Final adult height in kidney recipients who underwent highly successful transplantation as children: a single-center experience

Clin Exp Nephrol
DOI 10.1007/s10157-013-0842-4

ORIGINAL ARTICLE

Final adult height in kidney recipients who underwent highly successful transplantation as children: a single-center experience

Hiroshi Fujii · Hiroko Chikamoto · Yuko Akioka · Motoshi Hattori

Received: 22 April 2013 / Accepted: 3 July 2013

Abstract
Background Achieving a normal final adult height (FH) remains a challenge in the field of pediatric kidney transplantation (KTx). To examine the optimal approach to assuring normal FH following KTx, we retrospectively examined the post-transplant growth and FH of pediatric KTx recipients.
Methods Since the relevant factors affecting the FH of children following KTx are multifactorial and notably complex, KTx recipients with persistent good graft function and successful steroid minimization until FH attainment were selected for this study.
Results Thirteen patients were enrolled in this study. The mean estimated glomerular filtration rate was 72.1 ± 15.3 ml/min/1.73 m^2, and the mean corticosteroid dose was 0.05 ± 0.05 mg/kg on alternate days at the time of FH attainment. Despite highly successful KTx, four (30.8 %) patients (one who underwent KTx before puberty and three during puberty) showed a decrease in the height standard deviation score (hSDS) from the time of KTx until FH attainment. Moreover, of these, two male patients had an FH with an SD <−2.
Conclusion FH remained suboptimal despite highly successful KTx. Not only highly successful KTx but also further treatment such as steroid avoidance, early steroid withdrawal or using rhGH might be necessary to assure a normal FH in some pubertal patients.

Keywords Kidney transplantation · Children · Final adult height

Introduction

Growth retardation is a major clinical problem in children with chronic kidney disease [1]. An inadequate final adult height (FH) has been associated with an unmarried status, lower level of education and lower level of employment in adults who underwent transplantation during childhood [2]. Since growth retardation persists in magnitude despite kidney transplantation (KTx) [3], achieving a normal FH remains a challenge in the field of pediatric KTx [4].

Suboptimal growth following KTx is caused by multiple factors, the main ones being reduced graft function, corticosteroid treatment and age at KTx [3]. A reduced glomerular filtration rate (GFR) (<50 ml/min/1.73 m^2) for an extended period of time has been shown to have a significantly negative effect on FH [5], while corticosteroid treatment on alternate days (0.5 mg/kg per alternate day) reportedly has a salutary effect on growth [6]. The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) data indicated no significant change in the height standard deviation score for chronological age (hSDS) following KTx in the age groups 6–12 and >13 years [7]. In addition, a preexisting height deficit at the time of KTx [5] and reduced pubertal height gain [8] have been shown to be associated with an inadequate FH.

Since the relevant factors affecting the FH of children following KTx are multifactorial [1, 3], here we retrospectively examined the FH in KTx recipients who showed

H. Fujii
Department of Pediatrics, Koseiren Hiroshima General Hospital, 1-3-3 Zigozen, Hatsukaichi-shi, Hiroshima 738-8503, Japan

H. Chikamoto · Y. Akioka · M. Hattori (✉)
Department of Pediatric Nephrology, Tokyo Women's Medical University, School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan
e-mail: hattori@kc.twmu.ac.jp

Published online: 18 July 2013

persistent good graft function and successful steroid minimization prior to achieving FH in order to examine the optimal approach to assuring a normal FH in pediatric KTx recipients.

Patients and methods

Patients

Between January 1996 and December 2005, 94 patients under the age of 15 years received a renal allograft for the first time at the Department of Pediatric Nephrology, Tokyo Women's Medical University. Of these, 42 patients reached their FH by January 2010. In order to examine the sole effects of KTx on growth, patients ($n = 15$) with co-morbidities such as syndromal disorders that would impair growth were excluded from the present study. Patients ($n = 10$) with reduced graft function and/or failed steroid minimization were also excluded. Additionally, growth data could not be fully collected for four patients. As a result, a total of 13 patients were enrolled in this study. All 13 had persistent good graft function with successful steroid minimization until attaining their FH. Good graft function was defined as GFR >50 ml/min/ 1.73 m^2 based on a previous report [5]. All 13 patients enrolled in this study received minimal-dose corticosteroid therapy on alternate days (<0.5 mg/kg on alternate days) [6] from 10 to 12 weeks after KTx. The present study was approved by the local institutional review board (approval no.: 1003), and written informed consent was obtained from all patients.

