Adult Height in Patients with Advanced CKD Requiring Renal Replacement Therapy during Childhood

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Summary

Background and objectives Growth and final height are of major concern in children with ESRD. This study sought to describe the distribution of adult height of patients who started renal replacement therapy (RRT) during childhood and to identify determinants of final height in a large cohort of RRT children.

Design, setting, participants, & measurements A total of 1612 patients from 20 European countries who started RRT before 19 years of age and reached final height between 1990 and 2011 were included. Linear regression analyses were performed to calculate adjusted mean final height SD score (SDS) and to investigate its potential determinants.

Results The median final height SDS was −1.65 (median of 168 cm in boys and 155 cm in girls). Fifty-five percent of patients attained an adult height within the normal range. Adjusted for age at start of RRT and primary renal diseases, final height increased significantly over time from −2.06 SDS in children who reached adulthood in 1990–1995 to −1.33 SDS among those reaching adulthood in 2006–2011. Older age at start of RRT, more recent period of start of RRT, cumulative percentage time on a functioning graft, and greater height SDS at initiation of RRT were independently associated with a higher final height SDS. Patients with congenital anomalies of the kidney and urinary tract and metabolic disorders had a lower final height than those with other primary renal diseases.

Conclusions Although final height remains suboptimal in children with ESRD, it has consistently improved over time.

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Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

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Introduction

Growth failure remains one of the major long-term challenges in the management of childhood-onset ESRD. Poor growth in children with ESRD is multifactorial and influenced by nutritional, metabolic, and hormonal alterations (1–3) and has been associated with an increased risk of hospitalization and death (4). Short stature has major consequences for quality of life and self-esteem; more than one third of young adults with childhood-onset ESRD report to be dissatisfied with their body height (5). Short adult height is associated with major shortcomings in social and work life such as a lower level of education, a lower level of employment and a lower chance of being married (6). Achieving a normal final height is therefore a crucial issue for children on renal replacement therapy (RRT). Improvements in the management of CKD-related growth failure have led to better height attainment at the time of renal transplantation but following transplantation, growth is generally not sufficient to compensate for the deficit that has been acquired before transplantation (7,8).

In children, height is reported in SD scores (SDS) from the general population. In recent years, several single-center reports have specifically addressed final height after transplantation in childhood (9–13). The proportion of patients who achieved a final height within the normal range ranged from 47% to 75%, which appears considerably improved over early reports in which normal adult height was achieved in only 23%–38% (14,15). Growth is a marker of quality of care in childhood CKD and ESRD. Through improvement in the management of children with kidney diseases over decades, growth failure and therefore adult short stature seem to be decreasing in this population. In this study, we used the population-based dataset of the European Society for Pediatric Nephrology/European Renal Association and European Dialysis and Transplant Association (ESPN/ERA-EDTA) registry to describe the final height distribution of patients who started RRT while in pediatric care in Europe, to analyze trends over time and to identify potential determinants of final height SDS.

Methods

Data Collection

This study used data recorded in the ESPN/ERA-EDTA Registry. Within the registry, clinical data are collected annually as reported elsewhere (16,17). Data obtained for the purpose of this study included date of birth, sex, primary renal disease, date of start of RRT, treatment modality (hemodialysis [HD], peritoneal dialysis [PD], or transplantation) and dates of change in treatment modality, donor source, height at start of RRT and at last follow-up. We included patients who started RRT at <19 years of age and reached documented final height between January 1, 1990, and December 31, 2011. This included data from the following 20 countries and periods of reaching final height: Belarus (2010), Czech Republic (2007–2010), Estonia (2010), Finland (1992–2009), France (2004–2010), Greece (2010–2011), Hungary (2010–2011), Iceland (2009), Italy (1990–2011), Lithuania (2010–2011), the Netherlands (2008–2009), Norway (2008–2010), Poland (1991–2011), Portugal (2008–2010), Serbia (1997–2011), Slovakia (2010), Slovenia (2010), Spain (1990–2011), Switzerland (1990–2009), and the United Kingdom (1992–2010).

