Article

Patterns of Growth after Kidney Transplantation among Children with ESRD

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Abstract

Background and objectives Poor linear growth is a frequent complication of CKD. This study evaluated the effect of kidney transplantation on age-related growth of linear body segments in pediatric renal transplant recipients who were enrolled from May 1998 until August 2013 in the CKD Growth and Development observational cohort study.

Design, setting, participants, & measurements Linear growth (height, sitting height, arm and leg lengths) was prospectively investigated during 1639 annual visits in a cohort of 389 pediatric renal transplant recipients ages 2–18 years with a median follow-up of 3.4 years (interquartile range, 1.9–5.9 years). Linear mixed-effects models were used to assess age-related changes and predictors of linear body segments.

Results During early childhood, patients showed lower mean SD scores (SDS) for height (−1.7) and a markedly elevated sitting height index (ratio of sitting height to total body height) compared with healthy children (1.6 SDS), indicating disproportionate stunting (each $P<0.001$). After early childhood a sustained increase in standardized leg length and a constant decrease in standardized sitting height were noted (each $P<0.001$), resulting in significant catch-up growth and almost complete normalization of sitting height index by adult age (0.4 SDS; $P<0.01$ versus age 2–4 years). Time after transplantation, congenital renal disease, bone maturation, steroid exposure, degree of metabolic acidosis and anemia, intrauterine growth restriction, and parental height were significant predictors of linear body dimensions and body proportions (each $P<0.05$).

Conclusions Children with ESRD present with disproportionate stunting. In pediatric renal transplant recipients, a sustained increase in standardized leg length and total body height is observed from preschool until adult age, resulting in restoration of body proportions in most patients. Reduction of steroid exposure and optimal metabolic control before and after transplantation are promising measures to further improve growth outcome.

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Introduction

Poor linear growth remains an unresolved obstacle in children with CKD (1–3). Even after successful kidney transplantation (KTx), catch-up growth occurs far from regularly (4,5) and is modified by age at transplantation, graft function, and steroid exposure (1–4). Persistent growth failure not only hampers the psychosocial rehabilitation of patients with CKD but is strongly associated with excessive cardiovascular comorbidity (6–8). Uremia seems to have a nonuniform effect on growth of linear body segments. A recent comprehensive anthropometric analysis of a large cohort of boys receiving various treatment modalities for CKD revealed a preferential impairment of leg growth and a rather preserved trunk resulting in disproportionate stunting (9). This growth pattern seems to be characteristic for patients with CKD (10,11). However, the effect of KTx on disproportionate stunting in children with CKD with respect to individual body segments has not been analyzed so far.

We therefore performed a prospective observational study in a large transplant cohort to assess the effect of KTx on height and length of linear body segments covering the whole age range from early childhood to adulthood.

Material and Methods

Study Design and Population

From May 1998 until August 2013, a total of 401 children who underwent KTx were enrolled in the CKD Growth and Development Study, which is a prospective observational cohort study at two pediatric nephrology centers in Northern Germany (Hannover Medical School and Charité Universitätsmedizin, Berlin, Germany). Eligible children were aged 2–18 years. Patients were permitted to be enrolled into this study anytime after KTx. Patients with height-affecting skeletal abnormalities (n=12) were excluded for the present analysis. The clinical data for the resulting 389 patients are given in Table 1. The patients were followed up at yearly intervals for clinical and anthropometric assessment (median follow-up, 3.4 years; interquartile range, 1.9–5.9 years). A physical examination was done and

