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ORIGINAL ARTICLE

Normal adult height after steroid-withdrawal within 6 months of pediatric kidney transplantation: a 20 years single center experience

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Summary

Long-term corticosteroid treatment impairs growth in children after kidney transplantation (KTx). The impact of steroid withdrawal with respect to adult height remains to be elucidated. In this single-center retrospective analysis linear growth and graft function in 74 pediatric KTx patients transplanted between 1981 and 2001 was investigated. Mean follow up was 8.5 years. Steroids were weaned off between months 4 and 6. Steroid withdrawal resulted in sustained catch-up growth after KTx. Absolute and standardized height velocity in prepubertal patients during the first year post-KTx was 8.9 cm/year and +2.9 SD score (SDS), respectively ($P < 0.001$ versus healthy children). Mean adult height amounted to -0.5 ± 1.1 SDS and -1.0 ± 1.3 SDS in prepubertal and pubertal patients and was within the normal range (>−2 SD) in 94% and 80% of them. Multiple regression analysis revealed age and standardized height at KTx as independent predictors of adult height (model $r^2 = 0.48$). Overall graft survival at 5 and 10 years was 92% and 71%, respectively. Steroid withdrawal during month 4–6 after KTx in prepubertal patients results in an adult height within the normal range, whereas catch-up growth is limited in pubertal patients.

Introduction

Attainment of normal adult height remains to be a great challenge in the care of children with end-stage renal disease (ESRD). Young age at onset of ESRD, long duration of renal failure, male gender, and the presence of congenital nephropathies are the most relevant risk factors for attaining a poor final height [1,2]. Although many of the metabolic and endocrine disorders contributing to uremic growth failure are resolved by kidney transplantation (KTx), post-transplant catch-up growth is usually restricted to young children and occurs far from regularly. Apart from transplant function, age, and degree of stunting at time of transplantation as well as cumulative glucocorticoid intake are inversely associated with longitudinal growth [3,4].

Several uncontrolled single-center studies and three randomized trials evaluated the effects of decreasing glucocorticoid exposure or even complete avoidance in children [5–15]. Results are encouraging and provide evidence that the outcome with such an approach is quite comparable to standard steroid-containing protocols. A recent randomized trial on early steroid-withdrawal (day 5 post-KTx) in patients on IL-2 receptor antagonist induction (daclizumab), tacrolimus (Tac), mycophenolate mofetil (MMF), and steroids showed that height SD score (SDS) was significantly improved in steroid-free patients compared to controls, although the mean benefit was rather small (0.16 SDS within 6 months) [6]. In a randomized trial on *late steroid withdrawal* (>1 year post-KTx) in patients on concomitant treatment with cyclosporine A (CyA) and MMF, moderate catch-up growth

compared to controls was noted (i.e., change in height SDS; 0.6 ± 0.1 versus −0.2 ± 0.1 within 27 months) [7]. However, data on adult height after steroid withdrawal in pediatric KTx patients are lacking.

In 1981 we were one of the first centers to use CyA as the cornerstone of immunosuppression in pediatric KTx by taking part in an European multicenter study [16]. Encouraged by the excellent graft function and low rejection rates we established the general policy to wean-off corticosteroids in all children, except in those showing more than two rejection episodes within the first 3 months after KTx [17,18]. Later on, as other immunosuppressive medications such as Tac and MMF became available we kept this policy of steroid withdrawal. Here we report on our experience in a cohort of 74 pediatric KTx patients with respect to linear growth and adult height.

