Growth Hormone and the Kidney: The Use of Recombinant Human Growth Hormone (rhGH) in Growth-Retarded Children with Chronic Renal Insufficiency

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**ABSTRACT**
Hypothalamic production of growth hormone releasing hormone stimulates the anterior pituitary gland to release growth hormone (GH). The clinical manifestations of GH on tissues are either direct or are mediated by insulin-like growth factors (IGF). Both the somatic effects of GH and the renal manifestations of an increase in glomerular filtration rate and renal plasma flow are mediated by IGF. The increase in glomerular filtration rate/renal plasma flow that occurs with either exogenous or endogenous GH is not apparent in patients with chronic renal failure (CRF); therefore, it is unlikely that recombinant human growth hormone (rhGH) treatment of patients with CRF will result in glomerular hyperfiltration. Longitudinal studies are required to determine if the glomerulosclerosis and renal functional impairment occurring in GH and growth hormone releasing hormone transgenic mice occurs after rhGH treatment of growth-retarded children with CRF. Treatment of growth-retarded uremic rats with GH resulted in an improvement in growth velocity. This led to preliminary studies in growth-retarded children with CRF by using rhGH. The acceleration of growth velocity was dramatic despite the fact that GH levels are elevated in uremia. The elevated IGF carrier proteins in uremic children may contribute to the growth retardation. Treatment with rhGH may be efficacious by stimulating a net increase in the free (unbound) IGF levels. Hyposecretion of GH may contribute to the failure to achieve optimal growth after successful renal transplantation. Treatment with rhGH may be efficacious in improving the growth velocity of renal allograft recipients.

**Key Words:** Growth hormone, chronic renal insufficiency

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Human growth hormone (GH) is a single-chain polypeptide composed of 191 amino acids with a molecular mass of 22 kDa which is synthesized in the anterior lobe of the pituitary gland (1). The GH gene is present on the long arm of chromosome 17 (1).

Secretion of GH is regulated by the hypothalamic growth hormone releasing hormone (GHRH). Circulating GH exerts a negative feedback control by both inhibiting GHRH and stimulating somatostatin release. GH is secreted by the pituitary in surges, with the major peak occurring shortly after the onset of deep sleep. Other physiologic stimuli of GH release are physical exercise, hypoglycemia, and ingestion of a high-protein meal (2).

Circulating GH acts both directly on sensitive cells and/or by stimulation of insulin-like growth factor (IGF) production. Regulation of glucose metabolism is a direct effect, whereas stimulation of somatic growth is indirect (3).

IGF-I and IGF-II are single-chain insulin-like polypeptides composed of 70 and 67 amino acids, respectively. Both substances are bound tightly to carrier proteins, resulting in virtually no free IGF-I or IGF-II being measurable in the serum (2).

Growth hormone provides the major stimulus for IGF-I production in the liver, kidney, and other tissues, whereas IGF-II is produced in a number of tissues but is less GH dependent (2). The IGF may exert their effect on the cells producing them (autocrine growth factor) or on adjacent cells (paracrine growth factor); therefore, tissue rather than circulating levels of the IGF may be of physiologic significance (4).

Receptors for IGF-I are present in glomerular mes-
angial cells, and receptors for IGF-I and IGF-II have been identified in glomeruli and proximal tubular cells. Receptors for GH are also present in proximal tubular cells (5). IGF-I is synthesized by mesangial cells, which are GH independent, and by collecting duct cells, which are GH dependent (5).

The GH-IGF axis regulates various physiologic functions of the kidney and is involved in the development of renal hypertrophy and in the postischemic regeneration of the proximal renal tubule (5,6). These functions of GH will require consideration when the therapeutic use of recombinant human growth hormone (rhGH) in children with growth retardation consequent to renal insufficiency is contemplated.

GH LEVELS AND CHRONIC RENAL FAILURE

In 1966, Samaan et al. (7) noted elevated fasting GH levels and a paradoxical rise in GH levels after glucose administration in six adults with advanced chronic renal failure (CRF). Subsequent studies on a larger number of adults in 1968 by Horton et al. (8) and in 1970 by Samaan and Freeman (9) confirmed the above findings but noted that not all of the uremic patients studied exhibited abnormal GH levels. Indeed, Tchobroutsky et al. (10) failed to observe any paradoxical increase in GH levels after intravenous glucose administration to 11 uremic adults.