Table 1. Clinical characteristics of 389 pediatric renal transplant recipients

Variable	Mean±SD or Median	95% CI or IQR	Range	No. of Patients or No. of Measures
Nonrepeated measurements[a]				
Age at ESRD (yr)	8.3	4.1–12.1	0.1–17.2	389
Age at dialysis (yr)	7.9	3.7–11.6	0.1–17.0	247
Age at KTx (yr)	9.0	5.2–12.9	0.7–17.2	389
Time after KTx at first visit (yr)	0.7	0.4–2.5	0.2–13.8	389
Time after KTx at last visit (yr)	5.3	2.7–8.2	0.3–17.2	389
Menarcheal age (yr)	13.1±1.4	12.8–13.4	9.3–15.9	86
Gestational age (wk)	38.9	39.9–40.0	26.0–43.0	322
Birth weight (g)	3006±759	2923–3090	830–5000	319
Birth length (cm)	50.0	47.0–52.0	33.0–59.0	315
Umbilical cord artery pH	7.29	7.23–7.33	7.04–7.40	171
Mother's height (cm)	166.0	162.3–170.0	144.3–186.0	372
Father's height (cm)	178.4±7.7	177.6–179.1	156.0–198.0	369
Repeated measurements[b]				
eGFR (ml/min per 1.73 m^2)	56	54–58	4–190	1605
Steroid dosage (mg/kg)	0.08	0.07–0.08	0.0–0.89	1305
Plasma HCO_3 (mmol/L)	23.0	22.8–23.1	17.1–29.7	1542
Hemoglobin (g/dl)	11.1	11.0–11.2	6.2–15.5	1566
Bone age delay (yr)	−1.3	−1.1 to −1.5	−7.3 to 3.1	1005

KTx, kidney transplantation; 95% CI, 95% confidence interval; IQR, interquartile range.
[a]Basic data (nonrepeated measurements) are given as mean±SD and 95% CI in case of normal distribution and as median, interquartile range (25th–75th percentile), and range in case of non-normal distribution.
[b]Average values during the observation period based on annual values. Repeated measurements within the same individual were evaluated with linear mixed model.

history of medication and dietary intake was taken. In addition, venous blood samples were taken to assess white and red blood cell counts; serum levels of sodium, potassium, chloride, phosphate, creatinine, urea, albumin, protein, parathyroid hormone; and blood gas analysis. Radiography of the left wrist were done to assess bone age yearly in most patients (68% of all yearly visits).

The Ethics Committee approved the study, and the research was performed in accordance with the Declaration of Helsinki. Study participants and/or their parents gave consent prior to participation.

Newborns were classified as small for gestational age (SGA) if birth weight or length was <10th percentile (93 of 308 children with complete birth data [30.2%]) (12). Local reference data for rates of SGA birth were obtained from annual reports of the Center for Quality Management in Health Care, Germany, from 1996 to 2007 (13). Data on gestational age, umbilical cord artery pH, birth weight, and length were obtained from the children's health care booklets. Parental height data were available from 372 mothers (95.6%) and 369 fathers (94.9%). The mean heights of mothers (165.8 cm) and fathers (178.4 cm) did not significantly differ from those of the reference population (men, 178 cm; women, 165 cm) (14). ESRD was defined by start of dialysis or pre-emptive KTx. The dietary intake was assessed by a dietitian using a 3-day dietary record at intervals of 3 to 12 months according to the patient's age (more frequent assessments in infants and young children than in older children). The recorded dietary caloric/protein intake was at least 80% of the recommended dietary allowance for age in all patients. The eGFR was assessed using the recently revised Schwartz equation (15).

Most patients (361 of 389 [92.8%]) had received their first graft, 25 patients their second graft (6.4%), and three patients their third graft (0.8%). Immunosuppressive protocols included daily prednisolone treatment. The prednisolone dosage was tapered down to 4 mg/m^2 per day by week 8. Until 2007, all patients were kept on daily prednisolone. Since 2007, patients were weaned off of steroids between 6 and 12 months after KTx if graft function was stable and no rejection had taken place (80% of patients). Overall, steroids were withdrawn in 17% of patients during the observation period (1998–2013). Growth hormone treatment before KTx was given in 129 of 389 patients (33%) during a mean period of 2.6 years (95% confidence interval [95% CI], 2.3 to 2.9; range, 0.1–11.2 years). After KTx, only 7.2% of patients received growth hormone treatment during a relevant period of time (≥12 months). Underlying renal diseases were congenital CKD (49.7%), glomerulopathies (19%), hereditary diseases (26.9%), and others (4.4%).