Material and methods

In this retrospective single-center analysis linear growth and graft function after steroid-withdrawal in pediatric patients transplanted between January 1981 and January 2001 at the ''Abteilung für Transplantationschirurgie, Klinikum Großhadern, Ludwig-Maximilians-Universität'' and the ''Chirurgische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität'' (both Munich, Germany) is investigated. During this period, a total of 106 pediatric KTx in 92 patients were performed. Patients older than 17 years of age at time of KTx ($n = 5$), those experiencing early graft loss caused by surgical (vascular) complications within the first week after KTx ($n = 6$), and those requiring long-term steroid treatment caused by frequent rejections, that is, more than two rejections during the first 3 months ($n = 7$), were excluded. Thus, a total of 74 of 81 patients were successfully weaned-off steroids within the first 6 months post-KTx and were eligible for analysis of growth and graft survival (Table 1). All patients were under the supervision of Bernd Klare, MD and data were censored at the time of his retirement (December 2003). The mean age at time of KTx was 10.3 ± 4.0 years with a mean follow up of 8.5 years. Primary renal diseases were uropathy/renal dys- or hypoplasia ($n = 24$), glomerular diseases ($n = 29$), hereditary nephropathy ($n = 12$), and others ($n = 9$). Height was measured at least every 2 months post-KTx. For calculation of age- and gender-related SDS for height and height velocity (SDS values) the first Zurich Longitudinal Study was used as a reference [19]. Final (adult) height was defined as a height increment of < 1 cm/year in the preceding year in patients aged above 16 years. Boys and girls with Tanner stage ≥2 were defined as pubertal.

Table 1. Patient characteristics.

Number of patients	74
Number of grafts	75
1/2 grafts	74/1
Donor type: deceased/living	71/4
Gender	47 male/27 female
Age at KTx (years)	10.3 ± 4.0 (range 1.9–16.9)
Pubertal status (at time of KTx)	50 prepubertal (30 male/20 female)
	24 pubertal (17 male/7 female)
Height (cm)	
Prepubertal	117.9 ± 17.4
Pubertal	151.4 ± 12.6
Height (SDS)	
Prepubertal	−2.3 ± 1.2
Pubertal	−1.7 ± 1.5
Transplant period	
1981–1995	35
1996–2001	39
Follow up (years)	8.5 ± 5.2 (range 1.4–20.8)

Immunosuppression

The immunosuppressive protocol changed during the 20-year period. However, prednisolone was an invariant part of either immunosuppressive regimen during the first 3 months after KTx. Prednisolone was started with 300 mg/m^2 i.v. during transplantation procedure, followed by 60 mg/m^2/day p.o., and was continuously tapered down until a dosage of 4 mg/m^2/day was achieved at the end of month 3. In patients with mild-moderate immunological risk, that is, showing less than three rejection episodes within this interval and stable graft function, prednisolone was weaned off during month 4–6 by three-weekly dose reductions of 1 mg. In patients with previous graft loss induction therapy with ATG or ALG was given. Apart from this, immunosuppressive therapy was based on CyA only during March 1981 and July 1984. Thereafter, azathioprine (Aza; 3 mg/kg/day) was added. Since 1996 patients received MMF (1.200 mg/m^2/day) instead of Aza in combination with either CyA or Tac. MMF was reduced if leucopenia (<2.5 × 10^6/ml) or gastrointestinal side effects occurred. CyA was started at a dosage of 15 mg/kg/day* to achieve blood through levels (monoclonal assay) of 200–250 ng/ml (month 1–3), and 180 ng/ml (month 4–5). Thereafter, CyA dosage was gradually tapered down until month 12 in order to achieve blood through levels of 80–100 ng/ml. Tac was started at a dosage of 0.03 mg/kg/day i.v. on day 1 and continued orally in order to achieve blood through levels of 10–12 ng/ml (month 1–3), 5–10 ng/ml (month 4–12), and 3–7 (>12 months), respectively.

*i.v. on day 1 and continued orally from day 4 in order.

Overall steroids could be weaned off in 74/81 (91%) patients (50 prepubertal, 24 pubertal). In 7/81 KTx (9%) steroids could not be stopped, caused by frequent rejections (>2 within first 3 months after KTx). Biopsy proven rejection episodes were treated by methylprednisolone pulses (10 mg/kg/day for 3 days, followed by 5 mg/kg/day for 3 days), and CyA/Tac dosages were adapted in order to achieve trough levels of 200–250 ng/ml (CyA) and 10 ng/ml (Tac) for at least 4 weeks, respectively. In patients responding to rejection treatment steroids were weaned off again in case of less than three rejections during the first 18 months post-KTx. If necessary antihypertensive treatment was given to achieve blood pressure values between the 50- and 75-percentile for age of healthy children. None of the patients received previous treatment with recombinant human growth hormone (rhGH).

