Cerrahpaşa Med J 2023; 47(2): 182-186 ORIGINAL ARTICLE

Growth in Children After Kidney Transplantation

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Cite this article as: Saygılı SK, Kezer S, Karabağ Yılmaz E, et al. Growth in children after kidney transplantation. *Cerrahpaşa Med J.* 2023;47(2):182-186.

Abstract

Objective: Kidney transplantation can improve linear growth in pediatric recipients but may not ensure attainment of the target adult height. The aim of this study is to determine the prevalence of growth failure in pediatric kidney transplantation recipients and to investigate the factors that influence growth.

Methods: This single-center retrospective study included 62 kidney transplantation recipients (37 males) transplanted before 18 years of age. Patients' medical records were retrospectively reviewed for annual posttransplant anthropometric measurements. Target height was calculated based on mid-parental height. The standard deviation score of height was calculated for baseline (at transplantation), final (at study time), and target heights.

Results: The median age at transplantation was 11.9 (8.8-14.8) years, and the median follow-up time after transplantation was 5.9 (3.2-7.2) years. Forty-seven children (76%) had growth failure (standard deviation score of height < –1.88) at baseline. After transplantation, a significant increase in the standard deviation score of height was observed between baseline and final ($P < .001$); however, the final standard deviation score of height was significantly lower than the target standard deviation score of height ($P < .001$), and 38 patients (61%) still had growth failure at final examination. Twenty-seven patients (43.5%) achieved their target SD score of height. Children transplanted over 12 years had lower growth velocity (cm/year) than those transplanted at 2-5 years and 5-12 years ($P < .05$). A high final standard deviation score of height was independently associated with lower transplant age, higher baseline standard deviation score of height, and lower cumulative steroid dose ($P < .05$ for all).

Conclusion: Kidney transplantation improves linear growth in pediatric recipients, but growth failure is still common after transplantation, and most patients are unfortunately far from their target height.

Keywords: Growth failure, height, kidney transplantation, pediatric, short stature, target height

Introduction

Growth is impaired in children with chronic kidney disease (CKD) due to uremic milieu, metabolic disturbances, renal osteodystrophy, and abnormalities of the growth hormone–insulin-like growth factor-1 axis.[1,2] Kidney transplantation (KTx) is the best treatment option for end-stage kidney disease and has a positive impact on linear growth of pediatric recipients. Nevertheless, it is not always possible to normalize the height deficit and reach the target adult height after transplantation.[3,4]

There are several factors that influence growth after transplantation. Growth failure prior to transplantation is an important factor in achieving the target height in the posttransplant period.[1] Therefore, measures to improve growth before transplantation, such as nutrition, should be prioritized in pediatric CKD patients. It is also recommended that transplantation be performed in early childhood, as growth velocity is highest in healthy children.[5] In fact, the youngest children, especially children between 2 and 5 years old, have the best linear growth among pediatric KTx recipients.[1,6] Steroid use is another risk factor affecting growth. Immunosuppressive therapies aimed at steroid withdrawal or avoidance are indeed associated with improved growth velocity.[7] Another important determinant of final height is graft function, and a reduction in glomerular filtration rate (GFR) has a negative effect on it.[6,8] Other factors affecting growth after transplantation include primary kidney disease, duration of CKD before transplantation, the onset of puberty before transplantation, donor source, and degree of delay in bone age.[5]

The aim of this study is to determine the frequency of growth failure and catch-up growth in pediatric KTx recipients and to investigate the factors affecting growth.

Methods

Study Population

In this retrospective, single-center study, 104 KTx recipients transplanted before the age of 18 years between 2007 and 2021 and followed up in the Department of Pediatric Nephrology, İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, were evaluated. The exclusion criteria were as follows: (i) patients who followed up less than 1 year after transplantation, (ii) patients who did not have valid anthropometric measurements, (iii) patients with skeletal anomalies affecting height, (iv) patients who had reached their final height at the time of transplantation, (v) patients who had combined liver transplantation and KTx, (vi) patients with syndromic disorders associated with short stature, and (vii) patients

Received: January 2, 2023 **Accepted:** January 31, 2023
Publication Date: May 11, 2023
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DOI: 10.5152/cjm.2023.23002

who did not consent to participate in the study. Ultimately, a total of 62 KTx recipients were eligible for enrollment in the study. The study was approved by the Ethics Committee of İstanbul University-Cerrahpaşa (Date: 04.01.2018, Number: 4262). Informed consent was obtained from each eligible patient or their parents.