Anthropometry and Outcome Variables

Anthropometric measurements were done yearly and included total body height, sitting height, arm length, and leg length (9,16). The sitting height index was calculated as the ratio between sitting height and stature as a measure of body disproportion (17). All measurements were performed as recommended by the International Biologic Program (18) with standardized equipment (height: Dr. Keller, I Stadiometer-Limbach-Oberfrohna, Germany; all other measurements: Siber Hegner Anthropometer, Zürich, Switzerland; accuracy, 1 mm). All measurements were performed three times in each patient by the same investigator (M.Ž.), and average values were taken for further analysis. Standardized values were calculated (SD scores [SDS]) for each segment of linear growth, as well as for sitting height index according to the equation:

$$SDS = [\text{individual patient values-} (\text{mean values for age and sex-matched heathy peers})]/(\text{SD values for age- and sex-matched healthy peers}).$$

Reference limits were derived from a study of 5260 healthy children aged 2–18 years (16,19).

Statistical Analyses

Data are given as mean and 95% CIs if not indicated otherwise. All anthropometric data are presented as age- and sex-related SDS values. The normality of distribution was evaluated by the Kolmogornov–Smirnov test with and without Lilliefors correction and Shapiro–Wilk test for each parameter. All measurements were grouped according to age at time of examination, and 1-year intervals covering the age ranges from 2 to 18 years were defined. The linear mixed-effects models were used (MIXED procedure in SPSS software) for evaluation of age-related changes in linear body dimensions of post-transplant growth in 389 patients. Further detail can be found in the Supplemental Appendix. A cubic spline function was used in Figures 1 and 2 for graphical presentation of linear growth only. The standard statistical package SPSS for Windows, version 21.0 (IBM Corp., New York) was used for statistical calculations. Results were considered significant at a level of $P<0.05$.

Results

The clinical characteristics of 389 pediatric KTx recipients are given in Table 1. In 36% of patients living-related KTx and in 37.7% of patients preemptive KTx (*i.e.*, without prior dialysis treatment) was performed. Bone age was retarded by approximately −1.3 years compared with chronologic age and mean standardized height amounted to −1.74 SDS (each $P<0.001$ compared with values in healthy children). Mean age at menarche (13.1 years) did not differ from that in healthy females ($P>0.05$). Mean eGFR based on the mean annual values of each patient was 56 ml/min per 1.73 m^2; 51.4% and 21.8% of patients revealed mild (hemoglobin <12 g/dl) or moderate (<10 g/dl) anemia during the observation period, respectively. Metabolic acidosis (bicarbonate <22 mmol/L) was present in 28.9% of patients during the observation period. Severe metabolic acidosis (<18 mmol/L) was rare (0.2%). The proportion of patients with SGA history was significantly higher than in the normal population (29.5% versus 8.1%; $P<0.001$).

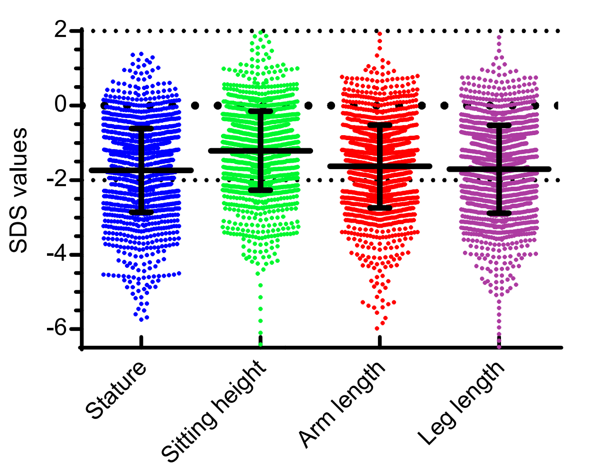

Figure 1. | Mean SD scores (SDS) for stature, sitting height, and arm and leg lengths as a function of age in 389 patients who had received transplants (1639 annual measurements). To assess age-related changes in linear body growth, all measurements were grouped according to age at the time of examination.Horizontal lines refer to the normal mean (0 SDS) and lower normal range (−2.0 SDS), respectively.

