The study purpose was to describe BMD and micronutrient status in adults with CF pre- and post-LTX.

Methods: Twelve patients with CF (29 ± 8 years) were recruited from the CF clinic at the University of Alberta Lung Transplant Program. BMD and vitamins A, D, E, K status, and parathyroid hormone were measured pre- and post-LTX.

Results: No significant differences pre- and post-LTX were observed at the different bone sites measured (lumber-spine, femoral-neck (FN), hip, and femoral-trochlea) (p > 0.05). BMD T-scores «-2) was present in lumbar-spine, FN, hip, and femoral-trochlea in 33%, 17%, 17%, and 25% of individuals pre-LTX and 58%, 33%, 58%, and 33% of individuals post-LTX, respectively. More than 50% of patients had suboptimal vitamin K levels (PIVKA-II values) > 3 ng/mL pre- and post-LTX.

Conclusion: Adults with CF pre- and post-LTX had reduced BMD and suboptimal vitamin K status.

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INTRODUCTION

Maintenance of bone health in patients with cystic fibrosis (CF) is an ongoing challenge, especially as the disease becomes more severe and the need for lung transplantation (LTX) becomes more eminent [1]. Pre-LTX and post-LTX, individuals with CF are at high risk for low bone mineral density (BMD) related to chronic use of corticosteroid and other immunosuppressive therapy (such as tacrolimus), antibiotic use and chronic undernutrition secondary to poor intake, increased energy expenditure, and pancreatic insufficiency [2-4]. Suboptimal fat-soluble vitamin intake due to inadequate or poor diet quality and/or noncompliance to prescribed vitamin supplementation can also contribute to low BMD. Several studies have shown that fat-soluble vitamins can be low pre-LTX [5-7], whereas post-LTX, hypervitaminosis A can contribute to low BMD [8].

The University of Alberta Lung Transplant Program provides LTX for patients with end-stage lung disease from Alberta, including individuals with CF who have a reported 60%-75% 5-year survival rate [9]. With increased survival,
poor bone health is a significant concern, especially as it relates to increased morbidity and mortality and overall quality of life [4, 10]. Limited exposure to sunlight in northern climates also increases the risk for vitamin D (vitD) deficiency and subsequent poor bone health. For these reasons, patients are routinely supplemented with commercially available fat-soluble vitamins (A, D, E, and K) pre- and post-LTX. Although suboptimal vitamin K (vitK) status has been shown to be a contributor to low bone health in many clinical populations [11], it is currently unknown what the current prevalence of suboptimal vitK status is in adult patients post-LTX. This is particularly relevant in the CF population, as ongoing fat malabsorption due to pancreatic insufficiency is not corrected or improved by lung transplantation. This pilot study describes BMD and fat-soluble vitamin status in adult CF subjects, pre- and post-LTX.

METHODS

Ethics approval (Pro 00001737) was obtained from the Human Research Ethics Board at the University of Alberta prior to study initiation. Adult CF patients (age >18 years) who were referred to the University of Alberta Lung Transplant program between 2005 and 2012 were recruited and enrolled over a 12-month period. Study inclusion criteria included those on anti-resorptive therapy, as this is part of routine clinical care. Exclusion criteria included terminal illness, intensive care unit stay >72 hours, and subjects who were unable to provide informed consent. A total of 25 patients with CF undergoing lung transplant assessment were screened for eligibility; 13 were excluded due to coinciding illness requiring hospitalization, early lung TX, and/or refusal to participate. No significant differences in demographic or anthropometric variables were noted between those who agreed to participate in the study and those who did not. Informed consent was obtained from all participants. Height and weight were measured using validated techniques.

Blood was collected for measurement of vitamins A, D, E, and K (protein indicated in vitamin K absence (PIVKA-II)) and parathyroid hormone (PTH) at LTX assessment and at 3, 6, and 12 months post-LTX. The samples were analyzed according to standardized methodologies in the Core Laboratory at Alberta Health Services [12]. Serum 25-hydroxy vitamin D (25(OH)D) concentrations were assessed according to the Canadian Endocrine Practice Guidelines (<75 nmol/L, insufficient/suboptimal; >75 nmol/L, optimal) [13]. BMD was measured using hologic dual-energy X-ray absorptiometry 450 at LTX assessment and at 9 and 18 months post-LTX (whole body, hip, femoral-neck (FN), femoral-trochlea, lumbar-spine).

