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Growth, body composition, and bone density following pediatric liver transplantation

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Abstract

Patients transplanted for cholestatic liver disease are often significantly fat-soluble vitamin deficient and malnourished pretransplant, with significant corticosteroid exposure post-transplant, with increasing evidence of obesity and metabolic syndrome post-LT. Our study aimed to assess growth, body composition, and BMD in patients post-pediatric LT. Body composition and bone densitometry scans were performed on 21 patients. Pre- and post-transplant anthropometric data were analyzed. Bone health was assessed using serum ALP, calcium, phosphate, and procollagen-1-N-peptide levels. Median ages at transplant and at this assessment were 2.7 and 10.6 years, respectively. Physiological markers of bone health, median *z*-scores for total body, and lumbar spine aBMD were normal. Bone area was normal for height and BMAD at L3 was normal for age, indicating, respectively, normal cortical and trabecular bone accrual. Median *z*-scores for weight, height, and BMI were 0.6, −0.9, 1.8 and 0.6, 0.1, 0.8 pre- and post-transplant, respectively. Total body fat percentages measured on 21 body composition scans revealed 2 underweight, 7 normal, 6 overweight, and 6 obese. Bone mass is preserved following pediatric LT with good catch-up height. About 52% of patients were either overweight/obese post-transplant, potentially placing them at an increased risk of metabolic syndrome and its sequelae in later life. BMI alone is a poor indicator of nutritional status post-transplant.

KEYWORDS

body composition, bone density, growth, obesity, pediatric liver transplantation

1 | INTRODUCTION

LT is a life-saving treatment and the current standard of care for most children with ESLD. It is now well established that outcomes following pediatric LT are very good with up to 94% patient survival and 84% graft survival at 5 years.[1] This has resulted in a greater focus on improving non-hepatic outcomes of LT such as growth and nutrition, cognition, intelligence quotient, and quality of life.[2-4]

Cholestatic liver disease and consequent liver failure remain the most common indicator for LT in children.[5] These patients are often profoundly vitamin deficient and malnourished in the pretransplant phase, despite intense nutritional and vitamin supplementation.[6] They also have significant corticosteroid exposure post-transplant, increasing their risk of metabolic bone disease. Almost all pediatric LT recipients remain on IS indefinitely. Common side effects such as hypertension, nephrotoxicity, and neurotoxicity are well known.[7,8] There are also increasing reports of obesity and metabolic syndrome post-LT.[9-11]

Abbreviations: aBMD, areal bone mineral density; ALP, alkaline phosphatase; BMAD, bone mineral apparent density; BMD, bone mineral density; BMI, body mass index; ESLD, end stage liver disease; IS, immune suppression; LT, liver transplantation; P1NP, procollagen-1-N-peptide; PICU, pediatric intensive care unit; PLB, protocol live biopsy; TBLH, total body less head.

TABLE 1 Patient demographics of 21 children undergoing liver transplant

	Number of patients (%)
Ethnicity	
New Zealand European	8 (38)
Māori	6 (29)
Pacific	4 (19)
Other	3 (14)
Indications for transplant	
Cholestatic disease	16 (76)
Acute liver failure	3 (14)
Paracetamol overdose	1 (5)
Maple syrup urine disease	1 (5)

With this in mind, we performed a pilot study to assess growth, BMD, and body composition in a cohort of patients who were at least 5 years post-LT in New Zealand.

2 | PATIENTS AND METHODS

The aim of our pilot study was to assess the growth, body composition, and BMD in patients who were at least 5 years post-pediatric LT. There were no specific exclusion criteria. We received a research grant from the New Zealand Society of Gastroenterology and ethics approval from the Health and Disabilities Ethics Committee of New Zealand (reference number 13/NTB/178).

A total of 21 patients (12 male) were recruited. Patients attending our liver transplant clinic for routine follow-up who were at least 5 years post-LT were asked to participate; the first 21 patients who signed consent were included. Pre- and post-transplant anthropometry data (weight, height, and BMI) were recorded in all patients. All patients also underwent a combined bone densitometry and body composition scan. Pretransplant data were collected from a retrospective analysis of our liver transplant registry and case notes, while post-transplant measurements were made at the time of scanning.

