Effect of Renal Graft on Longitudinal Growth in Prepubertal Children

Cagla Serpil Dogan, Erdem Durmaz, Elif Comak, Arife Uslu Gokceoglu, Mustafa Koyun, Sema Akman

Abstract

Objectives: Linear growth impairment frequently accompanies chronic kidney disease in children. Despite successful renal transplant, growth retardation may persist in renal allograft recipients. Materials and Methods: We recorded the longitudinal growth and biochemical data of prepubertal children during the first 2 years after renal transplant in 34 children (18 boys [52.9%]; mean age at renal transplant, 7.3 ± 2.5 y; range, 1.4 to 9.8 y). Height standard deviation scores were calculated. The patients were divided into 2 groups according to the increase in height standard deviation scores over the first 2 years after renal transplant: group 1 (increases in height standard deviation scores < 1) and group 2 (increases in height standard deviation scores > 1).

Results: Increases in height standard deviation scores were 0.12 ± 0.34 and 1.62 ± 0.52 for group 1 and group 2 (P < .001). The number of acute rejection episodes was significantly different between groups (P = .04). At renal transplant, increases in height standard deviation scores were negatively correlated with mean age (r: -0.354; P = .04) and height standard deviation scores (r: -0.353; P = .04). In the multivariate model, mean age and height standard deviation scores at renal transplant remained significantly associated with increases in height standard deviation scores (P = .018; β coefficient: -0.341, 95% CI: -0.17; -0.002; and P = .005; β coefficient: -0.431, 95% CI: -0.519; -0.101).

Conclusions: Renal transplant improves linear growth by providing moderate or accelerated growth in prepubertal children.

Key words: Chronic renal failure, Growth retardation, Renal transplant, Linear growth, Prepuberty

Introduction

Growth failure is frequently observed in children with end-stage renal disease. Although renal transplant corrects many of the metabolic and endocrine disorders owing to end-stage renal disease, posttransplant catch-up growth spurts are usually insufficient to achieve target final height. The degree of pretreatment growth deficit, age at transplant, graft function, steroid exposure, delayed puberty and shortened duration of pubertal period mainly affect growth after renal transplant (RTx).1-4 Short stature may have an effect on psychological and social development of the child; short final height of children receiving RTx is associated with a lower level of education, a lower marital status, and a lower level of employment as an adult.5,6 Therefore, posttransplant growth is admitted as a measure of success of pediatric RTx. Published data show that children who receive a transplant before the start of puberty show accelerated growth rates compared with baseline and even healthy children.1,7,8 In this study, we sought to analyze retrospectively the effect of RTx on prepubertal growth in pediatric RTx recipients.

Materials and Methods

One hundred seventy pediatric patients underwent renal transplant at Akdeniz University Medical Faculty in Antalya, Turkey, between July 1994 and December 2011. Our study population consisted of children within the prepubertal period at the time of
transplant who did not enter puberty during follow-up to eliminate the effect of pubertal height gain. We recorded longitudinal growth and biochemical data of prepubertal children with a functioning graft during the first 2 years after RTx. The records of children were evaluated for height data and sexual maturation at 3-month intervals posttransplant. Pubertal stage of the patients was assessed according to Taner. Current age, age at transplant, sex, cause of end-stage renal disease, length of follow-up, duration of dialysis, donor source, posttransplant immunosuppressive drugs, acute rejection episodes, number of pulse methylprednisolone (PMP) doses, and cumulative dosage of prednisolone (the dose of methylprednisolone was calculated as equivalent of prednisolone) during follow-up were recorded. Glomerular filtration rate (GFR) was estimated by the Schwartz formula, mean GFR level was calculated by GFR values at 3-month intervals for the first 2 years after transplant. No patients received recombinant human growth hormone therapy before or after RTx. Height standard deviation scores (hSDS) were calculated from published national standards at transplant, and 1 and 2 years after RTx. The formula used to derive hSDS was as follows: observed value—mean population value according to age, and sex/population standard deviation. Accelerated or catch-up growth was defined as the change in hSDS (ΔhSDS) ≥+0.5 SD/y. The patients were divided into 2 groups according to the increase in height standard deviation scores over the first 2 years after renal transplant: group 1 (increases in height standard deviation scores < 1) and group 2 (increases in height standard deviation scores > 1).

According to the immunosuppressive protocol, 500 mg/m² methylprednisolone was given during surgery, followed by a dosage of 80 mg/m²/d on the second day after transplant, tapered down to 5 mg/m²/d at the end of 3 months. All patients were receiving daily or alternate-day prednisolone therapy at the time of study. Mycophenolate mofetil was administered 1200 mg/m²/d in combination with cyclosporine (8 mg/kg/d) or 600 mg/m²/d in combination with tacrolimus (0.15 mg/kg/d) for the first 3 months and then reduced up to 50% of initial dosage. Acute rejection was biopsy proven. First-line anti-rejection treatment for cellular rejection consisted of methylprednisolone (30 mg/m²/d for 3-5 d). Corticosteroid resistant acute rejection episodes were treated with thymoglobulin. Antibody-mediated rejection was not determined in any patient during follow-up. All protocols were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration. Written, informed consent was obtained from all patients or their guardians.