Definition of Variables

Height SDS was calculated according to recent national growth charts whenever available (18–25), or to newly developed northern and southern European growth charts (26) for countries where recent growth reference data are unavailable. Height SDS values were calculated by the following equation:

$$SDS = (\textit{individual patient values} - \textit{mean values for age and sex - matched healthy peers}) / \textit{SDS values for age and sex - matched healthy peers}.$$

Growth retardation was defined by a height SDS < –1.88 (*i.e.*, the third percentile for height) and was categorized as moderate (–1.88 > SDS >–3.0) or severe (<–3.0 SDS). Final height was defined as the last height measurement available after 18 years of age, or, when not available, as the last height measurement when growth velocity per year was below 1 cm in boys >17 years old and girls >16 years old. Height at start of RRT was defined as first height available within 3 months after start of RRT or within 6 weeks for those who started RRT before 2 years of age.

To study the effect of height SDS change from start of RRT to final height measurement, we included only children with a potential for catch-up growth (*i.e.*, those <16 years old in this study). Time on RRT was defined as the time interval between start of RRT and either the last available height measurement or the age of 19, whichever occurred first. Renal diseases were grouped by primary renal disease code for pediatric patients, according to the ERA-EDTA Registry coding system (27).

Statistical Analyses

Patient characteristics are presented as median and interquartile range (IQR) for continuous variables and percentages for categorical variables. For comparison over time, only patients from countries with a complete follow-up of patients reaching final height over the last two decades were included.

Table 1. Demographic and clinical characteristics of the study population (*n*=1612)

Variable	Value
Sex	
Male	868 (53.8)
Female	744 (46.2)
Primary renal disease	
CAKUT	651 (40.4)
GN	288 (17.9)
Hereditary nephropathy	117 (7.3)
Cystic kidney disease	189 (11.7)
Hemolytic-uremic syndrome	48 (3.0)
Ischemic renal failure	22 (1.3)
Metabolic disorder	72 (4.5)
Vasculitis	54 (3.3)
Miscellaneous	93 (5.8)
Unknown or missing (12 missing)	78 (4.8)
Median age at start of RRT (yr)	12.8 (9.0–15.6)
Age at start of RRT	
0 to <2 yr	70 (4.3)
2 to <5 yr	98 (6.1)
5 to <13 yr	540 (33.5)
13 to <17 yr	713 (44.2)
≥ 17 yr	191 (11.9)
Median height SDS at start of RRT (*n*=915)	−1.56 (–2.75 to –0.44)
Treatment modality at start of RRT (33 missing)	
Hemodialysis	648 (41.1)
Peritoneal dialysis	654 (41.4)
Transplantation	277 (17.5)
Period of start of RRT	
<1990	224 (13.9)
1990–1999	693 (43.0)
2000–2011	695 (43.1)
Median age at time of final measurement (yr)	19.0 (18.1–20.0)
Number of RRT modalities	
1	418 (25.9)
2	685 (42.5)
≥3	509 (31.6)
Time on RRT at final height measurement	
0 to <2 yr	269 (16.7)
2 to <5 yr	422 (26.2)
5 to <10 yr	542 (33.6)
10 to <15 yr	260 (16.1)
≥15 yr	119 (7.4)
Median percentage of lifetime with functioning graft	15.9 (0.0–34.7)
Treatment modality at final height measurement (28 missing)	
Hemodialysis	272 (17.2)
Peritoneal dialysis	145 (9.1)
Transplantation	1167 (73.7)

Unless otherwise noted, values are number (%) of patients. Medians are accompanied by interquartile ranges. CAKUT, congenital anomalies of the kidney and urinary tract; RRT, renal replacement therapy; SDS SD score.

To investigate the relationship between final height SDS and potential determinants, univariable and multivariable linear regression analysis were used. Adjustments were made for possible confounders, which were chosen on the basis of *a priori* considerations and criteria for confounding (28). Adjusted mean final height SDS was recalculated using the distribution in all cases. Variables included in adjusted analyses were age at start of RRT (0 to <2 years, 2 to <5 years, 5 to <13 years, and ≥13 years), period of start of RRT by decade (<1990, 1990–1999, 2000–2010), country, sex, primary renal disease category, first modality of RRT (HD first, PD first or transplantation first), percentage of lifetime and on RRT time on transplantation, and height SDS at start of RRT. Statistical analyses were performed using SAS software, version 9.2.