Data Collection

Patients' medical records were retrospectively reviewed for data, including age, sex, primary kidney disease, duration of kidney replacement therapy (KRT), dialysis modalities before transplantation, donor and transplant characteristics (donor type and age, number of Human leukocyte antigen (HLA) mismatches, age at transplant, posttransplant follow-up time, and history of rejection), certain clinical and laboratory values during posttransplant follow-up (blood pressure, hemoglobin, creatinine, HCO_3, and parathyroid hormone), and medications (immunosuppressives, antihypertensives, sodium bicarbonate, and growth hormone).

Primary kidney diseases were grouped by disease codes for pediatric patients according to the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA) Registry coding system.[9] Hypertension was defined as systolic or diastolic blood pressure at or above the age-, sex-, and height-specific 95th percentile or use of antihypertensive medications. Anemia was defined as a hemoglobin level below an age- and sex-specific cutoff point based on the National Institute for Health and Care Excellence clinical guidelines or the use of erythropoietin-stimulating agents after transplantation.[1] The estimated glomerular filtration rate (eGFR) was calculated using serum creatinine at the last visit based on the revised Schwartz formula.[10] Metabolic acidosis was defined as a blood pH below 7.35 and a low bicarbonate level or the use of oral sodium bicarbonate to raise blood pH. Hyperparathyroidism was defined as a serum parathyroid hormone level greater than 100 pg/mL within the first 3 months after transplantation.

Assessment of Growth

Annual anthropometric measurements (weight and height) at baseline and at the first, second, third, fourth, and fifth years after transplantation and at the last visit were recorded retrospectively. Body mass index (BMI) was calculated for each individual (kg/m^2). Standard deviation scores (SDS) for weight, height, and BMI adjusted to height and age were calculated based on the reference values for Turkish children and adolescents.[11]

Baseline height was defined as height at the time of transplantation. Final height was defined as the height at study time or the height with a height velocity less than 2 cm per year for boys older than 16 years and for girls older than 14 years. Target height was calculated using midparental height as follows: target height (boys) = (father height + mother height + 13)/2 and target height (girls) = (father height + mother height – 13)/2. Target height interval was defined as midparental height ± 8.5 cm.[12] The SDS of height (H-SDS) was calculated separately for baseline, final, and target heights using national reference values.[11]

Growth failure was defined as H-SDS < −1.88 and classified as moderate (−1.88 and −3) or severe (< −3). Growth velocity was defined as the rate of change in height and calculated for the first, second, and subsequent years after transplantation.

Growth was assessed by transplant age, and patients were divided into age groups of 2-5 years, 6-12 years, and 12-18 years at the time of transplantation.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences v21.0 for Windows (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics were used to describe the characteristics of the study population. The Shapiro–Wilk test was used to test whether a continuous variable followed a normal distribution. Continuous data were presented as median (25th, 75th) as the data were not normally distributed. The Mann–Whitney *U*-test was used to compare continuous data between the 2 groups. The categorical variables were presented as numbers (percentages) and compared using the chi-square test. The Fisher's exact test was used in analyses where the chi-square assumptions were not met. Differences in annual change in H-SDS were analyzed using the Wilcoxon signed-rank test. The Spearman's correlation test was used to determine factors affecting the final H-SDS. Variables with a *P*-value of < .2 were analyzed with a multivariate logistic regression analysis to determine the independent predictors of final H-SDS. A 2-tailed *P*-value <.05 was defined as significant.