Age-Related Height and Linear Body Segments

In general, KTx patients showed lower SDSs for all four body dimensions during the observation period: mean stature, −1.74 SDS; sitting height: −1.22 SDS; arm length: −1.65 SDS; and leg length, −1.77 SDS (each $P<0.001$ versus healthy children) (Figure 1). Furthermore, the degree of impairment differed significantly between the four body dimensions, indicating disproportionate stunting (each $P<0.05$). Leg length was most impaired, whereas sitting height was best preserved.

Two periods of sustained catch-up growth were observed in the present study: after 2–4 years and after 12–14 years. In early childhood, mean standardized body height decreased during ages 2–4 years of age ($P<0.05$) (Figure 2). Thereafter, a sustained increase in standardized height was noted until the age of 12 years (Δheight SDS, 0.7; $P<0.01$), the time of expected onset of the pubertal growth spurt in healthy children. Thereafter, standardized height consistently decreased until mid-adolescence by 0.5 SDS (12 versus 14 years; $P<0.01$), followed by a late catch-up in late adolescence (0.4 SDS; age 14 versus 18 years; $P<0.01$). The significant transient dip of the height SDS curve translates to a delay of the pubertal growth spurt of approximately 2 years in KTx patients compared with healthy children. Adult height amounted to −1.65 SDS and was reduced (< −2.0 SDS) in 33% of patients.

Leg length showed the most pronounced age-dependent changes. It decreased from the age of 3 years until the age of 5 years (−1.8 versus −2.5 SDS; $P<0.05$), followed by a continuous increase until adult age, which was interrupted by a short decline at the time of expected maximal pubertal leg growth in healthy children (*i.e.*, at 13–14 years; each $P<0.05$).

Sitting height was the best-preserved linear body dimension (Figure 1). In contrast to height, standardized sitting height showed a significant increase in preschool age (0.5 SDS; 2 versus 6 years; $P<0.05$) (Figure 2). After the age of 6 years, standardized sitting height consistently decreased until age 15 years (−0.5 SDS; 6 versus 15 years; $P<0.05$), followed by a nonsignificant slight increase until adult height (0.3 SDS; 15 versus 18 years; $P=0.43$).

Arm length was the most stable linear body segment, ranging from −1.5 to −1.9 SDS (Figure 2). However,