Immunosuppression regimens

Nine patients who underwent transplantation before May 2002 received a triple immunosuppression regimen consisting of cyclosporine A (CSA) or tacrolimus (FK), mizoribine (MZ) or mycophenolate mofetil (MMF), and corticosteroid. Subsequently, four patients received induction therapy with basiliximab combined with the above triple regimen. CSA/FK and MZ/MMF were started 2 days before transplantation, and dosage adjustments of CSA and FK were based on trough whole blood levels as previously reported [9].

Corticosteroid was tapered to a dose of 0.5 mg/kg/day by 4 weeks post-transplantation. Over the next 4 weeks, the dose was further reduced by 0.25 mg/kg/day and then converted to a dose of 0.5 mg/kg on alternate days by 10 to 12 weeks post-transplantation. Following this, the dose was gradually reduced on alternate days, with some patients being completely weaned during the follow-up period at the judgment of the attending doctor.

Methods

Height values are expressed as hSDS compared with Japanese reference data [10]. FH was defined as a height velocity <1 cm/year for at least 1 year and radiographic epiphyseal closure. Genetic target height was calculated as mid-parental height +6.5 cm for males and −6.5 cm for females [10]. Onset of puberty was defined as achievement of Tanner stage 2. Bone age was evaluated using the Japanese version of the Tanner-Whitehouse 2 method [11]. Estimated GFR was determined using the Schwartz formula [12].

Statistical analysis

Data are presented as the mean ± SD and range, unless otherwise indicated. Bivariate associations were assessed with the use of Fisher's exact test or Student's t test; only two-tailed P values are reported. Simple linear regression analysis was also performed. $P < 0.05$ was considered statistically significant. Excel 2010 (Microsoft, Tokyo, Japan) was used for data analysis.

Results

Clinical data

Clinical data of the 13 study patients (6 males, 7 females) are summarized in Table 1. Primary kidney disease was congenital disorder in 9 children (hypoplastic kidney, $n = 5$; juvenile nephronophthisis, $n = 2$; reflux nephropathy, $n = 1$; and Alport's syndrome, $n = 1$) and acquired disease in 4 children (focal segmental glomerulosclerosis, $n = 1$; ANCA-associated nephritis, $n = 1$; membranous nephropathy, $n = 1$; unknown, $n = 1$). Mean age at the start of renal replacement therapy was 9.1 ± 3.6 years. Ten patients received peritoneal dialysis (PD) and 3 underwent pre-emptive KTx (PKTx). Mean duration of dialysis therapy was 2.8 ± 3.0 years, and mean age at KTx including PKTx was 12.0 ± 2.4 years. The deceased/living-related donor ratio was 2/11. Six patients received recombinant human growth hormone (rhGH) therapy before KTx, but none did so after KTx.

Mean eGFR was 86.8 ± 12.3 ml/min/1.73 m^2 at 1 year after KTx and 72.1 ± 15.3 ml/min/1.73 m^2 at the time of FH attainment. Mean dose of corticosteroid was 0.10 ± 0.06 mg/kg on alternate days at 1 year after KTx and 0.05 ± 0.05 mg/kg on alternate days at the time of FH attainment. Additionally, 5 of the 13 patients were weaned off corticosteroid after a mean period of 1.8 ± 0.5 years (range: 1.0–3.0 years) after KTx. By chance, all these 5 patients had undergone transplantation before puberty. Mean hSDS at the start of PD and at the time of KTx including PKTx were −1.6 ± 0.8 SDS and −1.4 ± 0.7 SDS, respectively.

Table 1 Clinical data of the 13 study patients

Sex (*n*) (%)	
Male	6 (46)
Primary kidney disease (*n*) (%)	
Congenital	9 (69)
Age at the start of RRT (years)	9.1 ± 3.6 (4.1–14.9)
PKTx (*n*) (%)	3 (23)
Duration of dialysis therapy (years)	2.8 ± 3.0 (0.5–10.5)
Age at KTx (years)	12.0 ± 2.4 (8.8–14.9)
Type of donor (*n*) (%)	
Living-related	11 (85)
Growth hormone before KTx (n) (%)	6 (46)
eGFR (ml/min/1.73 m^2)	
1 year after KTx	86.8 ± 12.3 (67.8–112.9)
At FH attainment	72.1 ± 15.3 (51.0–104.1)
Dose of corticosteroid (mg/kg on alternate days)	
1 year after KTx	0.10 ± 0.06
At FH attainment	0.05 ± 0.05
Steroid withdrawal (*n*) (%)	5 (38)
hSDS at start of PD	−1.6 ± 0.8 (−2.6–−0.5)
hSDS at KTx	−1.4 ± 0.7 (−2.5–−0.2)