Results

Clinical Characteristics

The median (25th-75th percentile) age at the initiation of KRT was 7.9 (3.0-11.8) years. The median duration of KRT before transplantation was 2.6 (1.1-6.2) years. Six children received preemptive transplantation, 35 were on peritoneal dialysis, and 21 were on hemodialysis before transplantation. The primary kidney diseases were congenital abnormalities of kidney and urinary tract (46.8%), glomerulopathies (22.6%), hereditary tubulopathies (14.5%), neurogenic bladder (3.2%), and others (12.9%).

The median age at transplantation was 11.9 (8.8-14.8) years and the median follow-up time after transplantation was 5.9 (3.2-7.2) years. All patients received their first transplant, and 43 patients (69%) received a kidney from a living donor. Immunosuppressive protocols included triple therapy in all patients except 2 with a steroid-free protocol. The prednisolone dose was gradually tapered to 5 mg per day at week 12 after transplantation and switched to alternate-day therapy at month 12. Thirteen (21%) patients had a history of rejection and received anti-rejection therapy. None of the patients lost their graft, and the median eGFR at the last visit was 70.0 (55.4-87.7) mL/min per 1.73 m^2.

Growth Failure

At the time of transplantation, 47 of 62 children (76%) had growth failure (H-SDS < –1.88). After transplantation, a significant increase in H-SDS was observed between baseline and final (P < .001); however, final H-SDS was significantly lower than the target H-SDS (P < .001) [H-SDS for baseline, final, and target as follows: –2.68 (–3.59, –1.97), –2.27 (–3.27, –1.18), and –0.68 (–1.33, –0.19), respectively]. A total of 38 patients (61%) still had growth failure according to their final H-SDS, and 20 of them (32%) had severe growth failure. Twenty-seven patients (43.5%) achieved their target H-SDS. In the entire cohort, 5 patients received growth hormone therapy; only 1 of them received GH before transplantation.

In children transplanted between ages 2 and 5 years, there were no significant differences between the final and target H-SDS (P = .33), but children transplanted between ages 5 and 12 years and older than 12 years had significantly lower final H-SDS than their target H-SDS (P < .001, for both) (Figure 1).

Growth Velocity

A significant increase in H-SDS was observed between baseline and the first year (P = 0.001), as well as between the first and second year (P = .004) [median H-SDS –2.68 (–3.59, –1.97), –2.50 (–3.18, –1,65), and –2.22 (–3.0, –1,62) at baseline, first, and

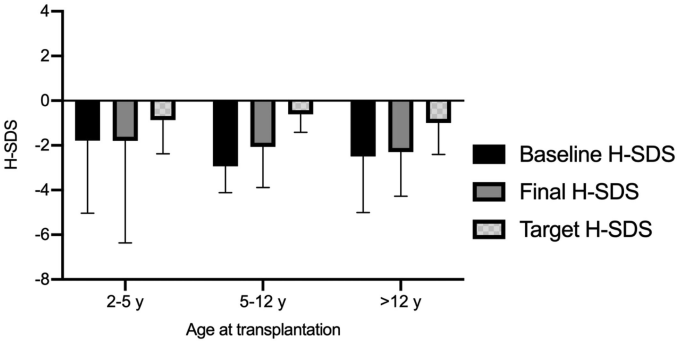

Figure 1. Height SDS at transplantation (baseline), at study time (final), and according to midparental (target) are given for 3 age groups defined by transplantation age (2-5 years, 5-12 years, and >12 years). Results are as follows: –1.79 (–3.9, –0.61), –1.80 (–3.88, 0.69), and –0.87 (–1.75, –0.23) for group 2-5 years; –2.94 (–3.48, –2.29), –2.07 (–3.11, –1.29), –0.61 (–1.00, –0.19) for group 5-12 years; and –2.50 (–4.29, –1.78), –2.31 (–3.31, –1.33), –1.0 (–1.63, –0.22) for group >12 years. In children transplanted at 2-5 years, there was no significant difference between the final and target H-SDS ($P = .33$). However, in children transplanted at age of 5-12 years and >12 years, the final H-SDS was significantly lower than their target H-SDS ($P < .001$ for both). y, years; H-SDS, standard deviation score of height.

second year, respectively]; however, the difference disappeared after the second year of transplantation.