Results

Baseline Characteristics

Data were obtained from 1612 children receiving RRT from 20 countries who reached adult height between 1990 and 2011. Median age at start of RRT was 12.8 years, 53.8% of patients were male, and median age at final height measurement was 19.0 years (Table 1). Congenital anomalies of the kidney and urinary tract (CAKUT) were the most frequent underlying disease (40.4%), followed by glomerulonephritides (17.9%). Similar proportions of children received PD (41.1%) and HD (41.4%) as initial RRT modality, whereas 17.5% started with a preemptive renal transplantation. Median time on RRT was 5.7 years (IQR, 2.9–9.4 years). At the time of final height measurement, 73.7% of patients had a functioning renal allograft, 17.2% were on HD, and 9.1% on PD (Table 1).

Final Height and Prevalence of Short Stature

Boys reached a median final height of 168 cm (IQR, 161–173 cm); median final height SDS was –1.57 (IQR, −2.56 to −0.81). Median final height in girls was 155 cm (IQR, 149–161 cm); median final height SDS for girls was –1.67 (IQR, −2.70 to −0.76). The difference between boys and girls was not significant (P=0.72). Overall, the median final height SDS was –1.65 (IQR, −2.64 to −0.78); 57.4% had attained an adult height within the normal range, whereas 23.5% exhibited moderate (−1.88 > SDS >−3.0) and 19.1% severe (<−3 SDS) adult height deficits. At the time of final height measurement, body mass index values were within the normal range in most patients, with a median of 21.2 (IQR, 19.2–24.0) in boys and 21.2 (IQR, 19.0–24.4) in girls.

Longitudinal Trends in Final Height

In the countries with complete follow-up information in the period 1990–2011 (n=981 patients), the overall proportion of patients with an adult height in the normal range rose from 49.6% in children who reached adulthood in 1990–1995 (median final height, −1.90 SDS) to 62.2% among those reaching adulthood in 2006–2011 (median final height, –1.41 SDS) (P=0.05) (Figure 1). Final height SDS improved significantly in both boys (from a median of –1.87 in 1990–1995 to −1.32 in 2006–2011) and girls (from a median of –2.15 in 1990–1995 to –1.67 in 2006–2011). The trend in final height change became more significant (from –2.06 in 1990–1995 to −1.33 SDS in 2006–2011) after adjustment for age at start of RRT and PRD.

Furthermore, the improvement over time became clearer when stratifying by age and period of start of RRT. Adjusted final height increased significantly from −1.93 SDS (IQR, −2.13 to −1.70) in children who started RRT before 1990, to −1.78 (IQR, −2.01 to −1.53) in children starting RRT in 1990–1999, and to −1.61 (IQR, −1.81 to −1.34) in those commencing RRT after 1999 (P<0.001) and the improvement in final height over time was seen within all categories of age at RRT start (Figure 2).

A height measurement at start of RRT was available for 566 patients (58%) in patients from countries with complete follow-up information. The adjusted height SDS change by year spent on RRT from start of RRT to final height measurement did not significantly differ by the period of