In 1976, Czernichow et al. (11) observed a paradoxical rise in GH levels after administration of thyrold stimulating hormone releasing factor to 13 children and adolescents with CRF. El-Bishti et al. (12) noted elevated fasting GH levels and a paradoxical rise in GH levels in response to glucose administration in 16 children undergoing hemodialysis. Similar findings were reported by Ijaiya (13) in 11 dialyzed and 6 nondialyzed children with CRF. In addition, exaggerated responses to both arginine infusion and insulin-induced hypoglycemia were noted by Ijaiya (13). In contrast, Bessarione et al. (14) failed to demonstrate an increase in fasting GH levels or an exaggerated response to insulin-induced hypoglycemia in 22 uremic children, 10 of whom were undergoing continuous ambulatory peritoneal dialysis. However, those authors did note a significantly higher response in uremic children compared with that in normal subjects after GHRH administration.

The elevated GH levels were attributed to malnutrition (15); however, the inverse correlation with serum albumin levels was inconsistent (16,17). Similarly, the correlation of elevated GH levels with the serum creatinine level or urea level was not uniform (15). Although the initial investigative efforts were directed toward determining the relationship between the elevated GH levels and the glucose intolerance of uremia, it was not possible to detect such a uniform correlation (8–10,15–18).

It can be concluded from the foregoing that GH metabolism is altered in uremia. The exact mechanism responsible for the alteration is unknown. No obvious clinical consequences are apparently related to the elevated levels. Indeed, the data did indicate that it was unlikely that GH deficiency contributes to the growth retardation associated with uremia. More recent studies by Schaefer et al. (19) indicated that pulsatile GH hypersecretion was present in peripubertal children with preterminal CRF and those undergoing dialysis, which did not correlate with growth velocity; however, GH hyposecretion was noted in renal transplant recipients. The latter could account for the pubertal growth failure observed after successful renal transplantation.

The elevation of GH levels in patients with CRF has been attributed to both impaired degradation and increased secretion. The disappearance rate of radiolabeled human GH in anephric uremic and nonuremic rats indicated that the kidney was unlikely to be an important site of GH degradation (20); however, the plasma disappearance rate of radiolabeled rat GH demonstrated that the kidneys accounted for 70% of GH turnover in the rat (21). Similarly, the metabolic clearance rate of radiolabeled human GH in four patients with renal failure was shown to be decreased by Cameron et al. (22) indicating that the kidney is an important site of metabolic disposal of GH and implicating decreased degradation as the cause of the elevated GH levels in uremia. In contrast, the disappearance rates of exogenous human GH in 5 hemodialysis patients after somatostatin administration were not different from those of normal subjects, prompting Pimstone et al. (23) to conclude that hypersecretion rather than impaired clearance accounted for the high GH levels. Therefore, the precise mechanism for the elevated GH levels remains unknown.

IGF (SOMATOMEDIN C) LEVELS AND CRF

IGF or somatomedins (Sm) have been measured in plasma by either bioassay with the incorporation of radiolabeled sulfate into cartilage or radioligand assay (RIA)/radioreceptor assay (RRA); IGF-I and Sm have been shown to be identical. Circulating Sm activity by bioassay was shown by Phillips and Kopple (24) to be decreased in adults with CRF and was even lower in those undergoing hemodialysis. Similarly, Phillips et al. (25) noted low levels of Sm activity in children undergoing hemodialysis. The fact that Sm activity increased after a single dialysis in both adults (24) and children (25), as well as after successful renal transplantation in children (26), implicated the presence of an uremic inhibitor of Sm activity for the low levels detected by bioassay. This
concept was supported by the data demonstrating elevated Sm activity in both adults (27) and children (28) when determined by RRA. The discrepancy in the levels when determined by the different methods was attributed to the inhibitor affecting performance of the assay. Phillips et al. (29) subsequently identified a circulating peptide in uremic serum of adult patients which blunted cartilage sulfate uptake. De- 

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The recent developments in IGF-I by specific RIA was found to be both low (30) and high (31), whereas measurement of IGF-II by both RIA (30) and RRA (31) was found to high. Removal of unsaturated carrier proteins by using acid chromatography as reported by Powell et al. (32) yielded serum IGF-I levels (RIA) in uremic patients which were not different from those in normal individuals and serum IGF-II (RRA) levels which were not lower than those in normal individuals. Powell et al. (33) subsequently measured serum IGF-I, IGF-II, and unsaturated carrier binding protein of IGF-I in 16 prepubertal children with CRF and 16 age- and sex-matched controls. The IGF-I levels in the children with CRF were not different from those of the normal children, but the IGF-II levels were significantly higher and the levels of unsaturated binding protein of IGF-I were elevated in children with CRF. A recently developed RIA for the 25-kDa IGF-binding protein (IGF-BP25) has shown this substance to be elevated in children with CRF (34). The IGF-BP25 has been shown to interfere with the physiologic functioning of IGF-I and the elevation of IGF-BP25 in children with CRF may play a role in the growth retardation of such children.