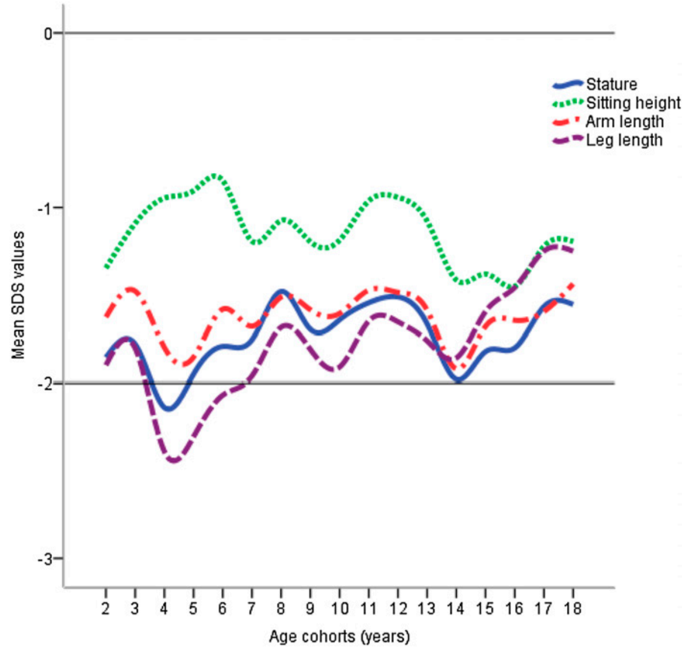

Figure 2. | Mean SDS for stature, sitting height, and arm and leg lengths in 389 children who received transplants and were followed up over a median period of 3.4 years (interquartile range 1.9–5.9 years). All linear body dimensions were significantly lower than those in healthy children (each P<0.001) and the degree of impairment differed significantly between the four body dimensions, indicating disproportionate stunting (each P<0.05). The black horizontal lines refer to the normal mean (0 SDS) and lower normal range (-2.0 SDS).

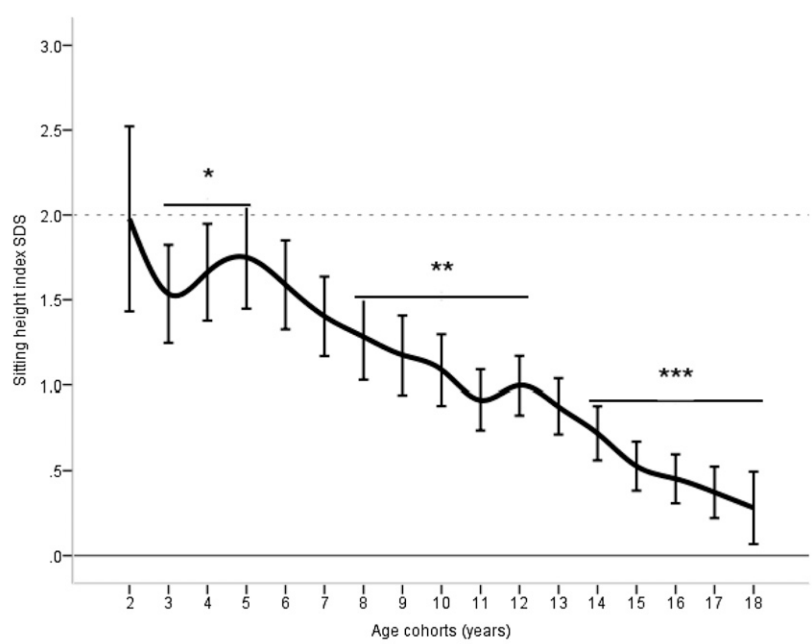

Figure 3. | Mean sitting height index (ratio between trunk length and total body height) as a function of age in389 renal transplant recipients. *P<0.05 for age cohorts of 3 years versus 5 years; **P<0.05 for age cohorts of 2–5 years versus 8–12 years; ***P<0.05 for age cohorts of 8–12 years versus 14–18 years. Data are given as mean and 95% confidence interval. Horizontal lines refer to the normal mean (0 SDS) and upper normal range (2.0 SDS).

standardized arm length increased significantly in prepubertal age (0.4 SDS; 5 versus 12 years; $P<0.05$), followed by a decrease at the time of expected puberty (-0.4 SDS; 11 versus 14 years; $P<0.05$) and a late catch-up until adulthood (0.4 SDS; 14 versus 18 years; $P<0.05$).

Age-Related Body Proportions

A comparison of paired parameters of the four linear body segments in each age cohort revealed a distinct pattern of disproportionate growth. At preschool age (3–5 years), the differences between sitting height and the other three linear body dimensions and consequently the sitting height index increased significantly (each $P<0.05$) indicating progressive body disproportion (Figures 2 and 3). Thereafter, body disproportion constantly improved until adulthood, as illustrated by the decreasing area between the curves of the best preserved (sitting height) and the most impaired (leg length) body dimension with increasing age in Figure 2. Consequently, sitting height index decreased by 1.5 SDS from midchildhood until late adolescence ($P<0.01$) (Figure 3) and was almost normalized by adult age (0.4 SDS).

