Transpl Int (1998) 11 [Suppl 1]: S69–S72

L. Ghio
D. Colombo
A. Edefonti
M. Picca
S. Loi
M. R. Grassi
F. Marchesi
B. Damiani
G. Oppizzi

Short-term anabolic effects of recombinant human growth hormone in young patients with a renal transplant

L. Ghio (✉) · D. Colombo · A. Edefonti · M. Picca · S. Loi · M. R. Grassi · F. Marchesi · B. Damiani
Nephrology Dialysis and Transplantation Unit, 2nd Department of Pediatrics, University of Milan, via Commenda 9, I-20122 Milan, Italy
Tel. +39-2-57992471; Fax +39-2-57992451

G. Oppizzi
Endocrinology, Ospedale Niguarda, piazza Ospedale Maggiore 3, Milan, Italy

Abstract Renal-transplanted children may present stunted growth, negative nitrogen balance (Nb), and alterations in body composition. Recombinant human growth hormone (rhGH) is a potent anabolic agent which improves nutritional status and Nb. In renal-transplanted children, rhGH increases growth velocity but its effect on nutritional status has not been reported. We evaluated the effect of 6 months of rhGH treatment on Nb, urea nitrogen appearance (UNA), anthropometric indexes, and growth velocity in 14 pediatric patients with a renal transplant. Nb improved significantly ($P = 0.02$) and was accompanied by a decrease of UNA. A significant improvement was observed also in mid-arm muscle circumference ($P = 0.002$), arm muscle are ($P = 0.001$), and arm fat are ($P = 0.017$). Growth velocity increased in prepubertal patients ($P = 0.003$). Creatinine clearance and the number of rejection episodes were not affected by rhGH treatment. In conclusion, short-term administration of rhGH improves Nb and UNA as well as the main indexes of body composition.

Key words Recombinant human growth hormone · Renal transplantation · Children · Nitrogen balance · Body composition

Introduction

The persistence of growth retardation after successful renal transplantation is a serious problem for many pediatric allograft recipients. These patients may also be characterized by alterations in body composition, with a negative nitrogen balance (Nb), abnormal plasma and muscle amino acid pattern, decreased muscle mass, and increased fat mass [8, 16, 17, 23, 26]. Multiple factors may cause these changes, such as hormonal and metabolic alterations, corticosteroid treatment, and inadequate nutrient intake [18, 21, 23].

Recombinant human growth hormone (rhGH) is a drug capable of enhancing protein synthesis and decreasing protein degradation [3], and of improving Nb and body composition in growth hormone deficiency and in various catabolic states such as severe burns, sepsis, post-operative conditions, chronic lung disease, and total parenteral nutrition [4, 12, 24]. Horber and Haymond [7] found that, in healthy volunteers, rhGH may have a definite role in preventing the protein loss associated with the administration of pharmacological doses of glucocorticosteroids. Other studies on the use of rhGH in adult uremic patients have reported decreased urea nitrogen appearance (UNA) and protein catabolic rate as well as an improvement of Nb in chronic hemodialysis and peritoneal dialysis patients [10, 11, 27].

Although the beneficial effect of rhGH on growth in uremic and kidney-transplanted pediatric patients has been clearly demonstrated [9, 15], its influence on body composition and Nb in such patients needs validation. This study was designed to evaluate the short-term effects and safety of rhGH on Nb, body composition, and statural growth in pediatric patients with renal transplant.

Materials and methods

Fourteen pediatric patients, ten male and four female, with a functioning renal transplant participated in the study. Their mean age at the beginning of rhGH treatment was 13.4 ± 2.3 years, with a post-transplant follow up of 4.4 ± 2.2 years. Nine patients were prepubertal and five pubertal. They were on immunosuppressive therapy with cyclosporine A (5.99 ± 1.56 mg/kg per day) and methylprednisolone (0.17 ± 0.07 mg/kg per day).

The patients were selected for rhGH treatment on the basis of the following criteria: growth retardation defined as height standard deviation score < − 2 and/or height velocity < 25 th percentile for chronological age; a functioning renal transplant for at least 12 months, with stable function for at least 6 months; the first sign of puberty in pubertal patients not more than 1 year previously; no clinical or biochemical signs of endocrine diseases or malignancy; no previous anabolic or sex steroid treatment.

