Consequences of immunosuppression after pediatric liver transplantation
Scheenstra, René

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Chapter 4

Growth and final height after liver transplantation during childhood

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Abstract

Aim
To evaluate the effect of end-stage pediatric liver disease and liver transplantation on growth and final height.

Patients and methods
We evaluated growth at 2 years (n=101) and 5 years (n=63) after pediatric liver transplantation (LTx). Twenty-three children reached final height. Height was expressed as a standard deviation score of the target height ($Z_{TH}$ score) of each individual patient.

Results
The first 2 years after LTx, the $Z_{TH}$ score significantly increased from -1.7 to -1.3 SD ($p<0.05$). Growth in the first 2 or 5 years after LTx, expressed as $\Delta Z_{TH}$ score was positively correlated with pre-transplant growth retardation ($p<0.05$). In comparison to patients with a non-cholestatic primary liver disease, patients with a cholestatic primary liver disease were more severely growth retarded before LTx ($Z_{TH}$ score -2.0 vs. -1.2 SD, $p< 0.05$), and had better growth in the first two years after LTx ($\Delta Z_{TH}$ score +0.6 vs. -0.1 SD, $p<0.05$). Twelve out of the 23 patients, who achieved final height, had a final height below -1.3 SD of their target height.

Conclusion
Growth retardation is a common finding in children before LTx, particularly in children with a primary cholestatic liver disease. After LTx, catch up growth was partial, and only prominent in cholestatic children that had been severely growth retarded before LTx. After LTx during childhood, approximately 50% of patients reach a final height lower than -1.3 SD of their genetic potential.

Abbreviations
LTx = pediatric liver transplantation
TH = target height
$Z_{TH}$ score = $Z$ score of the target height
SD = standard deviation
CsA = Cyclosporine
TAC = Tacrolimus
IGF = insulin-like growth factor
Introduction

Transplantation is a life-saving treatment in children with end-stage liver disease. Quality of life after pediatric liver transplantation (LTx) is not only determined by the function of the grafted organ, but also depends on factors such as growth and final height. Insufficient growth may be an additional psychological burden for the child.\(^1\) Many children have growth retardation before LTx.\(^2\)\(^-\)\(^4\) Several studies have indicated that growth retardation remains after LTx, while others have reported catch-up growth.\(^5\)\(^-\)\(^10\) So far, 7 reports have become available on growth during 5 years after LTx.\(^4\)\(^,\)\(^11\)\(^-\)\(^16\) Although final height is the most important growth parameter, there are only limited data on the final height in children after LTx.\(^17\) In the study of Viner et al.\(^4\) 14 patients reached final height with a mean Z score of -0.55.

In healthy children final height is predicted mainly by parental height.\(^16\)\(^,\)\(^20\) Normal growth is defined as being within 1.3 SD of the target height (TH). The TH is calculated from the parental height.\(^21\) The potential of a child’s growth is further dependent on bone age. Thus actual height in combination with bone age will provide information on the growth potential of the child.\(^22\)

In the present study, growth in relation to chronological age and bone age was evaluated in 101 children 2 years after LTx and in 64 children 5 years after LTx. We also report on final height after LTx, inasmuch as 25 % of our patients reached final height during follow-up.
Between 1982 and 2000, 200 liver transplant procedures were performed in 150 children younger than age 17 years in the University Medical Center Groningen, the Netherlands. Of those patients, 49 were followed for less than 2 years and were not included in this study. The remaining 101 patients were followed for at least 2 years. Sixty-four patients were followed for at least 5 years. In 23 children, final height was achieved during follow-up.