Figure 2 shows the growth velocity of children for 3 age groups. Children transplanted older than 12 years showed a lower growth velocity (cm/years) than the children transplanted between 2 and 5 years and between 5 and 12 years at the first, second, third, and fifth years ($P < .05$ for all).

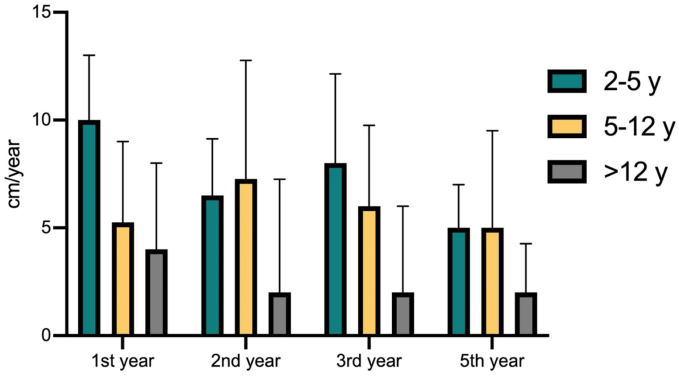

Figure 2. Median growth velocity at first year, second year, third year, and fifth year for 3 age groups defined by transplantation age (2-5 years, 5-12 years, and >12 years). Results were as follows: 10.0 (8.0, 11.0), 5.3 (5.0, 8.8), and 4.0 (2.0, 6.0) cm/year at the first year; 6.5 (5.1, 7.8), 7.3 (4.3, 9.8), and 2.0 (0, 5.3) cm/year at the second year; 8.0 (5.6, 9.8), 6.0 (4.0, 7.8), and 2.0 (0, 4.0) cm/year at the third year; and 5.0 (3.0, 5.0), 5.0 (2.8, 7.3), and 2.0 (1.0, 3.8) at the fifth year, respectively. In years 1, 2, 3, and 5, both children transplanted at age 2-5 years and children transplanted at age 5-12 years had significantly higher growth velocity than children transplanted at age >12 years ($P < .01$ for all). However, there was no difference in growth velocity between children transplanted at ages 2-5 and 5-12 years during any time period. cm, centimeter; y, years.

Factors Affecting Growth

As shown in Table 1, individuals with growth failure had lower baseline H-SDS (at the time of transplantation) ($P < .001$), lower eGFR at the last visit ($P = .007$), and a higher prevalence of hypertension ($P = .042$) compared to those with normal growth; however, there were no differences in age, sex, primary kidney disease, transplant age, cumulative steroid doses, prevalence of early hyperparathyroidism, metabolic acidosis, or anemia, or use of GH therapy between patients with and without growth failure.

Final H-SDS was positively correlated with baseline H-SDS ($r = 0.733$, $P > .001$), target H-SDS ($r = 0.431$, $P = .001$), and eGFR ($r = 0.299$, $P = .019$) and negatively correlated with cumulative steroid doses ($r = –0.405$, $P = .001$) but not with any other clinical and laboratory parameters.

Linear regression analysis including transplant age, sex, baseline and target H-SDS, eGFR, cumulative steroid dose, and presence of hypertension revealed that a high final H-SDS was independently associated with lower transplant age ($\beta = –0.297$, 95% CI: –0.154 to –0.006, $P = .035$), higher baseline H-SDS ($\beta = 0.808$, 95% CI: 0.632-0.985, $P < .001$), and lower cumulative steroid dose ($\beta = –0.544$, 95% CI: –5.272 to –1.721, $P < .001$).

Discussion

The results of this study suggest that although KTx improves linear growth in pediatric recipients, growth retardation is still common in the pediatric KTx population and, unfortunately, nearly half of the patients transplanted in childhood are far from their target height. This study also shows that growth velocity is the highest in the first 2 years after transplantation and that patients transplanted at ages 2-5 years and 5-12 years have better height gain than older children.