The patients were treated with rhGH 30 IU/m^2 of body surface area/week in daily subcutaneous administration for 6 months. Informed consent was obtained from the parents for each patient prior to their entry into the study.

At baseline and after 6 months of rhGH treatment, the following indexes were determined: Nb, UNA, protein and calorie intakes, body composition, and height velocity. The Nb study period lasted for 3 days. Nb was defined as nitrogen intake minus UNA minus non-urea nitrogen output. Nb was calculated by a dietitian on the basis of a 3-day diary kept by the parents. UNA was defined as the sum of urinary urea nitrogen and the change in body urea nitrogen, and non-urea nitrogen excretion as the sum of fecal nitrogen plus the difference between total urinary nitrogen and urinary urea nitrogen. Urine and feces were collected over 3 consecutive days. Urines were analyzed for nitrogen, urea, and creatinine. Nitrogen content in urine and feces was measured by the Kjeldhal method [1, 13, 14]. Nb was not adjusted for unmeasured losses in the skin, respiration, flatus, and blood samples. No patients had any infection, proteinuria or graft rejection at the time of the study. Height was measured with a Harpender stadiometer and height velocity was expressed as centimeters per 6 months. Weight was expressed as body mass index (BMI) [6]. Muscle mass and body fat reserve were evaluated as mid-arm muscle circumference (MAMC), arm muscle area (AMA), and arm fat area (AFA) [5]. The anthropometric indexes were expressed as SD score for chronological age.

Renal transplant function was evaluated by creatinine clearance, calculated according to Schwartz et al. [19], and episodes of rejection were recorded.

Pubertal stage was determined according to Tanner and Whitehouse [20].

Results are expressed as mean ± SD. Statistical analysis as carried out using Student's t-test. A P value < 0.05 was considered significant.

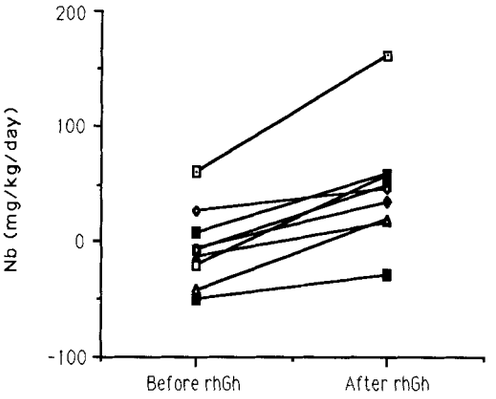

Fig. 1 Nitrogen balance *(Nb)* in individual pediatric patients with renal transplant before and after recombinant human growth hormone *(rhGH)* treatment

Table 1 Urea nitrogen appearance *(UNA)*, UNA/N intake, and nitrogen balance *(Nb)*/N intake in pediatric patients with renal transplantation before and after recombinant human growth hormone *(rhGH)* treatment. Values are mean ± SD

Nitrogen parameter	Before rhGH	After rhGH	*P*
UNA (mg/kg per day)	214.1 ± 52.8	190 ± 73.2	0.06
UNA/N intake	0.89 ± 0.15	0.70 ± 0.13	0.0001
Nb/N intake	− 0.047 ± 0.14	0.140 ± 0.13	0.0001

Table 2 Body composition and growth velocity in pediatric patients with renal transplant before and after recombinant human growth hormone *(rhGH)* treatment. Values are mean ± SD (*SDS* standard deviation score, *n.s.* not significant)

Parameter	Before rhGH	After rhGH	*P*
Mid-arm muscle circumference SDS	− 1.08 ± 0.70	− 0.83 ± 0.77	0.002
Arm muscle area SDS	− 1.19 ± 0.64	− 0.89 ± 0.66	0.001
Arm fat area SDS	− 0.41 ± 0.71	− 0.76 ± 0.35	0.017
Body mass index SDS	− 0.42 ± 1.40	− 0.46 ± 1.24	n.s.
Growth velocity (cm/6 months)			
Prepubertal	0.96 ± 0.73	2.92 ± 1.25	0.003
Pubertal	1.59 ± 1.08	1.44 ± 1.09	n.s.

Results

All children completed the study.