Statistics

The SPSS software package, version 18.0 (SPSS GmbH, Munich, Germany) was used for processing and statistical analysis of all data. Data are given as mean ± SD if not indicated otherwise. Actuarial survival rates were calculated according to Kaplan and Meier. To appreciate for the significant changes in the immunosuppressive protocols renal survival rates were calculated for two transplant periods separately (before and after 1996, i.e., introduction of MMF at our center). Between-group differences were assessed by Mantel's log-rank test for censored survival data. Intra- and interindividual differences for anthropometric data were calculated by paired *t*-test or Wilcoxon-test, respectively. Univariate linear regression analysis was employed to investigate age, gender, height, and pubertal status at the time of KTx, underlying renal disease, and GFR at 12 months post-KTx as predictors of standardized adult height. Variables associated with adult height with $P < 0.1$ on univariate analysis (height SDS and age at time of KTx, and GFR at 12 months post-KTx) were entered into the multiple regression model. All *P*-values are two-sided, and $P < 0.05$ was considered to be significant.

Results

Patients

The impact of steroid withdrawal during months 4–6 after KTx on linear growth and graft function in pediatric patients transplanted at our institution between January 1981 and January 2001 was analyzed. In all patients lacking early graft loss caused by surgical/vascular complications and experiencing less than three rejection episodes within the first 3 months post-KTx steroids were weaned off. This was successfully performed in 74/81 (91%) patients (Table 1). The overall patient-survival was 100% and 98.9% at 10 and 20 years, respectively. One female patient died secondary to lung edema at the age of 23 years while being back on hemodialysis. She was previously transferred to an adult center after loss of her fifth transplant because of noncompliance. One patient developed EBV driven post-transplant lymphoproliferative disease, which was successfully treated by anti-CD 20 antibody.

Linear growth in prepubertal patients

Steroid-withdrawal resulted in sustained catch-up growth in all prepubertal patients and persisted up-to 10 years post-KTx (Fig. 1a and b). The mean absolute and standardized height velocity during the first year post-KTx was 8.9 ± 2.0 cm and 2.9 ± 2.1 SDS, respectively (each $P < 0.001$ versus healthy children). For example, standardized height increased from −3.1 SDS to −0.5 SDS and from −0.9 SDS to 1.9 SDS at last observation in a 10-year-old boy and 6-year old girl, respectively (arrows in Fig. 1). Overall mean standardized height was increased from −2.3 ± 1.2 SDS to −0.7 ± 1.2 SDS at last observation ($P < 0.01$). Mean adult height amounted to 173.6 ± 6.3 cm and 162.4 ± 7.7 cm in boys and girls, respectively. Mean standardized adult height was −0.5 ± 1.1 SDS ($P < 0.001$ vs. baseline; Fig. 1c) and was in the normal range (>−2 SDS) in 34 of 36 patients (94%). Data on genetic target height were available for 27 patients and final height was within the predicted target height interval (± 10 cm) in 23 (85%) patients (Fig. 1d). In all except one male patient serum creatinine levels were below 2 mg/dl at final height. This boy showed a tremendous catch-up growth (first year height velocity, 14.2 cm/year at the age of 5.5 years) and a slight increase in serum creatinine concentration from 1.6 to 2.4 mg/dl during pubertal growth spurt.

Linear growth in pubertal patients

In pubertal patients, being weaned from steroids standardized height was increased from −1.7 ± 1.4 SDS at the time of KTx to −1.0 ± 1.3 SDS at final height ($P < 0.01$; $n = 26$, Fig. 1c). Mean final height amounted to 168.4 ± 8.7 cm and 162.1 ± 5.8 cm in male and female patients, respectively. Adult height was in the normal range (>−2 SD) and within the predicted target height interval (± 10 cm) in 77% and 79%, respectively (Fig. 1d).