Immunosuppressive medication after liver transplantation consisted of cyclosporine (CsA), prednisolone and azathioprine for most patients. CsA was introduced on the second day after transplantation (trough levels during the first 4 weeks post-transplantation, 200-250 μg/ml, after 4 weeks 100-150 μg/ml). Prednisolone dose was initially 1 mg/kg/day and subsequently tapered in the first 3 months after transplantation to 0.25-0.4 mg/kg/2days (alternate-day dosing). The azathioprine dose was 2 mg/kg/day. Between 1982 and 1998 cyclophosphamide was given in a dose of 3 mg/kg during the first 7 days after liver transplantation. Five patients underwent transplantation before 1986 and received a similar immunosuppressive regimen, but without CsA. The initial dose of prednisolone was similar, but the maintenance dose was tapered to 0.4-0.6 mg/kg/2 days, and the maintenance dose of azathioprine was 2.5 mg/kg/day. Fifteen patients underwent LTx after 1998, and were treated with a tacrolimus (TAC)-based regimen. This consisted of TAC (trough levels of 10-15 μg/l during the first 3 months post-transplantation, afterward, trough levels of 5-10 μg/l) and prednisolone (initially 1 mg/kg/day, subsequently tapered to a dose of 0.2 mg/kg/2 days, at 3 months). Rejection therapy in the first 4 weeks after LTx consisted of intravenous bolus injections of methylprednisolone of 20 mg/kg/day for 3 days. Thereafter, rejection was treated with increasing dosage of oral prednisolone to a maximum of 4 mg/kg. Twenty-three underwent transplantation more than once, two of these 23 patients more than twice. Most of these retransplantations were performed within 4 weeks after the previous LTx due to transplant-related complications. Because this study focuses on growth after LTx, the last LTx is taken as entry point of the study in patients who underwent LTx more than once. The following data were prospectively collected: height, weight and bone age. The underlying disease leading to liver insufficiency was also recorded.

Height was measured by use of the Harpenden stadiometer to the nearest 0.1 cm. Final height was recorded when radiography of the hand and wrist showed epiphysial closure.\(^{22,24}\) Height is expressed as the Z-score or standard deviation score (SDS) calculated by

\[
z(t) = \frac{x(t) - \mu(t)}{\sigma(t)}
\]

where \(x(t)\) denotes the individual’s body measurement score at age \(t\) (e.g. its height), \(\mu(t)\) denotes the population mean at age \(t\), and \(\sigma(t)\) the corresponding standard deviation. As reference values the Dutch nation-wide growth curves of 1997 were used.\(^{18}\) The target height (TH) of each patient was calculated using the formula according to Tanner\(^{21}\), adjusted for secular growth changes.\(^{18}\)
For boys: mother’s height + father’s height + 13/2 + 4.5 cm.
For girls: mother’s height + father’s height – 13/2 + 4.5 cm.
To correct for parental height for each patient a Z score of the target height ($Z_{TH}$ score) was calculated by subtracting the target height (expressed in SD) from the actual Z score delivering the $Z_{TH}$ score. Normal growth is considered as growth following a growth curve ± 1.3 SD from the TH, calculated from parental height. Catch-up growth is defined as changes in $Z_{TH}$ score of more than 0.25 SD a year. Bone age was determined on radiographs of the left hand using the calculation of the 20 bones. One investigator (RJO) performed these analyses. The height is expressed as $Z_{TH}$ score for bone age, the standard deviation score of the target height, using the bone age instead of the chronological age.

**Statistics**
Continuous variables were expressed as median and range and categorical variables as number with percentage. Categorical variables were compared using the Chi square test. Comparison of continuous variables between groups was done using Students T test. Paired continuous variables were compared with a paired samples T test. Correlations were determined by Pearsonís correlation coefficient. $P< 0.05$ was considered as being statistically significant.

**Results**

The clinical data of the patients included in the study are given in Table 1. The median age at LTx was 3.6 years (range 0.1-17.1) of the total group (n = 101) and 4.6 years (range 0.1-16.9) of the subgroup followed for 5 years (n = 64). In the subgroup that reached final height (n = 23) the median age at LTx was 13.3 years (range 2.8 -16.9). End-stage liver disease due to biliary atresia was the most frequent indication for LTx. Other indications can be found in Table 1.