Physiological markers of bone health were measured in all patients on the same day as their scan; these included serum ALP, calcium, phosphate, and P1NP levels.

Bone densitometry scans were performed using a Lunar Prodigy DXA scanner (GE Healthcare). Readings were measured and documented as follows. BMD was measured at the lumbar spine region (L1-L4) and the total body (less head). The results were expressed as standard deviation or *z*-scores derived from the manufacturer's reference ranges. The L1-L4 BMD *z*-score data largely represent trabecular bone. Because growth in part accounts for changes in BMD with age, we also calculated BMAD, an estimate of volumetric BMD. Average values for BMAD at L3 are ~0.24 g/cm^3 (age 8), ~0.28 g/cm^3 (age 12), ~0.32 g/cm^3 (age 16) with an SD of ~0.04.

In the whole body scan, bone mineral content and bone area were measured. The read-out includes the bone area centile for chronological age, a measure that is in part related to height (the greater a subject's height, the greater the bone area). The confounding effect of height can be accounted for using the method of Mølgaard et al[12] to produce the parameter "bone area-for-height," generated from the ratio of bone area centile to the height centile. This measure, which is automatically calculated by the densitometer's software and also expressed as a centile or *z*-score, largely reflects the width of long bones, which comprise mainly cortical bone. For the purposes of this study, reduced BMD was defined as a *z*-score of <−2 (total body less height),

Total body fat percentage was measured simultaneously on the same scanner and compared to normative data as documented by McCarthy et al.[13] Patients were defined as underweight, overweight, or obese if their *z*-scores were <2.0 (2nd centile), between 1.0-2.0 (85th to 98th centile), and >2.0 (98th centile), respectively.

Our pediatric liver transplant program began in 2002 and is a national service for all children in New Zealand. The IS protocol used is as follows. All patients receive intravenous methylprednisolone (10 mg/kg) at induction of anesthesia, and on return to the PICU post-operatively. Thereafter, the dose is gradually tapered to 0.3 mg/kg/d by the 8th post-operative day. Patients are switched to oral prednisone (tablets) or prednisolone (liquid) once clinically appropriate. Tacrolimus is commenced at 0.075 mg/kg twice daily on the first post-operative day, with target trough levels of 3-5 μg/L after 1 year post-LT. Patients with renal impairment (KDIGO Chronic Kidney Disease type III and below[14]) and those infants under 1 year receiving an ABO-incompatible graft receive two doses of intravenous basiliximab (at induction and day 4) and mycophenolate mofetil (10 mg/kg twice daily) in addition to standard corticosteroids. The former also get a delayed introduction of tacrolimus on Day 5 (target trough levels 6-8 μg/L). All patients undergo protocol liver biopsies (PLB) at 1 year post-LT, with steroids subsequently discontinued if the biopsy is normal.

3 | RESULTS

For the 21 patients included in the study, the median age at LT was 2.7 years (range 0.6-8.0 years) and the median age at the time of the study was 10.6 years (range 7.1-15.9 years). Sixteen of 21 patients included in the study were transplanted for cholestatic liver disease, 15 of whom had biliary atresia. Other indications for LT included acute liver failure (3/21), paracetamol overdose (1/21), and maple syrup urine disease (1/21) as outlined in Table 1. About 29% of our patients were Māori (indigenous people of New Zealand); the remaining ethnic make-up of the group included 38% New Zealand European, 19% Pacific Island, and 14% of either Indian or Chinese descent. This is representative of our pediatric liver transplant population in New Zealand, with Māori being overrepresented and biliary atresia being the most common indication for transplant.[15]