Analyses were performed using Statistical Analysis Software (SAS; version 9.4 SAS Institute, Cary, NC, USA). Data were analyzed by treating individual patient data as single measures, rather than repeated measures due to the small sample size at each individual time point. Continuous variables were expressed as mean ± SD. Normality was assessed using the Shapiro–Wilk test. Non-parametric variables were log transformed. Continuous variables were analyzed using dependent t test to assess differences pre- and post-LTX with adjustments for potential confounding variables (season, age, sex). Statistical significance was determined at P < 0.05.

RESULTS

Demographic, anthropometric, and laboratory data

Anthropometric and demographic data for the 12 patients pre- and post-LTX are shown in Table 1. No significant age difference at time of LTX assessment was observed between sexes (males, 29 ± 10 years vs. females, 31 ± 6 years; P = 0.70). A total of 42% (n = 5) and 17% (n = 2) of participants had a mean BMI reflective of suboptimal nutritional status (BMI < 18.5) pre- and post-LTX, respectively. Laboratory data are shown in Table 2. Although there was no significant difference in estimated glomerular filtration rate (GFR), values in 58% of patients were indicative of renal insufficiency (GFR < 60; stage 3 chronic kidney disease) post-LTX. In addition, significant differences in urea, creatinine, and PTH pre- and post-LTX were noted, indicating worsening renal function and secondary hyperparathyroidism in 83% of patients post-LTX. The majority of patients (67% pre-LTX and 58% post-LTX) had optimal 25(OH)D vitD levels (>75 nmol/mL), likely secondary to vitD supplementation (400–8700 IU/d) [13]. A total of 58% and 55% of patients had suboptimal vitK status (PIVKA-II values > 3 ng/mL) pre- and post-LTX, respectively. Laboratory data, despite routine recommendation for vitK supplementation

### Table 1. Anthropometric and bone health variables pre- and post-LTX in adult patients with cystic fibrosis.

<table>
<thead>
<tr>
<th>Anthropometrics</th>
<th>Pre-LTX (n=12; 7M, 5F)a</th>
<th>Post-LTX (n=12; 7M, 5F)a</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>29 ± 8 (19-49)</td>
<td>30 ± 8 (19-52)</td>
<td>0.371</td>
</tr>
<tr>
<td>Weight (kg)b</td>
<td>54.8 ± 9.0 (39.1-71.0)</td>
<td>60.3 ± 5.6 (51.4-67.8)</td>
<td>0.098</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.68 ± 0.08 (1.55-1.81)</td>
<td>1.68 ± 0.08 (1.55-1.81)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)b</td>
<td>19.3 ± 3.2 (15.1-25.7)</td>
<td>21.4 ± 2.4 (17.5-25.0)</td>
<td>0.103</td>
</tr>
<tr>
<td>Spine BMD (gm/cm²)c</td>
<td>0.86 ± 0.11 (0.69-1.03)</td>
<td>0.86 ± 0.10 (0.69-1.07)</td>
<td>0.992</td>
</tr>
<tr>
<td>Hip BMD (gm/cm²)c</td>
<td>0.82 ± 0.14 (0.57-1.08)</td>
<td>0.77 ± 0.12 (0.54-1.04)</td>
<td>0.262</td>
</tr>
<tr>
<td>Femoral-neck BMD (gm/cm²)c</td>
<td>0.71 ± 0.10 (0.56-0.90)</td>
<td>0.67 ± 0.11 (0.54-0.91)</td>
<td>0.324</td>
</tr>
<tr>
<td>Femoral-trochlea BMD (gm/cm²)c</td>
<td>0.60 ± 0.11 (0.43-0.82)</td>
<td>0.55 ± 0.10 (0.40-0.77)</td>
<td>0.166</td>
</tr>
</tbody>
</table>

aData are presented as mean ± standard deviation (range).
bThe number of measurements post-LTX was 11.
cThe number of repeated measurements post-LTX was 22.