Nb, evaluated in nine patients, improved significantly after 6 months of rhGH treatment from − 5.6 ± 51.1 to 45.7 ± 51.1 mg/kg per day (P = 0.0231). The improvement of Nb (Fig. 1) occurred in all patients, and negative Nb before rhGH became positive after 6 months of therapy except in one patient in whom Nb improved, although it remained negative. Daily protein intakes, estimated by diet diaries, increased slightly during the treatment period (1.55 ± 0.37 versus 1.73 ± 0.64 g/kg per day), as did daily calorie intake (41 ± 9 versus 47 ± 16 kcal/kg per day); these changes were not significant.

During the treatment period, UNA values fell but not significantly, and there was a significant improvement in the ratios between UNA and nitrogen intake and between Nb and nitrogen intake (Table 1). As reported in Table 2, MAMC, AMA, and AFA all showed

a significant increase and mean height velocity improved significantly in the prepubertal children although not in the pubertal ones. No significant changes of BMI occurred during the study. No child progressed to puberty on rhGH treatment.

Mean calculated creatinine clearance did not vary significantly in the 6 months of the study (52.27 ± 13.50 versus 54.69 ± 15.13 ml/min per 1.73 m^2). None of the patients had an acute injection episode during the study. The subcutaneous injections were well tolerated and no clinically evident adverse side effects were observed.

Discussion

Renal transplantation in childhood is often characterized by alterations in nutritional status including stunted growth, decreased muscle mass, increased fat mass, abnormal plasma and muscle amino acid pattern, and negative Nb [8, 16, 17, 23, 26].

rhGH treatment exerts a favorable effect on protein turnover in catabolic patients with normal renal function [4, 7, 12, 24] as well as in adult uremic patients [10, 11, 27]. In pediatric patients with renal transplant, rhGH improves growth velocity [9, 15] but knowledge of its effect on nutritional status, particularly on Nb, is incomplete. The present study revealed that short-term rhGH treatment induces a significant improvement in Nb and body composition in such patients as well as in growth velocity in prepubertal ones. The improvement in Nb occurred in all our patients and values became positive in all but one.

The anabolic effect of rhGH treatment is confirmed by the observation of a decrease in UNA and the ratio between UNA and nitrogen intake, both indexes of protein catabolism, and an increase in the ratio between Nb and nitrogen intake, an index of net protein utilization [25], with a slight increase of protein intake. These findings, not described so far in patients with renal transplant, are consistent with the previously demonstrated effect of rhGH in catabolic patients with normal and impaired renal function [4,7, 8, 11, 12, 24, 27].

The change in Nb was accompanied by a significant improvement of both muscle and fat mass, as shown by increases in MAMC and AMA and a decrease in AFA. These findings are in line with the few available studies on children with renal transplants [2, 21].

As already reported in children after renal transplantation [9], growth was stimulated significantly by rhGH treatment but only in our prepubertal patients, in whom height velocity was doubled. Growth did not improve in our pubertal patients. Height improvement has been observed in growth-retarded adolescents after renal transplantation [9] but a less consistent effect was reported by other authors [22].

We did not observe graft rejection or deterioration of creatinine clearance during the 6 months of rhGH treatment but this period was relatively short.

In conclusion, in pediatric patients with renal transplant, short-term rhGH therapy not only induces an improvement of growth but also has an anabolic effect and may also improve nutritional status.

Acknowledgements We thank Alix Green for editorial assistance.