Figure 1 shows the distribution of the height deviation score corrected for parental height ($Z_{TH}$ score) at LTx. The median of the $Z_{TH}$ score at LTx was -1.7 SD with a wide range from – 6.3 to + 1.7 SD. Of the 101 patients, 61 had a $Z_{TH}$ score below -1.3 SD and were therefore considered to be small. Thirty-eight had a $Z_{TH}$ score below -2.0 SD and were considered severely growth retarded. Figure 2 shows the distribution of the $Z_{TH}$ score at LTx and 2 years after LTx. There was a significant improvement of the $Z_{TH}$ score of the total group: -1.7 ± 1.6 SD before LTx, to – 1.3 ± 1.3 SD at 2 yr after LTx ($p < 0.005$). Two years after LTx, 54 patients had a $Z_{TH}$ score below -1.3 SD, and 29 had a $Z_{TH}$ score below -2.0 SD. Of the included 101 patients, 38 decreased in $Z_{TH}$ score (range of 0 to -2.2 SD) while 63 increased in $Z_{TH}$ score (range of 0 to 3.3 SD) as calculated for the period between LTx and 2 years thereafter. Of the 63 patients who gained height, 48 did so with at least 0.25 SD per year, which has been defined as catch-up growth. Of these 48 patients, 34 increased height with at least 0.7 SD, which is used as the criterion for a good reaction in international growth hormone studies.
Table 1. Clinical data of included patients who underwent liver transplantation (LTx) during childhood. Subgroup analyses were performed in patients with at least 5 years follow-up, and in patients, who reached their adult height. Abbreviations: The $Z_{TH}$ score is the height Z score adjusted for parental height (for details, see text). LTx = liver transplantation, PFIC = progressive familial intrahepatic cholestasis.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Subgroup 5 years follow-up</th>
<th>Subgroup Final height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>101</td>
<td>64</td>
<td>23</td>
</tr>
<tr>
<td>Age (yrs) at LTx (median and range)</td>
<td>3.6 (0.1–17.1)</td>
<td>4.6 (0.1–6.9)</td>
<td>13.3 (2.8–16.9)</td>
</tr>
<tr>
<td>Sex M/ F</td>
<td>47/54</td>
<td>31/33</td>
<td>8/15</td>
</tr>
<tr>
<td>Target Height (median and range)</td>
<td>0.2 (-2.1–2.6)</td>
<td>0.2 (-2.1–1.8)</td>
<td>-0.3 (-2.1–1.2)</td>
</tr>
<tr>
<td>$Z_{TH}$ score at LTx (median and range)</td>
<td>-1.7 (-6.3–1.7)</td>
<td>-1.7 (-6.3–1.7)</td>
<td>-1.0 (-4.6–1.0)</td>
</tr>
<tr>
<td>Patients with a previous LTx (n)</td>
<td>24 (24%)</td>
<td>13 (20%)</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>52 (52%)</td>
<td>34 (53%)</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>Metabolic Disease</td>
<td>24 (24%)</td>
<td>17 (26%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td>Acute Liver Failure</td>
<td>5 (5%)</td>
<td>4 (6%)</td>
<td>-</td>
</tr>
<tr>
<td>Intrahepatic cholestatic diseases (PFIC, Alagille)</td>
<td>7 (7%)</td>
<td>5 (8%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Other diseases</td>
<td>13 (13%)</td>
<td>4 (6%)</td>
<td>6 (26%)</td>
</tr>
</tbody>
</table>

Figure 1. Height at liver transplantation (LTx) for different pediatric ages. Height is expressed as $Z_{TH}$ scores, i.e. the height Z score adjusted for parental height (for details, see text).
**Figure 2.** Height expressed as $Z_{TH}$ score at the moment of LTx and at 2 years after LTx in 101 patients that were transplanted during childhood. $Z_{TH}$ score is the height Z score adjusted for parental height (for details, see text).

**Figure 3.** Height expressed as $Z_{TH}$ score at the moment of LTx and at 2 years and 5 years after LTx in 64 patients that were transplanted during childhood and of which at least 5 years follow up data were available. $Z_{TH}$ scores is the height Z score adjusted for parental height (for details, see text).
Figure 3 shows the ZTH scores of the 64 patients who were followed for 5 years. Between 2 and 5 years after LTx only a limited (further) improvement of the ZTH score was observed, from -1.4 ± 1.2 SD to -1.2 ± 1.2 SD (p < 0.05). Catch up growth was observed in 17% (11/64) between 2 years and 5 years after LTx.

