Long-Term Growth and Anthropometry after Childhood Liver Transplantation

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Objectives To describe longitudinal height, weight, and body mass index changes up to 15 years after childhood liver transplantation.

Study design Retrospective chart review of patients who underwent liver transplant from 1985-2004 was performed. Subjects were age <18 years at transplant, survived ≥5 years, with at least 2 recorded measurements, of which one was ≥5 years post-transplant. Measurements were recorded pre-transplant, 1, 5, 10, and 15 years later.

Results Height and weight data were available in 98 and 104 patients, respectively; 47% were age <2 years at transplant; 58% were Australian, and the rest were from Japan. Height recovery continued for at least 10 years to reach the 26th percentile (Z-score −0.67) 15 years after transplant. Australians had better growth recovery and attained 47th percentile (Z-score −0.06) at 15 years. Weight recovery was most marked in the first year and continued for 15 years even in well-nourished children. Growth impaired and malnourished children at transplant exhibited the best growth, but remained significantly shorter and lighter even 15 years later. No effect of sex or age at transplant was noted on height or weight recovery. Post-transplant factors significantly impact growth recovery and likely caused the dichotomous growth recovery between Australian and Japanese children; 9% (9/98) of patients were overweight on body mass index calculations at 10-15 years but none were obese.

Conclusions After liver transplant, children can expect ongoing height and weight recovery for at least 10-15 years. Growth impairment at transplant and post-transplant care significantly impact long-term growth recovery. *(J Pediatr 2013;163:537-42)*.

Growth normalization is an important measure of long-term success in the treatment of any chronic childhood illness, including liver transplantation. Poor growth after liver transplantation is well described, with many authors describing failure of these children to reach normal height despite initial catch-up growth following successful liver transplantation.[1-3] To date, only short- and medium-term follow-up studies have been reported, with a paucity of long-term data.[1-5]

Initial catch-up growth in the first 2 years after liver transplantation is well described and is most marked in the malnourished, and children transplanted before 2 years of age.[3-6] One study has also reported improved growth when the transplant was performed in children aged >2 years.[7] Superior growth recovery in boys has also been reported.[5,8] The initial causative pathology is also thought to play a role in subsequent growth, with poorer recovery reported in those with acute liver failure, tumors, or Alagille syndrome.[1,8,9] In contrast, using multivariate analysis, a report of patients with biliary atresia following live donor transplant described poorer growth with increased donor age and the development of hepatic vein stenosis post-transplant.[10] Therefore, a multitude of pre- and post-transplant factors can affect growth in children after transplant, including the underlying diagnosis, coexisting malnutrition, increased energy requirements, impact of medication, and any ongoing illness.[11]

All cholestatic diseases, of which biliary atresia is the most common in children, result in malabsorption and increased energy and nutritional requirements but these are expected to resolve with successful transplantation. Weight recovery tends to be more rapid and will often normalize within a year of transplant even among the malnourished.[10,12] These observations appear to be independent of the pre-transplant weight possibly being confounded by fluid retention and ascites.

Height recovery tends to be delayed compared with weight and is likely to be further affected by post-transplant factors. Height recovery has been reported up to 7 years after transplant, although the final height attained was only at the 27th percentile.[3,5] Growth however may not be completed until age 20 years in normal children and it is important to recognize this when monitoring infants and those with delayed bone age. With correction of malnutrition after transplant, ongoing height recovery beyond 7 years would have been expected as long as their post-transplant course is uncomplicated. One may then speculate that post-transplant management, including steroid use and graft function may

BMI	Body mass index
QLTS	Queensland Liver Transplant Service
WHO	World Health Organization

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have a greater role in determining final height attained than previously recognized.

There is currently very limited information available on height and weight changes in children beyond 10 years after liver transplantation. One small study, which evaluated long-term bone density, noted that 15 young adult subjects who were transplanted in childhood had mean height Z-scores of 0.04, which is approximately the 51st percentile.[13] This is higher than previously reported and occurred even though more than one-half remained on low dose steroid therapy. These results require further validation from larger studies.