Values are expressed as the number of patients (percentage) or mean ± SD (range) unless otherwise noted

RRT renal replacement therapy, *PKTx* pre-emptive kidney transplantation, *KTx* kidney transplantation, *eGFR* estimated glomerular filtration rate, *FH* final adult height, *hSDS* height standard deviation score, *PD* peritoneal dialysis

FH

FH was reached at 17.2 ± 1.2 (15.9–19.0) years in males and 16.5 ± 0.7 (15.1–17.2) years in females. FH data of the 13 study patients are shown in Table 2. Mean hSDS of the 13 patients on reaching their FH was −0.9 ± 1.0 SDS. Mean FH (cm) and mean hSDS at FH were 163.6 ± 6.8 cm and −1.2 ± 1.2 SDS in males and 154.5 ± 4.2 cm and −0.7 ± 0.8 SDS in females, respectively. The FH was 6.1 ± 2.3 cm below the target height in males and 2.4 ± 2.3 cm below the target height in females. Two males out of the total 13 patients (15.4 %) showed an FH with an SD <−2, whereas there were no differences in their parents' heights between the 2 males and the remaining 11 patients.

Although there was no statistical significance ($r = 0.38$, $P = 0.20$), a correlation was observed between hSDS at KTx and hSDS at FH (data not shown).

Growth data of patients who underwent transplantation before or during puberty

Seven patients (3 males, 4 females) underwent transplantation before puberty and 6 (3 males, 3 females) underwent transplantation during puberty. Figure 1 shows individual hSDS values at the time of KTx and at the time of FH attainment in patients following transplantation before ($n = 7$) and during puberty ($n = 6$). Improved hSDS was seen in 6 of 7 patients who underwent KTx before puberty and catch-up growth, defined by hSDS >+1 [5], was seen in 3 patients (one male, 2 females). On the other hand, no catch-up growth was seen in the 6 patients who underwent transplantation during puberty.

Four (30.8 %) patients (one who underwent transplantation before puberty and three during puberty) showed a decrease in hSDS from the time of KTx until FH attainment, as indicated by the dashed line in Fig. 1. All four patients had persistent good graft function (mean eGFR at the time of FH attainment: 75.8 ± 10.1 ml/min/1.73 m^2) and received a minimum corticosteroid dose (mean corticosteroid dose at the time of FH attainment: 0.04 ± 0.04 mg/kg on alternate days); of these, one patient (indicated by an arrow) discontinued steroid therapy 1 year after KTx.

Despite optimum graft function (eGFR at the time of FH attainment: 80.0 ml/min/1.73 m^2), successful steroid withdrawal 1 year after KTx and normal pubertal development, the growth curve of one male patient showed insufficient pubertal growth and subsequently an inadequate FH, 16.6 cm below his target height (Fig. 1 arrow, Fig. 2).

Discussion

To examine the optimal approach to assuring a normal FH following KTx, we retrospectively examined post-transplant growth and FH of KTx recipients within our

Table 2 Final adult height of the 13 study patients

	Total ($n = 13$)	Males ($n = 6$)	Females ($n = 7$)
FH (cm)	158.7 ± 7.1 (148.7–170.0)	163.6 ± 6.8 (152.7–170.0)	154.5 ± 4.2 (148.7–161.4)
hSDS at FH	−0.9 ± 1.0 (−3.1–0.6)	−1.2 ± 1.2 (−3.1–−0.1)	−0.7 ± 0.8 (−1.8–0.6)
Target height (cm)	164.0 ± 7.7 (154.0–176.0)	169.6 ± 5.0 (161.9–176.0)	156.9 ± 2.1 (154.0–158.5)