TABLE 2 Pre- and post-transplant anthropometric data

Anthropometrics	Pretransplant median *z*-score (range)	Post-transplant median *z*-score (range)	Delta median (range)
Weight	0.6 (−0.5 to 2.2)	0.6 (−1.5 to 2.7)	−0.3 (−1.8 to 2.0)
Height	−0.9 (−3.6 to 2.8)	0.1 (−2.0 to 2.0)	0.9 (−2.3 to 3.7)
BMI	1.8 (−0.2 to 3.9)	0.8 (−0.8 to 3.1)	−0.5 (−3.3 to 2.0)

3.1 | Anthropometrics

Pretransplant median *z*-scores for weight, height, and BMI were 0.6 (−0.5 to 2.2), −0.9 (−3.6 to 2.8), and 1.8 (−0.2 to 3.9), respectively; post-transplant median *z*-scores were 0.6 (−1.5 to 2.7), 0.1 (−2.0 to 2.0), and 0.8 (−0.8 to 3.1), respectively, giving a delta median of −0.3 (−1.8 to 2.0), 0.9 (−2.3 to 3.7), and −0.5 (−3.3 to 2.0) for weight, height, and BMI, respectively (Table 2). There were no abnormalities detected on BMI measurements pre- or post-LT.

3.2 | Body composition

In contrast to the measurements described above, total body fat measured on the body composition scans (Table 3) revealed significant abnormalities in our patient cohort. Only 7 patients (33.3%) had normal measured total body fat percentages (2nd-85th centiles). A total of 6 patients (28.6%) were overweight (85-98th centiles), 6 patients (28.6%) were obese (>98th centile), and 2 patients (9.5%) were underweight (<2nd centile).

Seven of 12 patients who had normal BMIs measured post-LT had abnormal body fat percentages when scanned (4 overweight, 1 obese, and 2 underweight). One patient who was overweight as per their BMI measurement (*z*-score 1.6) was actually obese by body fat percentage measurement (*z*-score 2.2).

3.3 | Bone health

Physiological markers of bone health were normal in all patients. The median bone area-for-height *z*-score was 0 (−1 to 3). The median *z*-scores for total body (less head) and lumbar spine aBMD were 0.0 (−1.0 to 2.2) and 0.0 (−0.9 to 1.3), respectively. Fourteen of 21 patients (67%) had a BMAD measured at L3 that was above the expected mean for age. None of our patients had reduced BMD (*z*-score<−2.0) post-LT. Table 4 summarizes the BMD findings on our patients.

Only 2 of the 21 patients in our study were still on steroids at the time of scanning. Both were transplanted for biliary atresia (1 male 8.8 years post-LT, and 1 female 10.1 years post-LT). The boy was significantly growth restricted with a height, BMI, and body fat percent *z*-score of −2.1, −0.3, and −6.2, respectively, while the girl's *z*-scores for the same parameters were −0.9, 0.8, and 1.5 (overweight), respectively. The TBLH BMD *z*-scores for both these patients were normal. All other patients had been on tacrolimus monotherapy since 1 year post-LT, except 1 child who had been switched from tacrolimus to sirolimus to manage significant eczema that he developed post-LT.

TABLE 3 Total body fat percentage measured post-transplant

	Number (%)
Underweight (<2nd centile)	2 (9.5)
Normal (2nd-85th centile)	7 (33.3)
Overweight (85th-98th centile)	6 (28.6)
Obese (>98th centile)	6 (28.6)

4 | DISCUSSION

Patients with end stage cholestatic liver disease are often profoundly vitamin deficient pretransplant, particularly vitamins A, D, and E. They are also malnourished and suffer from significant physiological bone disease in the pretransplant phase, despite intense nutritional and vitamin supplementation.[6] In addition, these patients are exposed to significant corticosteroid doses post-LT, some remaining on steroids for a number of years, if not indefinitely. While theoretically, children who undergo LT early in life should still have opportunity to accrue bone normally after transplant, few long-term studies exist that demonstrate whether this truly occurs in the setting of immune suppressive medication and other long-term drugs, which may affect bone acquisition. Assessment of bone health is difficult in the pretransplant phase as there are currently no normative data available for children less than 2 years of age, the age bracket within which the majority of pediatric liver transplants are performed.