Figure 4 shows the change in ZTH score from 0 to 5 years after LTx in relation to the ZTH score at LTx. Improvement of growth as expressed in ΔZTH during 2 or 5 years after LTx, was positively correlated with pre-transplant growth retardation (2 yr: r=0.63, p<0.001, 5 yr: r=0.62, p<0.001). Figure 4 also shows that in the majority of the patients improvement of growth occurred between LTx and 2 years after LTx. The improvement in growth between 2 and 5 year after LTx did not significantly correlate with pre-transplant growth retardation.

The mean final height was 158.9 ± 7.6 cm (range 139.5 - 170.0 cm) in female and 173.5 ± 6.1 cm (range 165 - 184 cm) in male patients. The height of these children at LTx had been -1.0 SD (expressed as ZTH score), compared to a final height of -1.4 SD. Twelve out of 23 patient had a final height below -1.3 SD, and 3 patients were severely growth retarded with a final height below -2.0 SD.

Patients younger than 2 years at LTx tended to have more severe growth retardation at LTx, than did patients older than 2 years, but this was not significant. These
younger patients had a greater improvement of the $Z_{TH}$ score in the first two years after LTx than did patients who underwent transplantation at the age of at least 2 years ($\Delta Z_{TH}$ score 0.6 ± 1.2 SD at age<2 years; 0.1 ± 0.9 SD at age≥2 years, $p<0.05$).

We did not find a significant relationship between the different immunosuppressive regimens and growth. Of the included patients 81 (80%) received an immunosuppressive regimen that consisted of CsA, azathioprine and prednisolone. Fifteen patients (15%) received an immunosuppressive regimen that consisted of TAC and prednisolone. Growth retardation in both groups before LTx was similar ($Z_{TH}$ score CsA: - 1.7 ± 1.5 SD, TAC: - 1.7 ±1.6 SD). The maintenance dosage of prednisone was higher in the CsA-based regimen compared with the TAC-based regimen (0.4 – 0.6 mg/kg/2days versus a dose of 0.2 mg/kg/2days). Nevertheless, the changes in $Z_{TH}$ score were similar in the first 2 years after LTx ($\Delta Z_{TH}$ score CsA: 0.3 ±1.1 SD, tacrolimus: 0.3 ±1.1 SD).

Evaluation of the primary liver disease and growth failure before LTx showed more severe growth retardation at LTx in the group with a primary cholestatic liver disease (biliary atresia, intrahepatic cholestatic diseases) versus the group with a noncholestatic primary liver disease ($Z_{TH}$ scores at LTx: - 2.0 ± 1.5 SD and -1.3 ± 1.5 SD, respectively, $p < 0.05$). The growth was significantly better in the cholestatic group during the first 2 years after LTx ($\Delta Z_{TH}$ score cholestatic disease versus noncholestatic disease at 2 years: 0.6 ± 1.0 SD vs. - 0.1 ± 1.1 SD; $p < 0.05$). This observation was also illustrated by the fact that catch-up growth in the first two years after LTx was more frequently found in children from the cholestatic group compared with those from

**Figure 5.** Relationship between bone age and chronological age at LTx. The bone age was determined based on the calculation of the 20 bones according to Tanner/Whitehouse. The bone age was positively correlated with the chronological age at LTx ($r = 0.99$, $p < 0.001$).
the noncholestatic group (33/60 or 55% and 10/41 or 24% respectively, \( p < 0.005 \)). Cholestatic disease as the indication for LTx was more prevalent in children who underwent transplantation before 2 years of age than in children of 2 years old or older (30/38 or 78% and 30/63 or 47%, respectively, \( p < 0.005 \)). In the group of children of 2 years or older, primary cholestatic disease was also significantly related with growth retardation before LTx (Z\_\text{TH} score: -2.0 ± 1.5 vs. -1.1 ± 1.6 in noncholestatic disease, \( p < 0.05 \)), and with better growth in the first 2 years after LTx (Δ Z\_\text{TH} score: 0.5 ± 0.9 vs. - 0.3 ± 0.8 in noncholestatic liver disease, \( p < 0.05 \)).