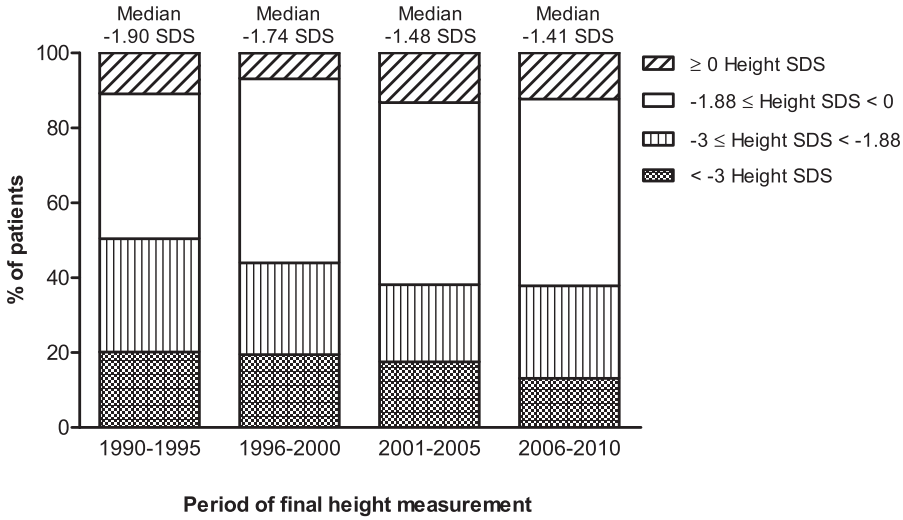

Figure 1. | Distribution of height SDS by period of reaching adulthood (n=1612). SDS, SD score.

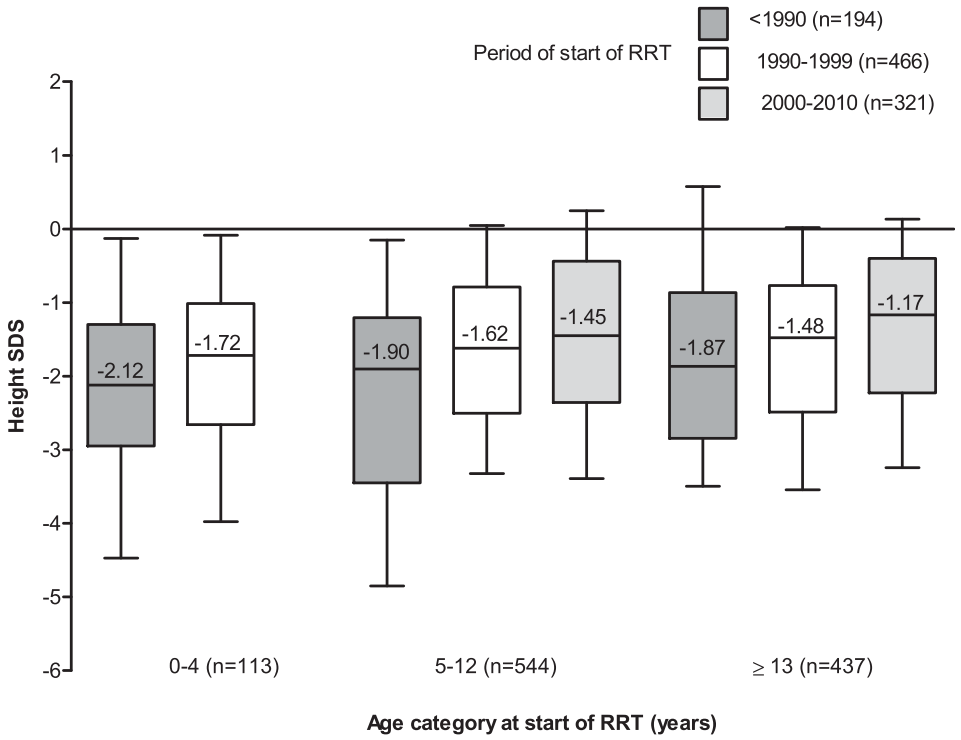

Figure 2. | **Changes in final height SD score (SDS) over time according to age and period of start of renal replacement therapy (RRT) (*n*=981).** The horizontal line in the middle of the box represents the median; the bottom and top of the box represent the lower and upper quartiles, respectively; and the ends of the whiskers represent the 10th and the 90th percentiles.