The development of obesity following liver transplant is a significant clinical problem for adult recipients with up to half developing metabolic syndrome in some centers.[14,15] It remains unclear whether those transplanted as children will also develop obesity. Weight changes traditionally have not been examined in most long-term studies as they can be affected by drugs, fluid retention, and ascites among other factors. The increasing incidence in obesity in the general population, however, will likely change this. A report from the North American Studies of Pediatric Liver Transplantation Research Group, using body mass index (BMI) measurements, reported 18% and 11% of their cohort were obese at 3 and 5 years post-transplant, respectively.[16] The rate of obesity at 5 years post-transplant, however, was similar to the 2003-2004 National Health and Nutrition Examination Survey population data.[16]

The aim of this study was therefore to describe longitudinal anthropometric (height, weight, and BMI) changes seen in children having received a successful liver transplant up to 15 years previously.

Methods

The Queensland Liver Transplant Service (QLTS) commenced in 1985 and has performed 317 transplants in 269 children up till December 31, 2011. In the early years, many overseas patients were transplanted by our service until the development of their own pediatric transplant programs. Retrospective chart review was performed on all patients transplanted between 1985 and December 31, 2004. Children surviving at least 5 years after initial transplant were considered long-term survivors. Only those in whom there were at least 2 measurements, of which 1 was ≥5 years post-transplant, were included to ensure that patients were analyzed longitudinally. This study was approved by the Ethics Committee of Royal Children's Hospital, Brisbane, where QLTS is based.

Time points of interest were at transplant (time zero), 1 year, 5 years, 10 years, and 15 years after liver transplant. In the pre-transplant patients, measurements on the day of transplant or a date as close as possible to this were recorded. With follow-up measurements, those as close as possible to the anniversary of transplant were used. Height and weight measurements were recorded at these time points as described. BMI was calculated for all patients using height and weight measurements for the same time intervals where BMI = weight (kg)/height (cm)^2. Height, weight, and BMI age- and sex-adjusted Z-scores were calculated based on World Health Organization (WHO) Child Growth Standards 2006 and WHO reference 2007 charts. Subjects aged ≥18 years were considered overweight if their BMI was ≥25 and obese if BMI ≥ 30. Children aged <18 years were considered overweight using a BMI reference table based on an international survey from 6 countries by Cole et al, which corresponds approximately to 90th percentile BMI for overweight and 99th percentile for obese.[17]

Patients were analyzed as a group but also divided by sex, age at transplant, country of residence, and whether they were malnourished or growth impaired at the time of transplant. As malnutrition at the time of transplant has been reported to cause persistent growth failure, we subdivided the cohort into those with Z scores either below or above the 10th percentile (equivalent to Z-score −1.28) at time of transplant to see if there was any difference in growth recovery. We considered patients to be growth impaired or malnourished when their height or weight Z-score was <−1.28, corresponding to the 10th percentile respectively. Statistical analyses were performed using the SPSS statistical package (SPSS Inc, Chicago Illinois). Student t-test, Fisher exact test, and Mann-Whitney tests were used in the data analyses. Results were considered significant if P value was <.05.

Results

A total of 228 children aged <18 years were transplanted by QLTS between 1985 and December 31, 2004. Of these, 78% (178/228) survived at least 5 years after initial transplant although 15 patients subsequently died more than 5 years after transplant; 98 patients were eligible to be included with at least 2 height measurements, of which 1 was ≥5 years after initial transplant. There was 94% (92/98) cohort retention at 5 years, 91% (89/98) at 10 years, and 49% (48/98) at 15 years after transplant. Only 55% (54/98) had measurements recorded 1 year after transplant. Thirteen children (10 Australian and 3 Japanese) had more than 1 transplant but survival was calculated from time after initial (first) transplant. Cyclosporine-based immune suppression was used in all patients until 1994 when this was changed to tacrolimus. All patients were maintained on low dose steroid therapy for at least 5 years after transplant for those on cyclosporine and at least 2 years for those on tacrolimus as was QLTS policy at the time.

There were slightly more Australian than Japanese patients and almost one-half (47%, 46/98) were <2 years old at transplant (**Table I**). Significant differences noted between Australian and Japanese patients include younger age at transplant in Australians ($P < .0001$), more biliary atresia in Japanese patients ($P = .014$), and more Japanese patients below 10th percentile for height ($P = .014$), but not weight at the time of transplant. Some of the height effect may be due to ethnicity even though WHO growth standards, which are based on multiracial cohorts, were used. All children with Alagille syndrome, alpha-1-antitrypsin deficiency, and acute liver failure were Australian.