Statistical analyses

All data are expressed as means ± standard deviation. Comparison between groups were performed by chi-square or Fisher exact test for categorical variables when appropriate. Statistical analyses of continuous variables consisted of the unpaired \( t \) test for parametric data and Mann-Whitney \( U \) test for nonparametric data. Degrees of associations between continuous variables and ΔhSDS were calculated by Spearman’s rank correlation coefficient, and those significantly associated with ΔhSDS were examined with a multivariate model. Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 16.0, IBM Corporation, Armonk, NY, USA), and a \( P \) value less than .05 was considered statistically significant.

Results

Thirty-four children (18 boys [52.9%], mean age, 9.3 ± 2.5 years; age range, 3.4-11.8 y; mean age at RTx, 7.3 ± 2.5 y; range, 1.4-9.8 y) were included in the study. Cumulative dosage of prednisolone was 6.0 ± 3.2 g/m²/2 y (range, 2.2-15 g). Ten patients experienced at least 1 episode of acute rejection and received a total of 57 doses of pulse methylprednisolone. All patients received a first transplant. Ten patients (29.7%) underwent preemptive transplant, and 27 of all the transplants (79.4%) were from living-related donors. Before transplant, 13 patients used corticosteroids for their primary disease. All children received prednisolone, 20 of the patients received tacrolimus, and 14 received cyclosporine. Mycophenolate mofetil was given to 33 patients and azathioprine was given to 1 patient.

Primary renal diseases included 15 (44.1%) with urinary tract anomalies, 12 (35.3%) with glomerulonephritis, 2 (5.9%) each with autosomal recessive polycystic kidney disease and dysplastic
kidney, and 3 (8.8%) with an unknown cause. No differences in sex, time on dialysis, donor source (living vs deceased donation), previous steroid treatment, pre-emptive RTx, posttransplant immunosuppressive therapy (tacrolimus vs cyclosporine), number of PMP, and cumulative dosage of prednisolone were determined between 2 groups ($P > .05$). Number of acute rejection episodes was significantly higher in group 1 than it was in group 2. Mean GFR was lower in group 1; although this result was not significantly different ($P = .051$; Table 1). Mean growth velocities during the first 2 years after transplant were 11.8 ± 2.7 cm and 17.9 ± 2.6 cm for group 1 and group 2. Younger children who had greater height deficits at the time of transplant exhibited remarkable catch-up growth at the end of 2 years (group 2) (Table 2).

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### Table 1. Clinical and Laboratory Characteristics of Groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=22, 64.7%)</th>
<th>Group 2 (n=12, 35.3%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>10/12</td>
<td>8/4</td>
<td>.236</td>
</tr>
<tr>
<td>Time on dialysis (mo)</td>
<td>17.6 ± 18.6 (0-66)</td>
<td>32.6 ± 5.19 (0-180)</td>
<td>.677</td>
</tr>
<tr>
<td>Donor source (n, %)</td>
<td>Living 17 (77.3)</td>
<td>10 (83.3)</td>
<td>.677</td>
</tr>
<tr>
<td>Previous steroid</td>
<td>10 (45.5)</td>
<td>3 (25)</td>
<td>.241</td>
</tr>
<tr>
<td>treatment (n, %)</td>
<td>Prednisolone (g/m²/2 y)</td>
<td>6.6 ± 3.7 (2.5-15)</td>
<td>.576</td>
</tr>
<tr>
<td></td>
<td>PMP (n)</td>
<td>53</td>
<td>.078</td>
</tr>
<tr>
<td></td>
<td>Pre-emptive RTx (n, %)</td>
<td>7 (31.8)</td>
<td>.677</td>
</tr>
<tr>
<td>Acute rejection (n)</td>
<td>18</td>
<td>1</td>
<td>.041</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>68 ± 19 (36-114)</td>
<td>83 ± 22 (50-127)</td>
<td>.051</td>
</tr>
<tr>
<td>Posttx immunosuppressive therapy</td>
<td>.440</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus (n, %)</td>
<td>14 (63.6)</td>
<td>6 (50)</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (n, %)</td>
<td>8 (36.4)</td>
<td>6 (50)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** GFR, glomerular filtration rate; PMP, number of pulse methylprednisolone; RTx, renal transplant

### Table 2. Clinical and Laboratory Characteristics of the Groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=22, 64.7%)</th>
<th>Group 2 (n=12, 35.3%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>10.2 ± 1.8</td>
<td>0.6 ± 2.7</td>
<td>.005</td>
</tr>
<tr>
<td>Mean age at RTx (y)</td>
<td>8.2 ± 1.8</td>
<td>5.6 ± 2.7</td>
<td>.005</td>
</tr>
<tr>
<td>Height at RTx (cm)</td>
<td>116.2 ± 12.2</td>
<td>96.7 ± 14.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>hSDS at RTx</td>
<td>-2.14 ± 0.97</td>
<td>-3.10 ± 1.23</td>
<td>.018</td>
</tr>
<tr>
<td>Height 2 years after RTx (cm)</td>
<td>128.0 ± 13</td>
<td>114.6 ± 13.7</td>
<td>.008</td>
</tr>
<tr>
<td>hSDS 2 years after RTx</td>
<td>-2.01 ± 0.96</td>
<td>-1.48 ± 1.06</td>
<td>.416</td>
</tr>
<tr>
<td>ΔhSDS</td>
<td>0.12 ± 0.34</td>
<td>1.62 ± 0.52</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Abbreviations:** hSDS, height standard deviation score; RTx, renal transplant