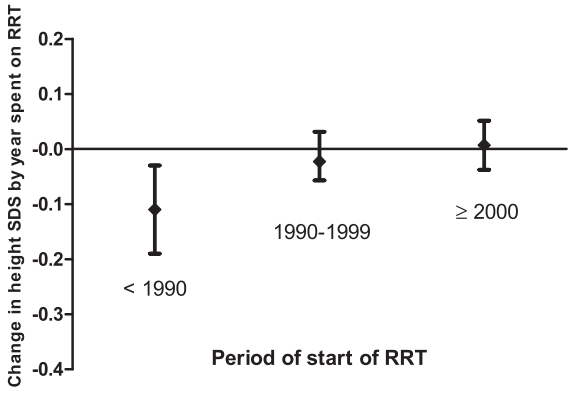

Figure 3. | **Mean yearly change in height SD score (SDS) from start of renal replacement therapy (RRT) to final height measurement by period of start of RRT (*n*=458).** In patients who started RRT at age <16 years, the change in height SDS between start of RRT and final height SDS significantly improved (*P*=0.02). Analyses were adjusted for age at start of RRT.

start of RRT. In the early period of RRT (before 1990), height SDS change was −0.04 per year on RRT (95% confidence interval [CI], −0.10 to 0.02 per year on RRT), whereas it was −0.11 per year on RRT (95% CI, −0.26 to −0.05 per year on RRT) in a more recent period of RRT (2001–2006). When we selected only patients who started RRT before 16 years of age (children with growth potential), there was a significant improvement over time in the change in height SDS from start of RRT to final height SDS (Figure 3). Although not significantly, height SDS at start of RRT improved over time; it was −1.65 in the early period of RRT and −1.32 upon starting RRT from 2001 to 2006 (*P*=0.37).

Factors Associated with Final Height

Older age at start of RRT (*i.e.*, children ≥13 years of age at start of RRT versus other age categories), a more recent period of start of RRT (2000–2010 and 1990–1999 versus before 1990), the percentages of lifetime on transplantation and RRT time on transplantation, and a higher height SDS at time of RRT start were independently associated with a significantly higher adjusted final height SDS (Tables 2 and 3). For 49.4% of the children commencing RRT before age 13 years, the final height SDS was below −1.88. Furthermore, after adjustment for sex, age, and period of start of RRT, patients with CAKUT were significantly shorter at final height than those with GN, cystic kidney diseases, hereditary nephropathy, hemolytic-uremic syndrome, vasculitis, and miscellaneous causes, while patients with metabolic disorders were significantly shorter than those with CAKUT (Table 2). In the subgroup of patients with cystinosis or oxalosis (*n*=66), the adjusted final height SDS was −2.54 (IQR, −2.91 to −2.16).

Preemptive transplantation as initial RRT modality was associated with a significantly better adult height SDS as compared with PD and HD, but after adjustment for time on transplantation no significant differences between initial treatment modalities were found (Table 2).

Table 2. Factors associated with final height SD score: categorical variables (*n*=1612)

Variable	Unadjusted		Adjusted	
	Mean Final Height SDS (95% CI)	*P* Value[a]	Mean Final Height SDS (95% CI)	*P* Value[a]
Sex				
Male	−1.80 (−1.91 to −1.70)	Reference	−1.79[b]	
Female	−1.77 (−1.92 to −1.62)	0.68	−1.79 (−1.93 to −1.64)[b]	0.94
Age at start of RRT				
≥17 yr	−1.49 (−1.60 to −1.39)	Reference	−1.48	Reference
13 to <17 yr	−1.55 (−1.79 to −1.30)	0.08	−1.60 (−1.85 to −1.35)[c]	0.33
5 to <13 yr	−2.03 (−2.27 to −1.78)	<0.001	−1.95 (−2.21 to −1.69)[c]	<0.001
2 to <5 yr	−2.26 (−2.63 to −1.89)	<0.001	−2.17 (−2.57 to −1.78)[c]	<0.001
0 to <2 yr	−2.16 (−2.58 to −1.75)	<0.001	−2.16 (−2.60 to −1.71)[c]	0.003
Period of start of RRT				
<1990	−2.40 (−2.60 to −2.20)	Reference	−2.17	Reference
1990–1999	−1.84 (−2.06 to −1.61)	<0.001	−1.76 (−1.99 to −1.53)[d]	<0.001
2000–2010	−1.54 (−1.86 to −1.32)	<0.001	−1.70 (−1.95 to −1.44)[d]	<0.001
Treatment at start of RRT				
Peritoneal dialysis	−1.91 (−2.02 to −1.79)	Reference	−1.86	
Hemodialysis	−1.73 (−1.89 to −1.56)	0.03	−1.81 (−1.99 to −1.62)[d]	0.52
Transplantation	−1.65 (−1.86 to −1.43)	0.02	−1.57 (−1.80 to −1.41)[e]	0.006
Primary renal disease				
CAKUT	−2.00 (−2.12 to −1.88)	Reference	−2.01	Reference
GN	−1.52 (−1.73 to −1.31)	<0.001	−1.56 (−1.77 to −1.36)[f]	<0.001
Hereditary nephropathy	−1.46 (−1.76 to −1.16)	<0.001	−1.30 (−1.60 to −1.01)[f]	<0.001
Cystic kidney disease	−1.75 (−2.00 to −1.51)	0.05	−1.70 (−1.95 to −1.46)[f]	0.01
Hemolytic-uremic syndrome	−1.41 (−1.86 to −0.96)	0.01	−1.28 (−1.72 to −0.84)[f]	0.001
Vasculitis	−1.19 (−1.61 to −0.77)	<0.001	−1.33 (−1.74 to −0.92)[f]	0.001
Metabolic disorder	−2.59 (−2.93 to −2.22)	0.002	−2.55 (−2.91 to −2.19)[f]	0.003
Miscellaneous	−1.59 (−1.89 to −1.29)	0.008	−1.61 (−1.90 to −1.31)[f]	0.008