A major challenge for pediatric patients with CKD is linear growth failure. Kidney transplantation is the best treatment option for KRT because it corrects many metabolic and hormonal imbalances and eliminates the problems caused by a uremic milieu. Nevertheless, it cannot always guarantee optimal growth, which is an important goal in childhood. There is limited information available on linear growth patterns in pediatric KTx recipients. According to the 2014 NAPRTCS Annual Report from North America, KTx did not result in significant changes in height in pediatric patients.[6] The European European Renal Association – European Dialysis and Transplantation Association (ESPN/ERA-EDTA) registry report showed that only 55% of pediatric KTx recipients achieved normal height during follow-up.[4] Another study from Spain found that more than two-thirds of pediatric KT recipients reached their final adult height. However, unlike the others in that study, more than half of the cases had normal height at the time of transplantation.[13] A study from Turkey showed that 19% of pediatric KTx recipients had an H-SDS of less than –2 in the posttransplant period, although growth improved significantly after transplantation.[14] Our study, in which growth failure was defined as an H-SDS less than –1.88, showed that 76% of KTx recipients had growth failure at the time of transplantation. Although linear growth improved significantly after transplantation, 61% of children still had growth failure based on their final height, and only 43.5% of children reached their target height.

Several factors are associated with posttransplant growth, with age at the time of transplantation being the most announced factor. It has been reported that growth of children younger than 5 years is significantly accelerated after KTx, whereas older children showed a poor growth pattern.[13] Tejani et al[15] reported that no catch-up growth was observed in patients older than 6 years at the time of transplantation, and the youngest children with the greatest

Table 1. Comparisons of Patients with Normal Growth and Growth Failure (Final Height SDS < –1.88)

Variables	Patients with Growth Failure (n = 38)	Patients with Normal Growth (n = 24)	*P*
Age at the time of study, years	18.0 (16.2-18.0)	17.9 (15.5-18.3)	.55
Sex, male, n (%)	23 (60.5)	14 (58.3)	.86
BMI SDS at the time of study	0.44 (–0.13 to 1.22)	0.13 (–0.82 to 0.90)	.09
Height SDS at the time of study	–3.09 (–3.94 to –2.40)	–1.04 (–1.57 to –0.23)	<.001
Primary renal disease, CAKUT/glomerular disease/tubulointerstitial disease/other, n	17/9/8/4	12/5/1/6	.16
Age at the initiation of KRT, years	7.5 (2.9-11.6)	9.2 (4.9-12.4)	.72
Duration on dialysis, years	3.1 (1.1-6.6)	2.2 (1.2-3.9)	.33
Modality of pretransplant KRT, preemptive/PD/HD, n	2/23/13	4/12/8	.32
Age at transplantation, years	12.7 (9.7-14.9)	11.5 (7.6-14.8)	.29
Height SDS at transplantation	–3.26 (–4.30 to –2.48)	–1.72 (–2.43 to –0.71)	<.001
Follow-up time after transplantation, years	5.5 (3.5-6.5)	6.5 (2.8-9.1)	.27
Deceased donor, n (%)	12 (31.6)	7 (29.2)	.84
History of rejection, n (%)	10 (26.3)	3 (12.5)	.19
Cumulative steroid dose, g/kg	0.20 (0.15-0.31)	0.16 (0.13-0.23)	.09
GH therapy, n (%)	4 (11.1)	1 (4.3)	.64
Hypertension, n (%)	29 (80.6)	13 (56.5)	.047
Hyperparathyroidism, n (%)	7 (21.2)	5 (21.7)	.96
Metabolic acidosis, n (%)	18 (47)	10 (42)	.66
Anemia, n (%)	13 (37.1)	3 (13.6)	.055
Final eGFR, mL/min/1.73m^2	64.2 (40.1-79.4)	80.3 (66.0-99.1)	.007