GH AND RENAL FUNCTION

Studies in rats have shown that GH decreases sodium and potassium excretion which are not dependent on the presence of adrenocortical steroids (35). Administration of extracted pituitary GH to man resulted in a reduction of sodium and potassium excretion, an increase in maximal tubular reabsorption of phosphate with a resultant decrease in phosphate excretion, hypercalciuria, and an increase in both glomerular filtration rate (GFR) and renal plasma flow (RPF) (36,37).

Endogenous excess GH secretion has a similar effect on GFR/RPF which is ablated after hypophysectomy. Ikkos et al. (38) studied 13 patients with acromegaly and demonstrated an increase in GFR, RPF, and extracellular water without any increase in the filtration fraction. Similar studies by Falkheden and Wickbom (40) before and after hypophysectomy demonstrated a decrease in GFR/RPF after hypophysectomy which occurred despite supplementation with adrenal, thyroid, and sex hormones. Serial observations of kidney size showed a roentgenographic reduction after hypophysectomy; however, the reduction in kidney size was smaller and it occurred at a considerably slower rate than the changes in GFR/RPF. Therefore, it was concluded that the changes in GFR/RPF were a functional phenomena and were not related to a reduction in renal mass.

What is the functional mechanism responsible for the GH-mediated increase in GFR/RPF? Acute GH infusion over a 2-h period to either animals (41) or humans (42) failed to produce an increase in GFR/RPF; whereas, 1 week of GH twice daily to seven healthy men resulted in an increase in GFR and RPF without any concomitant change in kidney size (43). The delay in response of GFR/RPF to GH was also noted by Hirschberg and Kopple (44) after the rhGH treatment of a GH-deficient patient. The delayed increase in GFR/RPF was correlated with the increase in plasma IGF-I levels and led those authors to hypothesize that it was IGF-I rather than GH that stimulated the increase in GFR/RPF. This hypothesis was advanced by the findings of Hirschberg et al. (45). Those authors administered rhGH to seven normal adults and followed the GFR and RPF for the following 3 days. The rise in the GFR/RPF was delayed until day 2 when the GH levels had fallen and the IGF-I levels were elevated.

Acute infusion of IGF-I to rats by Hirschberg and Kopple (46) produced an increase in GFR/RPF concomitant with a decrease in renal vascular resistance. The response to IGF-I was blocked by indomethacin, but not somatostatin, indicating that the vasodilating effects of eicosinoids may mediate the effect of IGF-I on GFR/RPF and that the effect is unlikely to be mediated by either renin, insulin, glucagon, or GH—which are all affected by somatostatin. Similarly, the absence of a relationship between the renin-angiotensin-aldosterone system and GH/IGF-induced increase in GFR/RPF was noted by Haffner et al. (47). Pretreatment of eight normal individuals with enalapril failed to abort the GH-induced increase in GFR/RPF.

It would appear, therefore, that GH induces the increase in GFR/RPF by stimulating the reserve renal function. Haffner et al. (48) administered rhGH for 3 days to seven healthy adults and seven patients with CRF. At 72 h, the inulin clearance increased from 120 to 133 mL/min in the healthy adults but no increase was noted in the patients with CRF (21 to 22 mL/min). The absence of any renal reserve in the patients with CRF probably accounted for the lack of increase in GFR/RPF after GH administration. Further studies are required to delineate the precise mechanism by which GH and/or IGF produce an increase in the GFR/RPF.
GH ADMINISTRATION TO GROWTH-RETARDED UREMIC RATS

In 1983, Mehls and Ritz (49) reported a significant increase in length and weight gain in rats made uremic by subtotal % nephrectomy after 1 and 2 wk of supraphysiological doses of porcine GH administered i.p. There was no concomitant increment in the IGF levels; however, the IGF carrier protein levels were increased after treatment. The discrepancy was attributable to methodological problems. No significant effect of physiologic doses of human GH were noted.