Bone age was evaluated in 96 children. Median height at transplantation expressed as Z\_\text{TH} score for bone age was -1.2 SD (range -6.4 - 2.5 SD). There was a significant strong correlation between bone age and chronological age at LTx, \( r = 0.99, p < 0.001 \) (Fig. 5). No change in median height expressed for bone age was observed in the period between LTx and 2 years thereafter (Table 2).

**Table 2.** Height before and after liver transplantation (LTx) during childhood. Subgroup analyses were performed in patients with at least 5 years follow up, and in patients who reached their adult height. Height expressed as Z\_\text{TH} score for chronological age and for bone age (median and range) at LTx, at 2 and 5 years follow-up and at final height. Z\_\text{TH} score is the height Z score adjusted for parental height (for details, see text).

<table>
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<tr>
<th>( Z_{\text{TH}} ) score for chronological age</th>
<th>All patients</th>
<th>Subgroup 5 years follow-up</th>
<th>Subgroup Final height</th>
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<tbody>
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<td>At LTx</td>
<td>n = 101</td>
<td>n = 64</td>
<td>n = 23</td>
</tr>
<tr>
<td></td>
<td>-1.7 (-6.3–1.7)</td>
<td>-1.7 (-6.3–1.7)</td>
<td>-1.0 (-4.6–1.0)</td>
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<tr>
<td>2 years</td>
<td>n = 101</td>
<td>n = 64</td>
<td>n = 23</td>
</tr>
<tr>
<td></td>
<td>-1.3 (-3.9–1.3)</td>
<td>-1.3 (-3.9–1.3)</td>
<td>-1.0 (-3.9–0.9)</td>
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<tr>
<td>5 years</td>
<td>n = 64</td>
<td>n = 64</td>
<td>n = 16</td>
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<td>n = 23</td>
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<td>-1.4 (-3.6–0.8)</td>
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</table>

<table>
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<th>( Z_{\text{TH}} ) score for bone age</th>
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<th>Subgroup 5 years follow-up</th>
<th>Subgroup Final height</th>
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</thead>
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<td>At LTx</td>
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<td>n = 61</td>
<td>n = 21</td>
</tr>
<tr>
<td></td>
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<td>2 years</td>
<td>n = 98</td>
<td>n = 63</td>
<td>n = 23</td>
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<td>-1.4 (-5.5–2.0)</td>
<td>-1.4 (-5.5–1.6)</td>
<td>-1.2 (-3.1–0.4)</td>
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<td>Final height</td>
<td>n = 15</td>
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<td>-1.2 (-3.2–0.8)</td>
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Discussion

We show in this study that growth retardation is a common finding in children before LTx, particularly in children with a cholestatic disease. Catch-up growth after LTx was related with growth retardation before LTx, and was predominantly observed in patients with a primary cholestatic liver disease. Improvement of growth was also seen in young children, but this could also be an effect of cholestatic disease, inasmuch as this was a common feature in these patients. Catch-up growth was mainly observed in the first 2 years after LTx. Our longitudinal data indicate that after LTx in childhood, approximately 50% of patients reach a final height of less than -1.3 SD of their genetic potential.

Several studies have evaluated growth after LTx. Our finding that children with the most severe growth retardation at the time of LTx show better growth after LTx is comparable to most studies. The finding of greater catch-up growth in children who underwent LTx at an age younger than 2 years was also comparable to most studies, although 1 report showed better growth if transplantation was delayed until the child was older than 2 years. Most studies show growth retardation at the moment of LTx with catch-up growth during the two years thereafter. At the beginning of this 2-year post-transplant period, growth may become further retarded, followed by catch-up growth during the next 18 months. The initial growth retardation has been attributed to the use of prednisolone. Decreasing the prednisolone dosage is thought to be accompanied by catch-up growth. Although the Z score at 2 or 3 years post LTx in most studies was higher than the Z score at the moment of LTx, the Z score was invariably still below zero in the majority of patients. Our data are comparable to those obtained in previously described cohorts. We also found improvement in Z score during the 2 years after LTx, but this improvement was less prominent thereafter. Growth did not return to the values expected from the target height. The majority of children after LTx with growth retardation at the moment of LTx can therefore expect to have a final height below their genetic potential. Our data further indicate that final height can be estimated from the growth curve 2 years after LTx. This is in accordance with the results from the children reaching final height.