While all of our 21 patients had normal BMD, there are numerous studies in the literature reporting low BMD in liver transplant recipients. One Canadian study reported low BMD (*z*-score<−2.0) in 5.8% and post-LT fractures in 21% of their patients.[16] The primary outcome measured in this study was BMD *z*-score for the lumbar spine. Another study reported 15% of 40 adolescents with low BMD post-LT[17]; this was on a mixed IS regimen of cyclosporine, azathioprine, and methylprednisolone. Guthery et al[18] reported low BMD in 7% of 109 patients (IS regimen not documented), while Helenius et al[19] reported low BMD in 17% of 84 patients who had received liver, kidney, or bone marrow transplant. Interestingly, in contrast to

TABLE 4 BMD results measured post-LT

	Median *z*-score (range)
aBMD (lumbar spine)	0.0 (−0.9 to 1.3)
aBMD (TBLH)	0.0 (−0.9 to 2.2)
Bone area-for-height	0.0 (−1.0 to 3.0)

these findings, Okajima et al[20] reported normal BMD in their entire cohort of 30 patients, all transplanted for biliary atresia, and whose IS regimen was similar to ours. Only 2 of 21 patients in our cohort were still on steroids at the time of the study; both of them had normal BMD. This finding may well be due to the small numbers of patients, and it will be interesting to see whether this remains true with a larger cohort of patients.

Rates of overweight and obesity in New Zealand are among the highest in the world; National Health Survey data estimate that 22% of children aged 2-14 years are classified as overweight, and a further 11% are classified as obese. Rates of obesity in New Zealand are particularly high among Pacific children (30%) and Māori (15%).[21] Of the 57% of patients in our study who were either overweight or obese according to body fat measurements, 42% were Māori and 16% Pacific Island. While the unique ethnic make-up of our population may explain some of the findings, our study cohort was too small to make a further sub-analysis possible.

Our anthropometric data showed that there is significant growth failure pretransplant, with good catch-up growth, particularly height, post-transplant. This is in keeping with an Australian study, which also showed good catch-up height post-LT for up to 15 years.[22] Data from a large cohort in North America showed impaired linear growth in 23% of patients at 10 years post-LT.[23] In contrast, other older studies from the last decade of the 20th century showed significant growth impairment post-LT,[24,25] likely indicative of older IS regimens.

The common side effects of IS such as hypertension, nephrotoxicity, and neurotoxicity [7,8] are well known. Agents such as tacrolimus, cyclosporine, and sirolimus are also thought to reduce pancreatic insulin secretion.[26] There are also increasing reports of obesity and metabolic syndrome post-LT,[9,10,22,27,28] with one North American study reporting obesity rates of 19%, 18%, and 11% at 1, 3, and 5 years post-LT, respectively.[11] The majority of studies to date that have examined growth post-LT use anthropometric measurements (BMI) as an outcome measure. Our study is unique in that we used body composition scanning and compared it to BMI. The BMI measurements pre- and post-transplant in our cohort were all normal; but body compositions scans revealed that more than half of our cohort was either overweight or obese, suggesting that BMI alone is a poor indicator of nutritional status post-LT.

The major limitation of our study was the small cohort of 21 patients, as the intention was a pilot study to determine whether routine BMD was required as part of a long-term effects monitoring program following pediatric LT. This may explain why our BMD results differ from other reported studies. However, the significant rates of obesity post-LT that we noted are in keeping with the increasing body of evidence in the international literature in this group of patients indicating that pediatric liver transplant recipients are at an increased risk of developing obesity, metabolic syndrome, and its sequelae in later life. Further large prospective studies are required to study these findings prospectively with a view to determining cause and potential interventions strategies.

AUTHORS' CONTRIBUTIONS

Data collection/interpretation/analysis, drafting manuscript. Interpretation of bone densitometry (DEXA) scans. Study design/concept, data interpretation, critical revision & approval of manuscript.

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