Values are expressed as the mean ± SD (range) unless otherwise noted

FH final adult height, *hSDS* height standard deviation score

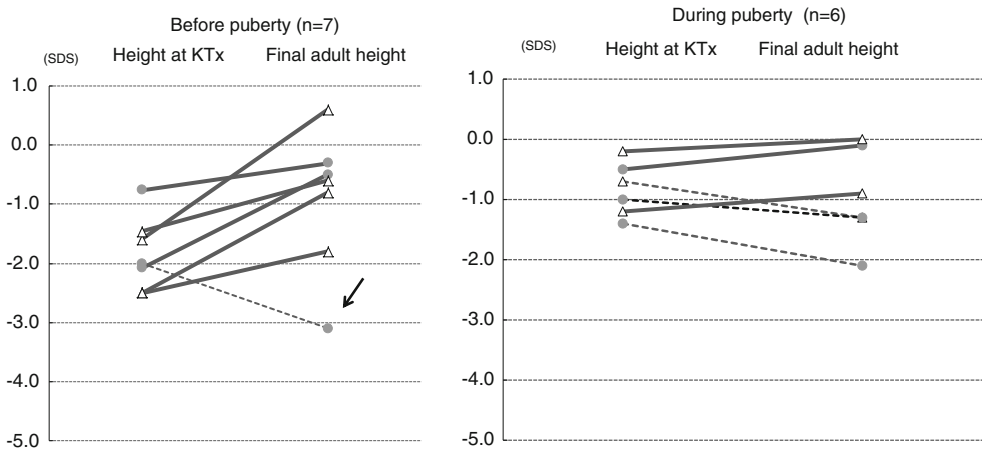

Fig. 1 Changes in height standard deviation score (hSDS) from the time of kidney transplantation (KTx) until attainment of FH. Changes in the individual hSDS of patients who underwent transplantation before puberty (*left panels*) and during puberty (*right panels*) are shown. Males and females are indicated by *solid circles* and *open triangles*, respectively. Patients showing a decrease of hSDS are shown as a *dashed line*

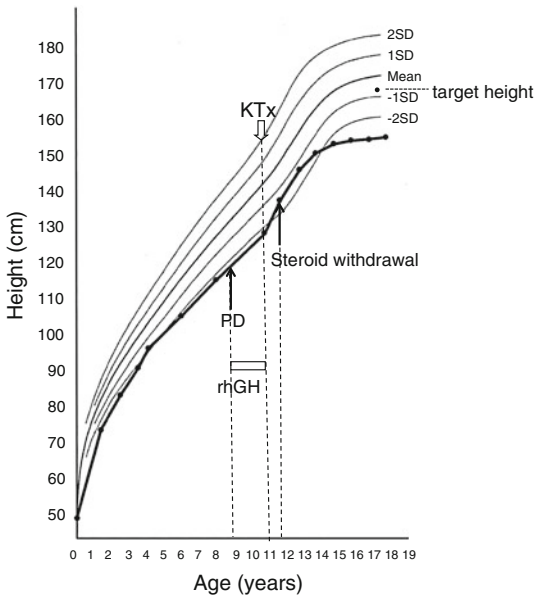

Fig. 2 Growth curve of a male patient before and after kidney transplantation (KTx). The patient received a kidney allograft at age 11 years. Following KTx he showed accelerated growth for 2 years. However, despite optimum graft function (eGFR: 80.0 ml/min/1.73 m^2), successful steroid withdrawal 1 year after KTx and normal pubertal development, the patient's growth velocity was insufficient to provide an adequate growth spurt during puberty. As a result, his FH was 16.6 cm below target height. *PD* peritoneal dialysis, *rhGH* recombinant human growth hormone

department. Since the relevant factors affecting the FH of children following KTx are multifactorial [1, 3], 13 patients who showed persistent good graft function and successful steroid minimization prior to achieving FH were selected for this study. The NAPRTCS reported that GFR >60 ml/min/ 1.73 m^2 is required to maintain normal growth [7]. Among our patients, the mean eGFR was 72.1 ± 15.3 ml/min/1.73 m^2 at the time of FH attainment. Although the precise growth-suppressing dose of corticosteroid has not been definitively delineated [13], a maintenance dose of 0.1 mg/kg on alternate days has been shown to result in good post-transplant growth and FH [14]. In our patients, the mean dose of corticosteroid was 0.05 ± 0.05 mg/kg on alternate days at the time of FH attainment. Thus, all patients enrolled in this study underwent highly successful KTx and reached their FH. On the other hand, the number of enrolled patients resulted in a small sample size because of the above-mentioned entry criteria in this study.

Despite highly successful KTx, 4 (30.8 %) patients showed a decrease in hSDS from the time of KTx until FH attainment. Moreover, of these, 2 male patients had an FH with an SD <−2.