Predictors of final adult height

In the univariate regression analysis, adult height was significantly correlated with standardized height ($r = 0.53$, $P < 0.01$) and age ($r = -0.30$, $P < 0.05$) at time of KTx,

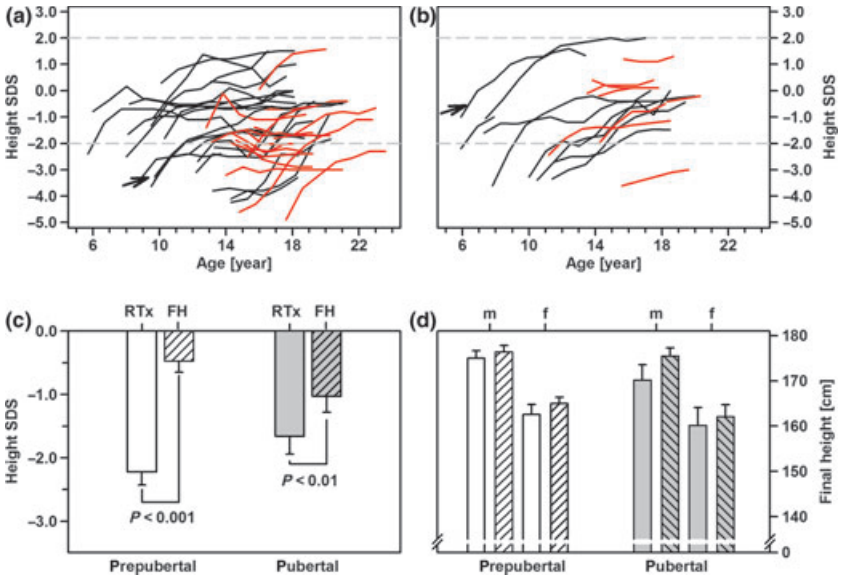

Figure 1 Individual growth-curves, mean standardized height at time of KTx compared to adult height and comparison of adult height with genetic target heigt in patients with steroid-withdrawal during month 4–6 post-KTx. Growth-curves from male (a) and female (b) prepubertal (black lines) and pubertal (red lines) KTx patients with steroid-withdrawal and at least 2 yearly height measurements during the observation period are shown. Catch-up growth was observed in all patients and persisted up-to 10 years post-KTx. The arrows indicate representative growth curves of a 10- and 6-year-old boy and girl, respectively. (c) Mean standardized height at the time of KTx and final height in prepubertal (n = 36) and pubertal (n = 24) patients. (d) Mean adult height (open bars) and genetic target height (hatched bars) in boys (n = 25) and girls (n = 17), respectively. Data in (c) and (d) are given as mean ± SEM.

Table 2. Predictors of adult height: multiple regression analysis.

	Unstandardized coefficients			
	Beta	Standard error	*P*	Adjusted R^2
Constant	1.686	0.38	<0.001	0.48
Height SDS*	0.545	0.09	<0.001	
Age*	–0.117	0.03	<0.001	

*at time of KTx.

and the transplantation period ($r = 0.30$; $P < 0.05$), whereas GFR at 1 year post-KTx was of borderline significance ($r = 0.25$; $P = 0.09$). Multiple linear regression analysis revealed standardized height and age at the time of KTx as independent predictors of final height explaining together 48% of the overall variability (Table 2). In contrast, gender, pubertal stage, underlying renal disease, transplant period, and GFR at 12 months were no independent correlates and thus were excluded from the final model.

Graft survival and acute rejection episodes

The overall graft survival in first kidney graft recipients was 92%, 71%, and 57% at 5, 10, and 15 years, respectively (Fig. 2). Comparing the renal graft survival rates at