SDS, SD score; CI, confidence interval; RRT, renal replacement therapy; CAKUT congenital anomalies of the kidney and urinary tract.
[a]Difference from reference population.
[b]Adjusted for age at start of RRT and period of RRT.
[c]Adjusted for period of RRT, sex, and primary renal disease.
[d]Adjusted for age at start of RRT and primary renal disease.
[e]Adjusted for age at start of RRT, period of RRT, sex, and primary renal disease.
[f]Adjusted for age at start of RRT, period of RRT, and sex.

Discussion

This Europe-wide adult height study, the first of its kind since early reports by the ERA-EDTA Registry (29), demonstrates the size of the problem of growth failure in children with ESRD. Around 50% of the children requiring RRT before their 13th birthday grew to a final height below the third percentile. A fifth of patients with childhood-onset ESRD attained an adult height more than 3 SDs below the mean, a degree of stunting highly likely to affect social integration and quality of life (5,6,30). These growth outcomes are in keeping with data of the NAPRTCS registry (8); the slightly better mean adult height SDS figures in the North American Registry (−1.46 versus −1.65 in this study) are largely explained by differences in the reference datasets (26), whereas absolute heights were almost identical to or even slightly better than those in the NAPRTCS (girls, 154 cm; boys, 166 cm) and our registry (girls, 155 cm; boys, 168 cm).

At first glance the analysis of longitudinal trends in height outcomes appears disappointing, with a global height gain of 0.49 SDS (*i.e.*, 2.5 cm) between the patients attaining adult height before 1995 and those who did after 2005. However, this modest improvement was clearly related to changes in population characteristics, as an increasing fraction of children with early-onset ESRD due to severe renal malformations or multisystem disease was admitted to pediatric RRT programs and survived to adulthood over time. Also, patients with congenital malformations and inherited metabolic disorders achieved a significantly smaller adult height than patients with disorders typically manifesting in later childhood. After adjustment for the age at RRT start and primary renal diagnosis, a more significant 0.73 SDS increase in adult height over time became apparent.

Multivariable analysis revealed several factors related to the timing and choice of RRT that appear critical for final height outcomes in childhood-onset ESRD. The most important predictor of an acceptable final height was a late need for RRT during the pediatric age. However, height SDS did not change significantly between onset of RRT and final measurement. The overall effect of RRT on final height was neutral throughout the observation period,

Table 3. Factors associated with final height SD score: continuous variables (*n*=1612)