Note: LTX, lung transplantation; M, male; F, female; BMI, body mass index; BMD, bone mineral density.
Biochemical & Pre-LTX (n=12)* & Post-LTX (n=12)* & Normal reference ranges & P &
Vitamin A (µmol/L)* & 1.4 ± 0.3 (0.8–2.0) & 2.7 ± 0.8 (1.3–4.0) & 1.5–3.5 & <0.001 &
PIVKA II (ng/mL)* & 80.0 ± 171.9 (0.1–427.8) & 6.4 ± 14.2 (0.1–64.2) & ≤3 & 0.206 &
Vitamin E (µmol/L)* & 26 ± 9 (10–43) & 40 ± 18 (13–86) & 12–45 & 0.010 &
Calcium (mmol/L)* & 2.25 ± 0.10 (2.08–2.38) & 2.26 ± 0.13 (2.10–2.80) & 2.10–2.60 & 0.773 &
PTH (pmol/L)* & 4.4 ± 3.9 (1.4–16.0) & 9.8 ± 11.9 (2.1–61.0) & 1.2–6.8 & 0.025 &
25(OH)D (nmol/L)* & 83 ± 40 (10–154) & 85 ± 23 (43–141) & ≤75 & 0.798 &
Urea (mmol/L)* & 4.3 ± 1.5 (1.2–6.8) & 7.1 ± 2.8 (1.9–10.7) & 2.5–8.0 & 0.006 &
Creatinine (µmol/L)* & 64 ± 18 (35–99) & 108 ± 35 (48–166) & M: 50–115 F: 50–105 & <0.001 &
GFR (ml/min/1.73 m²)* & 60 ± 0 (60–60) & 53 ± 9 (30–60) & >60 & 0.090 &
Hemoglobin A1C (%)* & 6.34 ± 0.57 (5.5–7.4) & 6.11 ± 0.47 (5.4–7.1) & <6.1 & >0.05 &

*Data are presented as mean ± standard deviation (range).

Bone mineral density
BMD data are shown in Table 1 and Figure 1. No significant differences pre- and post-LTX were observed at the different sites measured (lumbar-spine, FN, hip and femoral-trochlea) (P > 0.05). With the exception of spinal-BMD (absolute; females, 0.91 ± 0.08 vs males, 0.82 ± 0.09 gm/cm²; P = 0.002) and T scores (females, -1.27 ± 0.79 vs males, -2.25 ± 1.26; P = 0.015), no significant differences in absolute or T scores were observed between sexes at the different sites measured (P > 0.05). BMD T scores (<2) indicative of osteoporosis were present in lumbar-spine, hip, FN, and femoral-trochlea in 33%, 17%, 17%, and 25% individuals pre-LTX, respectively. In contrast, BMD T scores (<-2) were present in lumbar-spine, hip, FN and femoral-trochlea in 58%, 33%, 58%, and 33% individuals post-LTX, respectively.

DISCUSSION
This is a descriptive, pilot study that describes fat-soluble vitamin status and BMD in adults with CF pre- and post-LTX in a northern Canadian LTX program. A significant finding is that the majority of participants had reduced BMD and suboptimal vitK status, despite healthcare practitioner recommendation for fat-soluble vitamin supplementation. Several factors may have influenced these findings such as low patient adherence to prescriber recommendation, ongoing pancreatic insufficiency and malabsorption refractive to pancreatic enzyme replacement therapy, poor diet quality, reduced weight-bearing activities, and use of immunosuppressive medications such as corticosteroids, tacrolimus, and antibiotics (e.g., tobramycin) [14, 15]. Many patients in this cohort were underweight at the time of LTX and hence had suboptimal nutritional status. Although, weight status improved post-LTX, deficits in nutritional intake and weight-bearing activity, ongoing pancreatic insufficiency and the use of corticosteroid therapy (typically 10–15 mg/d, but tapered down to alternative day therapy and/or discontinuation by 6–12 months), and/or
other medications such as tacrolimus may have contributed to reduced BMD [9, 15-17].

Suboptimal vitD status is highly prevalent in northern climates like Alberta [18, 19]. Although patients in general had serum 25(OH)D levels above 75 nmol/L and normal PTH levels, higher vitD levels in conjunction with weight-bearing activities may be needed to optimize bone health pre- and post-LTX. Findings regarding poor bone health are similar to other LTX centres where ongoing nutritional challenges in adult LTX recipients place them at high risk for poor bone health [20]. A major limitation in this study includes the small sample size, which limits the overall generalizability of the findings. However, a post-hoc power test indicated sufficient power (β > 0.8) to discriminate reduced BMD at the different sites pre- and post-LTX.

Unique findings include the high prevalence of suboptimal vitK status post-LTX. These findings underscore the importance of routine follow-up by healthcare practitioners in patients with CF undergoing LTX. Future studies should focus on assessing adherence to vitamin therapy, and the impact of vitK supplementation on bone health parameters.

RELEVANCE TO PRACTICE

Patients with CF are at high risk for poor bone health and micronutrient insufficiency. This underscores the need for highly specialized medical teams to address ongoing micronutrient deficiencies in this population. Registered Dietitians are uniquely positioned to help optimize bone health and micronutrient status by developing effective nutrition care plans and exploring the barriers and facilitators to achieving nutritional goals in complex care populations.

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References