Predictors of Linear Body Dimensions

Time after KTx, congenital CKD, bone maturation, steroid exposure, degree of metabolic acidosis and anemia, a history of intrauterine growth restriction, and parental height were significant predictors of linear body dimensions and/or sitting height index after KTx (each $P<0.05$) (Table 2). In contrast, age at end-stage CKD or KTx, type of KTx (living-related versus cadaveric KTx; preemptive KTx versus prior dialysis treatment), eGFR, gestational age, umbilical cord pH, and sex were no significant correlates. In general leg length was the most "sensitive" body segment, being significantly influenced by all except one (hemoglobin) of the above-mentioned significant predictors (Table 2). Contrary, the most "inert" body segment was sitting height, which was associated only with steroid dosage, bone age delay, SGA history, and parental height (Table 2). Interestingly, the strongest predictor of body proportions (*i.e.*, sitting height index) was time after KTx ($P<0.01$), followed by steroid dosage ($P<0.05$) and parental height ($P<0.05$).

Discussion

In a comprehensive approach to analyze statural growth after KTx in children, lengths of four linear body components were prospectively measured in a large cohort, covering the whole age range from early childhood until adulthood.

In early childhood, age-related lengths of all linear body dimensions (height, arm and leg lengths, and sitting height) were significantly lower compared with those in healthy children. Stunting was disproportionate with preferential impairment of leg growth and preserved trunk growth. After early childhood, we observed a distinct pattern of restoration of disproportionate stunting with a sustained increase in standardized leg length and constant decrease in standardized sitting height, resulting in substantial catch-up growth and almost complete harmonization of body proportions by adult age. This pattern of growth after KTx in childhood was associated with several important factors, which could be identified in this study: time after KTx, congenital CKD, bone maturation, steroid exposure, degree of metabolic acidosis and anemia, intrauterine growth restriction, and parental height.

Interestingly, leg length showed the most pronounced age-dependent changes compared with the other body segments. Mean standardized leg length increased by 1.2 SDS from age 4 to 18 years, whereas standardized sitting height decreased only slightly, by 0.3 SDS, during this age period. Therefore, KTx-induced catch-up growth and harmonization of body proportions were mainly due to improved leg growth.

In the present study, a continuous catch-up growth in arm and leg lengths, and consequently of total body height, was observed during the age cohorts from 4 to 12 years. Prepubertal catch-up growth was followed by a constant decrease in standardized leg and arm lengths during pubertal age, indicating a delayed onset of pubertal growth spurt. The mean delay of the pubertal growth spurt by 2 years was similar to that in previous reports on pubertal growth in pediatric KTx patients (4,20). Although a late catch-up in linear body dimensions was observed during late adolescence, this could not fully compensate for the delayed pubertal growth spurt resulting in reduced adult height (< -2.0 SDS) in 32% of patients. Nevertheless, age at menarche was not delayed compared with that in healthy female patients, which is in line with a recent study showing normal sexual maturation in adolescents after KTx (21).

Steroid exposure was significantly associated with post-transplant linear growth in the present study, and, overall, steroids were withdrawn in 17% of patients during the 15-year observation period. Recent studies have demonstrated that early/intermediate steroid withdrawal and complete steroid avoidance are associated with improved growth outcome after KTx, especially in prepubertal patients (22–24). Our observations further extend these findings; prolonged steroid exposure hampers catch-up growth and restoration of body proportions and was associated with shorter leg length.

Catch-up growth after KTx is usually limited in patients with poor graft function (*i.e.*, GFR<50 ml/min per 1.73 m^2 in the first year after KTx) (4). In the present study, we could not demonstrate an association between eGFR and lengths of linear body dimensions. This discrepancy might be at least partly related to the rather good graft function (mean eGFR, 56 ml/min per 1.73 m^2; 95% CI, 54 to 58 ml/min per 1.73 m^2) in our patient cohort; only 10% of patients presented with severe CKD (eGFR< 30 ml/min per 1.73 m^2) and only 8.5% of patients entered ESRD during the median observation period of 3.4 years.