References

1. Campbell WR, Hanna I (1937) The determination of nitrogen by modified Kjeldhal methods. J Biol Chem 119: 1–9
2. Cochat P, Braillon P, Feber J, Hadj-Aissa A, Dubourg L, Liponski I, Said MH, Glastre C, Meunier PJ, David L (1996) Body composition in children with renal disease: use of dual energy X-ray absorptiometry. Pediatr Nephrol 10: 264–268
3. Davidson M (1987) Effect of growth hormone on carbohydrate and lipid metabolism. Endocrinol Rev 8: 115–131
4. Douglas R, Humberstone D, Haystead A, Shaw J (1990) Metabolic effects of growth hormone: isotopic studies in the postabsorptive state and during total parenteral nutrition. Br J Surg 77: 785–790
5. Frisancho AR (1981) New norms of upper limb fat and muscle area for assessment of nutritional status. Am J Clin Nutr 34: 2540–2545
6. Hammer LD, Kraemer HC, Wilson DM, Ritter PL, Dornbush SM (1991) Standardized percentile curves of body mass index for children and adolescents. Am J Dis Child 145: 259–265
7. Horber F, Haymond M (1990) Human growth hormone prevents protein catabolic side effects of prednisone in humans. J Clin Invest 86: 265–272
8. Hoy WE, Sargent JA, Hal D, McKenna BA, Pabico RC, Freeman RB, Yarger JM, Byer BM (1985) Protein catabolism during the postoperative course after renal transplantation. Am J Kidney Dis 5: 186–190
9. Ingulli E, Tejani A (1995) An analytical review of growth hormone studies in children after renal tansplantation. Pediatr Nephrol 9: S61–65
10. Izikler TA, Wingard RL, Breyer JA, Schulman G, Parker RA, Hakim RM (1994) Short-term effects of recombinant human growth hormone in CAPD patients. Kidney Int 46: 1178–1183
11. Kang DH, Lee SW, Kang SW (1994) Recombinant human growth hormone improved nutritional status of undernourished adult CAPD patients. J Am Soc Nephrol 5: 494–499
12. Kaplan S (1993) The newer uses of growth hormone in adults. Adv Intern Med 38: 287–301
13. Kopple JD, Monteon FJ, Shaib JK (1986) Effect of energy intake on nitrogen metabolism in nondialyzed patients with chronic renal failure. Kidney Int 29: 734–742
14. Maroni BJ, Steinman TI, Mitch WE (1985) A method for estimating nitrogen intake of patients with chronic renal failure. Kidney Int 27: 58–65

15. Mehls O, Haffner D, Wuhl E, Tonshoff B, Schaefer F, Heinrich U (1996) Growth hormone as a treatment modality for short children with chronic renal failure. The German Study Group for growth hormone treatment in chronic renal failure. Horm Res 46: 230–235
16. Perfumo F, Canepa A, Divino Filho JC, Nilsson E, Carrea A, Verrina E, Gusmano R, Bergström J (1994) Muscle and plasma amino acids and nutritional status in kidney transplanted children. Nephrol Dial Transplant 9: 1778–1785
17. Qureshi AR, Lindholm B, Alvestrand A, Bergström J (1994) Nutritional status, muscle composition and plasma and muscle free amino acids in renal transplant patients. Clin Nephrol 42: 237–245
18. Rees L, Greene SA, Adlard P, Jones J, Haycock GB, Rigden SPA, Preece M, Chantler C (1988) Growth and endocrine function after renal transplantation. Arch Dis Child 63: 1326–1332
19. Schwartz GJ, Haycock G, Edelman C, Spitzer A (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58: 259–263
20. Tanner JM, Whitehouse RH (1976) Longitudinal standards for height, weight-height, height velocity and stages of puberty. Arch Dis Child 51: 170–179
21. Tejani A, Cortes L, Sullivan EK (1996) A longitudinal study of the natural history of growth post-transplantation. Kidney Int Suppl 53: 103–108
22. Tonshoff B (1993) Efficacy and safety of growth hormone treatment in short children with renal allografts: three year experience. Kidney Int 44: 199–207
23. Vaisman N, Pencharz PB, Geary DF, Harrison JE (1988) Changes in body composition in children following kidney transplantation. Nephron 50: 282–287
24. Voerman HJ, Strack van Schindel RJM, Groeneveld ABJ, Boer H de, Nauta JP, Vee EA van der, Thijs LG (1992) Effects of recombinant human growth hormone in patients with severe sepsis. Ann Surg 216: 648–653
25. Walser M (1981) Conservative management of the uremic patient. In: Brenner BM, Rector FC Jr (eds) The kidney, 2nd edn. Saunders, Philadelphia, pp 2383–2424
26. Whitner FC, Evans DH, Dutton S, Ross G, Luger A, Nolph KD, Bauer JH, Brooks CS, Moore H (1985) Nutrition in renal transplantation. Am J Kidney Dis 6: 405–411
27. Ziegler TR, Lazarus JM, Young LS, Hakim RM, Wilmore DW (1991) Effects of recombinant human growth hormone in adults receiving maintenance hemodialysis. J Am Soc Nephrol 2: 1130–1135