Continuous data presented as median (25th, 75th) and compared with the Mann–Whitney *U*-test. Categorical variables were compared with the Fisher's exact test.
BMI, body mass index; CAKUT, congenital abnormalities of kidney and urinary tract; eGFR, estimated glomerular filtration rate; GH, growth hormone; HD, hemodialysis; KRT, kidney replacement therapy; PD, peritoneal dialysis; SDS, SD score.

deficit at transplantation gained the most height after transplantation. Consistent with previous studies, our findings showed that younger children had a better growth pattern than older children. In our cohort, not only children transplanted between the ages of 2 and 5 years but also children transplanted between the ages of 5 and 12 years had better growth than older children over 12 years.

Graft function, represented as GFR, is a widely demonstrated factor associated with growth improvement in both children with CKD and children with a kidney transplant.[4,6,9] Glomerular filtration rate appears to be an important determinant of final height in pediatric KTX recipients, and a long duration of GFR < 50 mL/min/1.73 m^2 has a negative effect on growth.[8] It has also been shown that the greatest improvement in H-SDS in the first year occurred in children with the highest GFR.[16] The results of our study have shown that patients with growth failure had lower eGFR than patients with normal growth. Additionally, higher GFR is an independent predictor of better final H-SDS, and as previous studies have demonstrated, good graft function contributes significantly to better growth after transplantation.

Preemptive transplantation, early steroid withdrawal, or complete steroid avoidance are also important factors associated with better growth.[1,7,16] Our cohort consists of only 2 children with a steroid-free immunosuppressive regimens. Therefore, we were unable to show the effect of withdrawal or avoidance of steroids on growth. However, the results of our study demonstrated that lower cumulative steroid doses are associated with higher final H-SDS. Taken together, all evidence points to the use of non-steroidal regimens or, at the very least, reduced steroid doses in pediatric KTx recipients.

Our study also reveals that baseline H-SDS is another determinant of final H-SDS. Our results showed that a high final H-SDS was associated with a higher baseline H-SDS. Jung et al[17] reported that 75% of KTx recipients reached a final height *z*-score of 1.88, which was strongly correlated with baseline height, with the taller children eventually reaching a greater adult height.[17] The findings of previous studies suggest the importance of early intervention to prevent the loss of height prior to transplantation.[18,19]

As a result, growth is a challenging problem in pediatric KTx recipients even after successful transplantation. It is recommended that a more aggressive approach be taken before and after transplantation in order to improve growth: transplantation in early childhood, optimal nutritional support, early detection of growth

retardation, close monitoring of growth velocity, and ensuring good graft function.

The retrospective design of the study is the major limitation in determining the risk factors for growth. In addition, due to the extremely small number of patients who received steroid-free treatment, it was not possible to evaluate its effects on growth patterns. Another limitation of our study is the lack of information on bone age at the time of transplantation and follow-up to determine the final height.

Conclusion

The present study shows that although growth improves after KTx, catch-up growth is not sufficient, and the children remain far from their target adult height. The present study also shows that transplant age, pretransplant height deficit, graft function, and steroid doses are significant determinants of growth after transplantation. Consequently, avoiding a growth deficit prior to transplantation, transplanting at a young age, maintaining graft function, and avoidance or reduced steroid doses seem to be crucial for achieving the maximal final height.

Ethics Committee Approval: This study was approved by the Ethics Committee of İstanbul University-Cerrahpaşa (Date: 04.01.2018, Number: 4262).

Informed Consent: Informed consent was obtained from each eligible patient or their parents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.S., N.C.; Design – S.S., N.C.; Supervision – M.E., N.C.; Data Collection and/or Processing – S.S., S.K., E.K.Y, R.G., E.B.D.; Analysis and/or Interpretation – S.S, A.A.; Literature Review – S.S., S.K., E.K.Y.; Writing – S.S., E.K.Y.; Critical Review – M.E., N.C.

Declaration of Interests: The authors declare no conflict of interest.

Funding: The authors declared that this study has received no financial support.

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