In line with previous studies investigating linear growth in children with CKD before KTx, we noticed a negative association between the degree of metabolic acidosis and anemia with linear body dimension length (25,26). Whether a more vigorous treatment will translate into better growth outcome in KTx patients needs to be proven in future trials. Intrauterine growth restriction and parental height are significant predictors of total body height in the general population and in children with CKD (27–31). Malnutrition is an important factor contributing to growth failure in children with CKD, especially during young age. Although all children were regularly followed up by a dietitian and the prescribed caloric intake was at least 80% of recommended daily allowance, we cannot exclude the possibility that some patients were malnourished before KTx. Half of the patients in the present study had congenital CKD, which turned out to be a significant negative predictor of linear body dimensions after KTx.

Overall, the present study indicates that growth after KTx appeared to proceed in a coordinated pattern of restoration of normal body dimensions and shape. Changes

Table 2. Linear mixed-effects models of predictors of standardized linear body dimensions in 389 pediatric KTx

Parameter	Stature	Leg Length	Arm Length	Sitting Height	Sitting Height Index
Congenital CKD[a]	−0.57[b] (−1.02 to −1.11)	-0.52[b] (-0.97 to -0.07)	-0.54[b] (-0.98 to -0.09)	−0.38 (−0.81 to 0.53)	0.32 (−0.17 to 0.80)
Age at end-stage CKD (in yr)	−0.01 (−0.16 to 0.31)	−0.13 (−0.36 to 0.10)	−0.03 (−0.26 to 0.20)	−0.01 (−0.23 to 0.21)	0.06 (−0.19 to 0.32)
Age at KTx (in yr)	0.08 (−0.31 to 0.15)	0.19 (−0.04 to 0.42)	0.04 (−0.19 to 0.27)	−0.04 (−0.27 to 0.18)	−0.19 (−0.44 to 0.06)
Time after KTx (in yr)	0.00 (−0.02 to 0.02)	0.03[c] (−0.01 to 0.06)	0.01 (−0.02 to 0.03)	−0.01 (−0.04 to 0.01)	−0.05[c] (−0.08 to −0.02)
LRD versus CAD[d]	0.25 (−0.12 to 0.61)	−0.12 (−0.25 to 0.48)	0.22 (−0.14 to 0.58)	0.30 (−0.05 to 0.65)	0.03 (−3.37 to 0.43)
Preemptive KTx[e]	0.12 (−0.31 to 0.55)	0.26 (−0.16 to 0.69)	−0.07 (−0.50 to 0.35)	0.09 (−0.51 to 0.32)	−0.23 (−0.71 to 0.24)
Steroid dosage (in mg/kg)[f]	−1.89[c] (−2.68 to −1.10)	−1.89[c] (−2.70 to −1.07)	−2.31[c] (−3.13 to −1.49)	−1.01[b] (−1.80 to −0.10)	1.31[b] (−0.27 to 2.35)
eGFR (in 100 × ml/min per 1.73 m^2)[f]	−0.22 (−0.59 to 0.16)	−0.11 (−0.50 to 0.27)	0.04 (−0.35 to 0.42)	−0.12 (−0.51 to 0.28)	−0.07 (−0.41 to 0.55)
Plasma HCO_3 (in 10×mmol/L)[f]	0.42[b] (−0.07 to 0.77)	0.38[b] (0.03 to 0.74)	0.31 (−0.51 to 0.66)	0.37[b] (−0.01 to 0.74)	−0.1 (−0.46 to 0.45)
Hemoglobin (in g/dl)[#]	0.05[b] (−0.00 to 0.10)	0.05 (−0.01 to 0.10)	0.03 (−0.02 to 0.09)	0.04 (−0.01 to 0.10)	0.02 (−0.05 to 0.09)
Bone age delay (in yr)	−0.13[c] (−0.18 to −0.08)	−0.15[c] (−0.20 to 0.10)	−0.13[c] (−0.19 to −0.08)	−0.16[c] (−0.22 to −0.11)	0.05 (−0.02 to 0.11)
Gestational age (in wk×10)	0.03 (−0.63 to 0.69)	−0.03 (−0.67 to 0.62)	−0.31 (−0.96 to 0.34)	0.07 (−0.55 to 0.70)	0.02 (−0.07 to 0.07)
Umbilical cord artery pH	1.76 (−0.65 to 4.16)	1.25 (−1.12 to 3.63)	1.41 (−0.96 to 3.79)	1.71 (−0.57 to 4.00)	−0.37 (−2.96 to 2.20)
SGA history	−0.60[b] (−1.03 to −0.17)	−0.55[b] (−1.12 to −0.98)	−0.52[b] (−0.95 to −0.09)	−0.42[b] (−0.83 to −0.01)	0.27 (−0.20 to 0.74)
Sex	0.01 (−0.37 to 0.39)	0.16 (−0.22 to 0.54)	0.23 (−0.15 to 0.61)	−0.11 (−0.48 to 0.25)	−0.03 (−0.44 to 0.39)
Parental height (in m)	2.15[c] (1.25 to 3.05)	2.26[c] (1.37 to 3.15)	1.69[c] (0.80 to 2.58)	1.55[c] (0.70 to 2.41)	−1.30[b] (−2.27 to −0.33)