There are different reasons why growth retardation may be prevalent at the moment of LTx. It might be due to the malabsorption caused by liver insufficiency and/or insufficient intake of energy and proteins. This possibility is supported by the observation in our study that growth retardation was especially prominent in patients with a primary cholestatic liver disease. In addition, endocrine factors may also play a part in the poor growth observed in children with chronic liver disease. The liver produces insulin-like growth factor-I (IGF-I) and IGF-binding proteins. Also, growth hormone is degraded in the liver. In patients with chronic liver disease, increased levels of growth hormone and decreased levels of IGF-1 and IGF-B3 have been described. A decrease in IGF-I level and GH insensitivity may be secondary to a combination of impaired hepatic function and protein calorie malnutrition. Catch-up growth may be due to the elimination of the factors causing the delay in growth during the illness. When the growth delay occurs during the so-called criti-
cal period of life, the first few years in human life, imprinting may prevent a complete restoration of growth.\textsuperscript{19} Catch-up growth in our patients did not result in a complete restoration of normal height of the children. In the youngest children, especially the group with primary cholestatic disease, this may be caused by the growth retardation in early life. Return to normal values, however, was also not found in children transplanted at an older age, despite the fact that liver failure in this group started predominantly after infancy.

The growth delay in patients after LTx is often attributed to the use of corticosteroids. Bartosh et al\textsuperscript{5} observed a negative correlation between the dose of prednisolone and growth. However several arguments draw into question, that the delay in growth in patients after LTx is exclusively or primarily due to the use of prednisolone. First the main delay in growth occurs before transplantation, a period when prednisolone is usually not administered. Second, we did not observe a more prominent improvement of the Z score in patients who were treated with a TAC-immunosuppressive scheme and a much lower prednisolone dosage (0.2 mg/kg/2 days). Third, interference with growth was found in children after LTx at a prednisolone dose of 0.25 mg/kg/day\textsuperscript{5,39} which is considerably higher than that given to our patients: in most of our patients prednisolone started with a dose of 1 mg/kg/day and was tapered to 0.25 –0.4 mg/kg/2days within 12 weeks. Fourth, catch-up growth did occur in almost 50% of the patients during the first two years after transplantation, despite the fact that in this period prednisolone was given. Finally, steroid withdrawal does not always show clear benefit on linear growth.\textsuperscript{17,39,40} although some studies show a favorable effect of early steroid withdrawal.\textsuperscript{41} These considerations suggest that the use of prednisolone might not be the only cause of the persistently delayed growth in pediatric liver transplant patients. We do realize however, that a steroid-free immunosuppressive scheme showed significantly improved linear growth in the first year after liver transplantation.\textsuperscript{42} It can not be excluded that prednisolone irreversibly impedes catch-up growth.\textsuperscript{25}

In our study bone age corresponded to chronological age (Fig. 5). Bone age was not delayed in children with severe growth retardation, suggesting that growth retardation was not due to delayed maturation. The increase in height Z score (Fig.4) and the close correlation between bone age and chronological age during follow up indicate that puberty was not delayed and did not influence the growth effect of LTx. Expressing the height in Z scores minimizes the influence of puberty. During puberty the standard deviation of the reference population is much higher than before or after puberty. Only in the case of extreme early or late puberty, will the patient’s Z score be abnormal.

In summary, growth retardation in children with LTx mainly originates in the period before LTx. After LTx there is some catch-up growth in the youngest and most severely growth-retarded patients, which correlates with a primary cholestatic liver disease. In general, however, transplanted children do not have a complete catch-up growth and achieve a final height below their genetic potential. The present data indicate that improving final height of children that are candidates for LTx should be aimed at the period before LTx. Studies to determine the cause of growth retardation before LTx are needed.
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References