Several factors influence pubertal growth after KTx [8], in which a significant negative correlation has been shown between peak height velocity during puberty and prednisolone dosage after KTx [15]. Maxwell et al. [16] reported that significant catch-up growth can occur after KTx even in children of pubertal age; the authors speculated that this significant pubertal growth may be related to early introduction of a low-dose, alternate-day steroid regimen. In contrast, Klare et al. [17] reported that steroid withdrawal in pubertal patients during the 4–6 months after KTx resulted in incomplete pubertal growth despite excellent graft function and suggested that even short-term steroid exposure might result in a permanent growth deficit.

The steroid-tapering regimen employed in our department is similar to that reported by Maxwell et al. [16]. Moreover, compared to Maxwell et al. [16], the maintenance dose of steroid was smaller among our patients (0.05 ± 0.05 mg/kg on alternate days in this study vs. 0.21 mg/kg on alternate days in the Maxwell et al. study). However, in the present study, no catch-up growth was seen among the 6 patients who underwent transplantation during puberty; moreover, 3 patients showed a decrease in hSDS from the time of KTx until FH attainment. Given this

result and considering recent reports [18–20], attainment of a normal FH might require early steroid withdrawal (≤7 days) or complete steroid avoidance in children who undergo transplantation during puberty.

On the other hand, an alternative approach to treating suboptimal pubertal growth in patients who undergo transplantation during puberty might be the use of rhGH. It has been suggested that rhGH can be considered in pubertal recipients in order to maximize the pubertal growth spurt [13]. Although no patients were treated with rhGH after KTx in this study, rhGH therapy might be an effective option in pubertal patients not qualifying for steroid avoidance or early steroid withdrawal [21].

In the present study, an increase in hSDS was observed in 6 of the 7 patients who underwent transplantation before puberty. Additionally, catch-up growth was seen in 3 patients who underwent late steroid withdrawal (1 year after KTx). These results are in line with those of previous reports [22, 23].

However, one male patient who underwent transplantation before puberty showed a highly inadequate FH, despite persistent good graft function and successful late steroid withdrawal. Although delayed onset of puberty in KTx patients reportedly results in an eventual loss of height potential [8], no delay in pubertal onset was observed in this patient, as shown previously [24]. In addition, no acceleration in bone maturation was noted in this patient. Hokken-Koelega et al. [25] and Fine used rhGH therapy in KTx recipients during puberty and found that rhGH increased the increment in height [3]. Therefore, appropriate use of rhGH is an additional key point in attaining a normal FH in pubertal children following KTx [13].

Finally, a preexisting height deficit at the time of KTx is reportedly associated with an inadequate FH [5]. In the present study, 4 patients (30.8 %) did not attain FH within the predicted target height interval; one of these was due to a preexisting height deficit at the time of KTx. Therefore, efforts to avoid a height deficit before KTx are also essential in attaining a normal FH in children following KTx [4, 13].

In conclusion, the FH observed here remained suboptimal despite highly successful KTx. Not only highly successful KTx, but also further treatment such as steroid avoidance, early steroid withdrawal or using rhGH might be necessary to assure a normal FH in some pubertal patients. Further studies are required to verify these approaches to treating suboptimal pubertal growth.

Acknowledgments The authors gratefully acknowledge Drs. Masataka Hisano, Kiyonobu Ishizuka and Noriko Sugawara, Department of Pediatric Nephrology, Tokyo Women's Medical University, for providing care for these patients.

Conflict of interest The authors have declared that no conflict of interest exists.