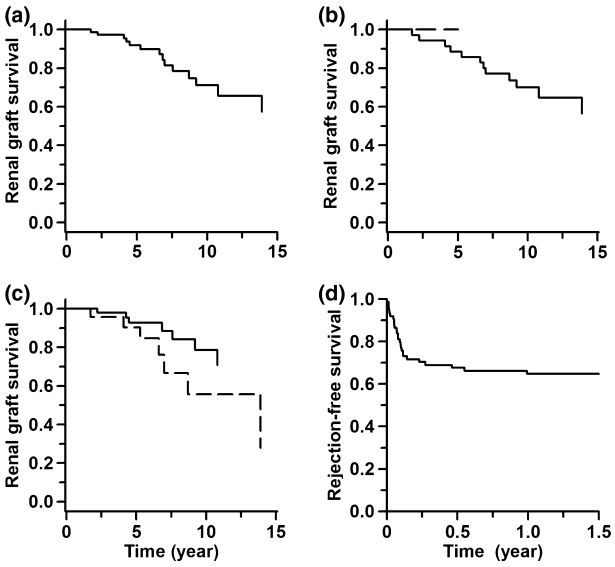

Figure 2 Probability of renal graft survival and rejection episodes in first transplant recipients with steroid withdrawal. (a) All first grafts (n = 74; (b) Patients in transplant periods 1981–1995 (solid line; n = 35) and 1996–2001 (dashed line; n = 39; $P > 0.05$). (c) Prepubertal (solid line; n = 50) versus pubertal patients (dashed line; n = 24; $P > 0.05$). (d) Acute rejection episodes during 18 months post-KTx occurred in 35% of patients.

5 years with respect to the transplantation period (1996–2001 vs. 1981–1995) revealed a slight but not significant improvement over time (95.5% vs. 88.6%, $P > 0.05$). Renal graft survival tended to be better in prepubertal compared to pubertal patients (5 years, 93% vs. 90%; 10 years, 79% vs. 56%, $P = 0.07$). During the first 18 months post-KTx acute rejection episodes occurred in 35% of patients being weaned off steroids (Fig. 2). During follow up late rejections occurred in 7 (10%) of patients (all Banff I) and all rejections were sensitive to corticosteroids. Overall, renal graft survival tended to be better in patients without ($n = 48$) compared to those with ($n = 26$) previous acute rejections episodes before steroid-withdrawal (5 years, 98% vs. 88%; 10 years, 81% vs. 53%, 15 years, 60% vs. 53%; each $P > 0.05$). In addition, the incidence of acute rejection episodes after steroid withdrawal appeared to be lower in those on Tac/MMF compared to CyA/Aza (21% vs. 38%, $P > 0.05$).

Discussion

In this single-center study we could demonstrate that steroid-withdrawal within 6 months post-KTx in pediatric patients results in continuous catch-up growth and an adult height within the normal range in the majority of patients. Although complete catch-up growth was observed in almost all patients being prepubertal at time of KTx, incomplete catch-up was seen in 20% of pubertal patients. Within the whole patient population, age and standardized height at KTx together explained 48% of the overall variability of adult height.

This retrospective single-center analysis was not directed to assess the efficacy and safety of a specified steroid-sparing protocol in pediatric KTx patients. Instead, we want to report our experience with strict steroid-withdrawal in parallel to the evolution of immunosuppressive therapy during the last 30 years. Indeed, patients in the early 80s were started on CyA and prednisolone treatment, only. Since 1984, Aza was added and replaced by MMF in the mid-90s. From 1997 onwards Tac instead of CyA was increasingly used as the main immunosuppressive agent. In our center, monoclonal or polyclonal antibodies were only given in patients with a history of graft loss but not in first KTx recipients. Only one patient developed EBV driven PTLD and this was successfully treated by rituximab.

The overall renal graft survival in first kidney graft recipients was 92%, 71%, and 57% at 5, 10, and 15 years, respectively and thus well comparable to that in steroid-containing standard immunosuppressive protocols used during comparable time periods [20,21]. In line with previous studies renal outcome improved over time, tended to be better in patients with concomitant MMF or Tac treatment and was poorer in adolescent patients. The latter seems mainly to be related to reduced compliance with drug medication in this particular age group [22].

The efficacy of steroid withdrawal with respect to attainment of an adult height within the normal range was striking. The mean cumulative increase in standardized height in prepubertal patients amounted to 1.6 SDS and almost all children (94%) attained a normal adult height. NAPRTCS data indicate that final height in pediatric KTx patients improved during the past 2 decades. However, this is mainly related to preservation of growth during the pre-transplant period rather than post-transplant catch-up growth [2]. In the pre-transplant period both, ensuring adequate caloric intake in infants with congenital CKD and/or long-term treatment with rhGH are proven measures to achieve normal adult height [1]. However, the overall height benefit related to the 5-year period of rhGH treatment in short CKD patients amounted to approximately 1.2 SDS, which is obviously less than what has been observed in the present study [23,24]. Long-term rhGH treatment is rather costly (approximately 35.000$ per year in a child weighing 30 kg) and failed to normalize height in about one-third of patients [24]. However, in most studies rhGH was initiated when severe stunting has already occurred (i.e., height <−3.5 SDS). In contrast, our patients presented with a lower degree of stunting at the time of KTx (height SDS, −2.2 SDS) and this certainly has also contributed to the superior outcome. Indeed, multiple regression analysis revealed standardized height at the time of KTx as the most important predictor of adult height. This highlights once again that all efforts (e.g., enteric feeding, rhGH treatment) should be undertaken to prevent severe growth retardation already in the pre-transplant period.