Variable	Unadjusted		Adjusted	
	Mean Final Height SDS (95% CI)	*P* Value	Mean Final Height SDS (95% CI)	*P* Value
Height at start of RRT				
Per 1 SDS increase	0.38 (0.34 to 0.43)	<0.001	0.37 (0.32 to 0.41)[a]	<0.001
Percentage of lifetime RRT				
Per 10% increase	−0.09 (–0.12 to −0.06)	<0.001	0.04 (−0.01 to 0.09)[b]	0.11
Percentage of lifetime with functioning graft				
Per 10% increase	0.008 (–0.03– to 0.04)	0.64	0.19 (0.15 to 0.24)[b]	<0.001
Percentage of RRT time with functioning graft				
Per 10% increase	0.06 (0.04 to 0.08)	<0.001	0.10 (0.07 to 0.12)[b]	<0.001
Years with functioning graft				
Per additional year	0.004 (−0.01 to 0.02)	0.62	0.10 (0.08 to 0.12)[b]	<0.001
Percentage of RRT time on dialysis				
Per 10% increase	−0.06 (−0.08 to −−0.04)	<0.001	−0.10 (−0.12 to –0.08)[b]	<0.001
Years on dialysis				
Per additional year	−0.16 (−0.19 to −0.13)	<0.001	−0.14 (−0.17 to –0.11)[b]	<0.001

SDS, SD score; CI, confidence interval; RRT, renal replacement therapy.
[a]Adjusted for age at start of RRT, period of RRT, sex, and primary renal disease.
[b]Adjusted for age at start of RRT, period of RRT, sex, primary renal disease, and initial RRT modality.

among the overall population. Moreover, height at start of RRT increased by 0.4 SDS from the early period to the more recent years of starting RRT. This would suggest that the observed moderate improvement of final height over time was mainly due to better growth management during the pre-ESRD period and that any strategies to prevent or correct CKD-associated growth failure (31–34) are most likely to be effective before ESRD has occurred. However, when we analyzed only patients with a greater "growth potential" on RRT, namely only the patients <16 years of age at start of RRT, the change between height at start and final height measurement significantly improved over time (Figure 3). This finding that height SDS no longer declines after RRT also suggests overall improvement in the care of ESRD over the years.

Regarding the choice of RRT once required, the fraction of childhood lifetime spent on dialysis adversely predicted final height. This finding is consistent with reported longitudinal data on growth on dialysis demonstrating a decrease in height SDS over time (1,8), and the negative effect of the fractional lifetime spent on dialysis on adult height previously noted in patients receiving long-term recombinant human growth hormone (rhGH) therapy (34). Conversely, the time spent with a functioning allograft was positively associated with final height outcome.

In our study, no data on dose and duration of rhGH were available to estimate its effect on final height, but we found that only a small proportion of the population (approximately 20%) has been treated by rhGH while receiving RRT. Although previous reports suggested a positive effect of rhGH on final height in children with CKD (34,35) and support its use during RRT, it is noteworthy that the currently approved European indication for the drug is limited to patients undergoing dialysis and allograft recipients with impaired GFR.

Further research will be required to develop optimization strategies that will facilitate better growth outcomes in this challenging population.

This study has several limitations. The lack of detailed data on treatments such as steroids, supplemental feeding, and rhGH precluded an assessment of the relative effect of these therapies on final height. We also did not have sufficient information on ethnicity, syndromic short stature, or comorbid conditions that influence growth and final height (36), nor did we have data on pubertal status or mid-parental height. Also, one might imagine that children who died were more likely to be shorter than those who survived and reached final height (4). Finally, although adult height has been assessed at an average age of 19 years, some patients might not have reached their definite final height at last measurement. Indeed, delayed puberty has been associated with late growth after age 18 in children with ESRD (11,37). This finding, however, has not been reported in more recent studies reporting normal puberty after transplantation (38). The strengths of the study include the large data set; the long-term follow-up, including complete coverage of sequential RRT modalities; and the rather detailed patient characterization, all of which allow a comprehensive analysis of potential effectors of final height. Even if we cannot fully ascertain case completeness in the ESPN/ERA-EDTA Registry, most national registries have specific procedures ensuring data quality and coverage.

In conclusion, although more and more challenging pediatric patients have been accepted into RRT programs, including neonates and children with severe comorbid

conditions, final height has consistently improved over the years. New approaches are needed to improve longitudinal growth and adult height prognosis after childhood-onset ESRD.

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Disclosures

None.

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