References

1. Harambat J, Cochat P. Growth after renal transplantation. Pediatr Nephrol. 2009;24:1297–306.
2. Broyer M, Le Bihan C, Charbit M, Guest G, Tête MJ, Gagnadoux MF, Niaudet P. Long-term social outcome of children after kidney transplantation. Transplantation. 2004;77:1033–7.
3. Fine RN. Management of growth retardation in pediatric recipients of renal allografts. Nat Clin Pract Nephrol. 2007;3:318–24.
4. Cochat P, Harambat J. Maximizing growth in children after renal transplantation. Transplantation. 2009;88:1321–2.
5. Hokken-Koelega AC, van Zaal MA, van Bergen W, de Ridder MA, Stijnen T, Wolff ED, de Jong RC, Donckerwolcke RA, de Muinck Keizer-Schrama SM, Drop SL. Final height and its predictive factors after renal transplantation in childhood. Pediatr Res. 1994;36:323–8.
6. Broyer M, Guest G, Gagnadoux MF. Growth rate in children receiving alternate day corticosteroid treatment after kidney transplantation. J Pediatr. 1992;120:721–5.
7. 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;25:739–46.
8. Nissel R, Brázda I, Feneberg R, Wigger M, Greiner C, Querfeld U, Haffner D. Effect of renal transplantation in childhood on longitudinal growth and adult height. Kidney Int. 2004;66:792–800.
9. Hattori M, Akioka Y, Chikamoto H, Kobayashi N, Tsuchiya K, Shimizu M, Kagami S, Tsukaguchi H. Increase of integrin-linked kinase activity in cultured podocytes upon stimulation with plasma from patients with recurrent FSGS. Am J Transplant. 2008;8:1550–6.
10. Suwa S, Tachibana K, Maesaka H, Tanaka T, Yokoya S. Longitudinal standards for height and height velocity for Japanese children from birth to maturity. Clin Pediatr Endocrinol. 1992;1:5–13.
11. Murata M. Japanese specific bone age standard on the TW 2. Clin Pediatr Endocrinol. 1993;2(Suppl 3):35–41.
12. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987;34:571–90.
13. Fine RN. Etiology and treatment of growth retardation in children with chronic kidney disease and end-stage renal disease: a historical perspective. Pediatr Nephrol. 2010;25:725–32.
14. Englund MS, Tydén G, Wikstad I, Berg UB. Growth impairment at renal transplantation: a determinant of growth and final height. Pediatr Transplant. 2003;7:192–9.
15. Schaefer F, Seidel C, Binding A, Gasser T, Largo RH, Prader A, Schärer K. Pubertal growth in chronic renal failure. Pediatr Res. 1990;28:5–10.
16. Maxwell H, Haffner D, Rees L. Catch-up growth occurs after renal transplantation in children of pubertal age. J Pediatr. 1998;133:435–44.
17. Klare B, Montoya CR, Fisher DC, Stangl MJ, Haffner D. Normal adult height after steroid-withdrawal within 6 months of pediatric kidney transplantation: a 20 years single center experience. Transplant Int. 2012;25:276–82.

18. Delucchi Á, Valenzuela M, Lillo AM, Guerrero JL, Cano F, Azocar M, Zambrano P, Salas P, Pinto V, Ferrario M, Rodriguez J, Cavada G. Early steroid withdrawal in pediatric renal transplant: five years of follow-up. Pediatr Nephrol. 2011;26:2235–44.
19. Grenda R, Watoson A, Trompeter R, Tönshoff B, Jaray J, Fitzpatrick M, Murer L, Vondrak K, Maxwell H, van Damme -Lombaerts R, Loirat C, Mor E, Cochat P, Milford DV, Brown M, Webb NJ. A randomized trial to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: The TWIST study. Am J Transplant. 2010;10:828–36.
20. Li L, Chang A, Naesens M, Kambham N, Waskerwitz J, Martin J, Wong C, Alexander S, Grimm P, Concepcion W, Salvatierra O, Sarwal MM. Steroid-free immunosuppression since 1999: 129 pediatric renal transplants with sustained graft and patients benefits. Am J Transplant. 2009;9:1362–72.
21. Grenda R. Effects of steroid avoidance and novel protocols on growth in paediatric renal transplant patients. Pediatr Nephrol. 2010;25:747–52.
22. Höcker B, Weber LT, Feneberg R, Drube J, John U, Fehrenbach H, Pohl M, Zimmering M, Fründ S, Klaus G, Wühl E, Tönshoff B. Prospective, randomized trial on late steroid withdrawal in pediatric renal transplant recipients under cyclosporine micro emulsion and mycophenolate mofetil. Transplantation. 2009; 87:934–41.
23. Motoyama O, Hasegawa A, Aikawa A, Shishido S, Honda M, Tsuzuki K, Kinukawa T, Hattori M, Ogawa O, Yanagihara T, Saito K, Takahashi K, Oshima S. Final height in a prospective trial of late steroid withdrawal after pediatric renal transplantation treated with cyclosporine and mizoribine. Pediatr Transplant. 2012;16:78–82.
24. Tainio J, Qvist E, Vehmas R, Jahnukainen K, Hölttä T, Valta H, Jahnukainen T, Jalanko H. Pubertal development is normal in adolescents after renal transplantation in childhood. Transplantation. 2011;92:404–9.
25. Hokken-Koelega AC, Stijnen T, de Ridder MA, de Muinck Keizer-Schrama SM, Wolff ED, de Jong MC, Donckerwolcke RA, Groothoff JW, Blum WF, Drop SL. Growth hormone treatment in growth-retarded adolescents after renal transplantation. Lancet. 1994;343:1313–7.