In older (pubertal) patients incomplete catch-up growth despite excellent graft function was observed in 20% of patients. This observation is in line with previous studies reporting a decrease of the potential for catch-up growth with increasing age [25]. Furthermore, even short-term steroid exposure might result in permanent growth deficit. In fact, animal experiments revealed incomplete catch-up growth secondary to transient local application of glucocorticoids to the tibial growth plate [26,27]. Thus, for attainment of normal adult height complete steroid avoidance may be more effective compared to steroid-withdrawal within the first 6 months post-KTx.

Pubertal patients are at a higher risk for (late) graft loss and obviously benefit less from steroid-withdrawal compared to younger children. Therefore, in adolescent patients the potential of steroid-withdrawal has to be balanced with the increased risk for non-compliance to the immunosuppressive regimen [22].

Our study is limited because of its retrospective non-randomized design. We report on our 20-year single-center experience following the general policy to wean-off steroids in all patients experiencing less than three rejection episodes within the first 3 months post-KTx. This was successfully performed in all 74 patients. However, we have to confess that this approach was rather courageous in the 80s and early 90s when potent immunosuppressive drugs like MMF and Tac were not available. Therefore, prospective randomized studies using modern immunosuppressive protocols are required to confirm the safety and efficacy of steroid withdrawal with respect to long-term graft survival and attainment of a normal adult height.

In conclusion, we have shown that steroid withdrawal within 6 months post-KTx was possible even at the beginning of pediatric KTx and resulted in normal adult height in the vast majority of patients. However, catch-up growth is limited in pubertal patients. Therefore, adequate measures to prevent severe stunting at the time of KTx are of outmost importance. Prospective studies utilizing newer immunosuppressive protocols are warranted to elucidate the long-term efficacy and safety of complete steroid avoidance in children suffering from ESRD.

Authorship

BK, CM, and MS: collected the data and contributed to writing the paper. DF and DH: were responsible for data analysis and writing the paper.