Data are presented as β values (95% confidence intervals). LRD, living-related donor; CAD, cadaveric donor; SGA, small for gestational age.
[a]Congenital CKD (2) versus others (1). The numbers in parentheses indicate the dummy variable used for parameters in the LMM model.
[b]$P<0.05$.
[c]$P<0.01$.
[d]Living-related donor graft (LRD=1) versus cadaveric donor graft (CAD=2).
[e]Preemptive KTx (1) versus previous dialysis treatment (2); SGA history=2, non-SGA=1; sex (female=1, male=2).
[f]Mean annual value.

in the size of body parts rather than of the body as a whole is a natural phenomenon known as "phenotypic flexibility" (32). In animals, phenotypic flexibility is defined as the reversible within-individual variation of the sizes of organ systems in relation to metabolic demand. The possibility of intraindividual phenotypic variation seems to be of evolutionary benefit for animals to survive and reproduce during seasonal or stochastic fluctuations of environmental conditions (32). Disproportionate short stature in humans is not confined to CKD but rather is seen in a variety of unrelated diseases, such as skeletal dysplasia, hypophosphatemic rickets, *SHOX* gene mutations, or chronic illness (*e.g.*, thalassemia major) (11,33–36). The theoretical basis for this was provided more than 50 years ago by Isabel Leitch (37), who used the cephalocaudal gradient in animal models to argue that malnutrition during childhood results in disproportionate stunting with preferential impairment of leg growth rather than trunk growth and preserved head growth. It was postulated that the body concentrates on the preservation of vital organs (head and thorax) at the expense of the less vital limbs (38). Consequently, relative leg length is increasingly used as a biomarker of childhood nutrition in epidemiologic studies (39–41).

Short adult height is associated with major shortcomings in social and work life in patients with CKD, such as lower level of education, a lower level of employment, and a lower chance of being married (8,42). Therefore, the observed regression of disproportionate stunting after KTx in patients with CKD seems to be of major importance with respect to psychosocial rehabilitation in this patient group and may have further implications as well. Severe growth failure (below the first percentile) in children with ESRD is associated with a 2-fold higher risk of death (7). Therefore, the beneficial effects of KTx on body growth may at least partly explain the reported lower mortality rates in children who have received a transplant children compared with those undergoing dialysis (43).

In conclusion, children with ESRD present with disproportionate stunting. In pediatric renal recipients a sustained increase in standardized leg length and total body height is observed from preschool until adult age, resulting in restoration of body proportions in most patients. The phenotypic flexibility of post-transplant linear growth was significantly associated with time after KTx, congenital CKD, steroid exposure, and metabolic control. Therefore, future trials should focus on the latter factors to improve long-term growth outcome in these patients.

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Disclosures

None.

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