### Discussion

According to data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2010,13 younger male children aged (between 2 and 5 years) and those with prior transplants had greater height deficits at the time of transplant. In this study,
growth patterns differed by age at transplant. Younger children achieved accelerated linear growth with growth improvement of +0.68 SD/2 years after transplant. Children aged 6 to 12 exhibited linear growth that is stable, at about 2 SD below the normal population, and the older children demonstrated no improvement in hSDS. Nissel and associates\(^1\) observed a significant increase in SDS even in children up to 9 years of age at the time of RTx. In that study, the height velocity in boys and girls significantly increased within 2 years after RTx (boys \(P < .002\) and girls \(P < .01\), exceeding that of healthy children. Fine and associates\(^7\) showed that catch-up growth was observed in the young age groups (6 to 8 y and 9 y) during first 2 to 3 years after transplant. In another study, Qvist and associates\(^8\) evaluated posttransplant growth in children who were given a transplant during infancy or early childhood. Eight children > 2 years of age at RTx improved their hSDS from -2.0 ± 0.9 to -0.4 ± 0.8 (\(P < .0001\)) 7 years after RTx and 9 children < 2 years of age at RTx had a hSDS of -1.2 ± 0.9 at RTx and -1.1 ± 0.5 at 7 years (\(P = .04\)). Qvist and associates found that hSDS at RTx was inversely correlated with postransplant growth. However, when both variables (age and hSDS at Tx) were used in a multiple regression model, only hSDS at RTx showed a significant correlation with \(\Delta\)hSDS from Tx to 7 years after RTx (\(P = .002\)). In our study, similar to previous studies, catch-up growth occurred in younger children who had greater height deficits at transplant.

Published data show that GFR is another strong predictor of prepubertal catch-up growth after RTx. Nissel and associates\(^1\) demonstrated that all patients with a GFR < 50 mL/min/\(1.73\) m\(^2\) did not show an increase in standardized height during the first 2 posttransplant periods. Qvist and associates\(^8\) found that GFR at 5 years after transplant correlated with the subsequent growth rate from 5 to 7 years after RTx. The mean GFR at 5 years was significantly lower in the group without catch-up growth (\(P = .03\)). Fine and associates\(^7\) showed that allograft function decreasing over time was one of the risk factors negatively affecting catch-up growth after the initial 2 to 3 years after transplant. In another study, Tejani and associates\(^14\) determined that each increase in serum creatinine concentration of 1 mg/dL was associated with -0.17 decrease in the height Z score (\(P < .001\)). In our study, although mean GFR was not significantly different between groups, the \(P\) value was borderline (\(P = .051\)).

Methylprednisolone, prednisone, and prednisolone are corticosteroids widely used in maintenance immunosuppressive therapy and in treatment of acute rejection in pediatric RTx despite their adverse effects. Growth retardation is a well-known adverse effect of corticosteroids. Reduction in the daily administered dosage of steroids, use of alternate day dosing regimens, steroid withdrawal after transplant, and complete steroid avoidance have been used to minimize their adverse effects.\(^{15-17}\) Seikku and associates and Sarna and associates\(^{18,19}\) demonstrated that the area under the serum concentration—time curve of methylprednisolone, rather than dosage—was related to growth inhibition in pediatric liver and renal transplant recipients. However, Chavatte and associates\(^{20}\) reported that pharmacokinetics studies of prednisone and prednisolone were not predictive of growth retardation in children with RTx. In our study, all but 2 patients were on low-dose daily steroid treatment (2 to 7 mg/\(\text{m}^2/\text{d}\)) and pharmacokinetics studies of prednisolone or methylprednisolone were not available. We calculated the dosage of methylprednisolone as equivalent of prednisolone in our study. Although the dosage of cumulative prednisolone and number of PMP was lower in group 1, there was no significantly difference between groups, probably because of the high standard deviation and small number of patients. Therefore, we could not exclude the effect of high dose of steroids on linear growth in our patients.

In our study, while the number of acute rejection episodes was significantly higher in group 1, there was no correlation between \(\Delta\)hSDS and acute rejection episodes. However, we thought that recurrent rejection episodes could affect linear growth by decreasing mean GFR and/or increasing the dosage of cumulative prednisolone and number of PMP doses.

In conclusion, RTx may ensure moderate or accelerated growth during prepubescence. Early transplant, long-term maintenance of graft function, possible steroid withdrawal, and monitoring of alterations in bone and mineral metabolism are necessary to improve growth failure. In addition, these patients should be carefully followed-up in terms of growth throughout puberty.
References