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References

1. Haffner D, Nissel R. Growth and puberty in chronic kidney disease. In: Geary DF, Schaefer F, eds. *Comprehensive Pediatric Nephrology*. Philadelphia: Mosby Elsevier, 2008: 709–32.
2. Fine RN, Martz K, Stablein D. What have 20 years of data from the North American Pediatric Renal Transplant Cooperative Study taught us about growth following renal transplantation in infants, children, and adolescents with end-stage renal disease? *Pediatr Nephrol* 2010; **25**: 739.
3. Tejani A, Fine R, Alexander S, Harmon W, Stablein D. Factors predictive of sustained growth in children after renal transplantation. The North American Pediatric Renal Transplant Cooperative Study. *J Pediatr* 1993; **122**: 397.
4. Nissel R, Brazda I, Feneberg R, *et al.* Effect of renal transplantation in childhood on longitudinal growth and adult height. *Kidney Int* 2004; **66**: 792.
5. Benfield MR, Bartosh S, Ikle D, *et al.* A randomized double-blind, placebo controlled trial of steroid withdrawal after pediatric renal transplantation. *Am J Transplant* 2010; **10**: 81.
6. Grenda R, Watson A, Trompeter R, *et al.* A randomized trial to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study. *Am J Transplant* 2010; **10**: 828.
7. Höcker B, Weber LT, Feneberg R, *et al.* Improved growth and cardiovascular risk after late steroid withdrawal: 2-year results of a prospective, randomised trial in paediatric renal transplantation. *Nephrol Dial Transplant* 2010; **25**: 617.
8. Delucchi A, Valenzuela M, Ferrario M, *et al.* Early steroid withdrawal in pediatric renal transplant on newer immunosuppressive drugs. *Pediatr Transplant* 2007; **11**: 743.
9. Ellis D. Growth and renal function after steroid-free tacrolimus-based immunosuppression in children with renal transplants. *Pediatr Nephrol* 2000; **14**: 689.
10. Hamiwka LA, Burns A, Bell L. Prednisone withdrawal in pediatric kidney transplant recipients on tacrolimus-based immunosuppression: four-year data. *Pediatr Transplant* 2006; **10**: 337.
11. Li L, Chang A, Naesens M, *et al.* Steroid-free immunosuppression since 1999: 129 pediatric renal transplants with sustained graft and patient benefits. *Am J Transplant* 2009; **9**: 1362.
12. Pape L, Lehner F, Blume C, Ahlenstiel T. Pediatric kidney transplantation followed by de novo therapy with everolimus, low-dose cyclosporine A, and steroid elimination: 3-year data. *Transplantation* 2011; **92**: 658.
13. Shapiro R, Ellis D, Tan HP, *et al.* Antilymphoid antibody preconditioning and tacrolimus monotherapy for pediatric kidney transplantation. *J Pediatr* 2006; **148**: 813.
14. Knight JF, Roy LP, Sheil AG. Catch-up growth in children with successful renal transplants immunosuppressed with cyclosporin alone. *Lancet* 1985; **1**: 159.
15. Tejani A, Butt KM, Khawar MR, *et al.* Cyclosporine experience in renal transplantation in children. *Kidney Int Suppl* 1986; **19**: S38.
16. Cyclosporin in cadaveric renal transplantation: one-year follow-up of a multicentre trial. *Lancet* 1983; **2**: 986.
17. Klare B, von Walter J, Hahn H, Emmrich P, Land W. Cyclosporin in renal transplantation in children. *Lancet* 1984; **2**: 692.
18. Klare B, Strom TM, Hahn H, *et al.* Remarkable long-term prognosis and excellent growth in kidney-transplant children under cyclosporine monotherapy. *Transplant Proc* 1991; **23**: 1013.
19. Prader A, Largo RH, Molinari L, Issler C. Physical growth of Swiss children from birth to 20 years of age. First Zurich longitudinal study of growth and development. *Helv Paediatr Acta Suppl* 1989; **52**: 1.

20. North American Pediatric Renal Trials and Collaborative Studies Report 2010. (https://web.emmes.com/study/ped/annlrept/2010_Report.pdf). Accessed on December 5, 2011.
21. Jungraithmayr TC, Wiesmayr S, Staskewitz A, *et al.* Five-year outcome in pediatric patients with mycophenolate mofetil-based renal transplantation. *Transplantation* 2007; **83**: 900.
22. Smith JM, Ho PL, McDonald RA. Renal transplant outcomes in adolescents: a report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Transplant* 2002; **6**: 493.
23. Haffner D, Schaefer F, Nissel R, Wuhl E, Tonshoff B, Mehls O. Effect of growth hormone treatment on the adult height of children with chronic renal failure. German Study Group for growth hormone. Treatment in chronic renal failure. *N Engl J Med* 2000; **343**: 923.
24. Nissel R, Lindberg A, Mehls O, Haffner D. Factors predicting the near-final height in growth hormone-treated children and adolescents with chronic kidney disease. *J Clin Endocrinol Metab* 2008; **93**: 1359.
25. Haffner D, Wuhl E, Schaefer F, Nissel R, Tonshoff B, Mehls O. Factors predictive of the short- and long-term efficacy of growth hormone treatment in prepubertal children with chronic renal failure. The German Study Group for growth hormone treatment in chronic renal failure. *J Am Soc Nephrol: JASN.* 1998; **9**: 1899.
26. Baron J, Klein KO, Colli MJ, *et al.* Catch-up growth after glucocorticoid excess: a mechanism intrinsic to the growth plate. *Endocrinology* 1994; **135**: 1367.
27. Gafni RI, Baron J. Catch-up growth: possible mechanisms. *Pediatr Nephrol* 2000; **14**: 616.