Mehls et al. (50), in 1988, extended these studies to a larger group of animals who received rhGH i.p. for 2 wk. The rhGH significantly improved, but did not normalize, the growth velocity and weight gain in uremic rats. Food consumption was not significantly affected by rhGH administration; however, food utilization was significantly increased, indicating an anabolic effect. The dry weight of skeletal muscle was increased in the group of rats receiving rhGH. No effect of rhGH on the serum creatinine level was noted; therefore, the increment in height was not attributable to an improvement in GFR by rhGH treatment. As in the previous study (49), the IGF levels remained unchanged after rhGH treatment whereas the IGF total protein binding capacity increased. Those authors indicated that the latter observation required further elucidation.

Powell et al. (51), in 1988, examined the effects of rhGH in the 5/6 nephrectomized rat model and essentially confirmed the findings in the previous reports from Mehls and colleagues (49,50). Uremic rats given 4 wk of rhGH manifested an increase in length without consuming additional food. There was no difference in the IGF-I, glucose, or insulin levels, and the creatinine clearance remained unchanged, after rhGH administration. Those authors concluded that uremic rats treated with rhGH have an increase in length, use ingested calories more efficiently, and fail to develop insulin resistance. The normal IGF-I levels in the uremic rats suggested to those authors that perturbations in serum IGF-I levels are not a major cause for the growth failure in uremic rats.

Because dietary protein restriction may modulate the progressive decline of renal function, Nakano et al. (52) investigated the effects of exogenous rat GH administered for 3 wk to 75% nephrectomized rats receiving an 8% protein diet. Compared with the uremic control rats, those given rat GH had significantly improved growth, food efficiency, and serum albumin levels without any change in creatinine clearance despite the low-protein diet. In the previous studies (49-51), the rats were fed a 22 to 24% protein diet. These data of Nakano et al. (52) suggested that children with CRF who were receiving a protein-restricted diet to delay the progression of renal failure would respond favorably to rhGH treatment with an increment in growth velocity.

Lastly, Foreman et al. (53), using the same model as that described by Nakano et al. (52) but with the addition of 1,25 dihydroxy vitamin D3, noted a significant increase in the magnitude of hypercalciuria when GH and 1,25 dihydroxy vitamin D3 were administered concomitantly. This finding raised the concern that the combined use of rhGH and 1,25 dihydroxy vitamin D3 in growth-retarded children with CRF would result in sufficient hypercalciuria to produce nephrocalcinosis, thereby leading to further impairment of renal function. To date, no clinical phenomena in children treated with rhGH comparable to the observation in uremic rats have been reported.

Despite the absence of any adverse effect of rhGH on GFR in uremic rats, caution regarding this potential consequence is required. Studies in transgenic mice noted an increase in glomerular size and progressive glomerulosclerosis in those mice expressing the GH and GHRH genes but only an increase in size in the mice transgenic for IGF-I (54). Renal failure was the primary factor contributing to the shortened life span in these animals (54,55). Therefore, accurate serial GFR measurements are required in patients receiving rhGH in order to assess the long-term impact on renal function.

rhGH ADMINISTRATION TO GROWTH-RETARDED CHILDREN WITH CRF

On the basis of the findings of Mehls and Ritz (49), an investigational new drug application was submitted by me to the Food and Drug Administration for the use of supraphysiological doses of rhGH in growth-retarded children with CRF. The initial 6-month data of five children with CRF treated with rhGH were reported at a symposium in 1987 (56). The annualized growth velocity increased from 4.94 ± 1.4 cm/yr for the year before treatment to 10.08 ± 1.97 cm/yr after treatment (P < 0.01). A subsequent report published in 1989 (57) noted that the actual growth velocity after 1 yr of treatment in these five children was 9.8 ± 1.2 cm/yr (P = 0.006). The long-term (3-yr) outcome of nine patients with CRF treated with rhGH, which included the five children from the previous two reports (56,57), indicated that the acceleration in growth velocity continues during the second and third year of rhGH treatment (58,59). The mean growth velocity of these nine patients increased from 5.0 ± 1.4 cm/yr to 8.5 ± 1.3 (P = 0.0001), 8.2 ± 1.8 (P < 0.004), and 8.1 ± 1.8 (P < 0.05) cm/yr after 12, 24, and 36 months of rhGH treatment, respectively. The mean standard deviation score (SDS) improved from −3.19 ± 1.2 at the
Initiation of treatment to $-1.29 \pm 1.3$ ($P < 0.03$) after 36 months of treatment. Six of the seven patients who had been treated for >24 months had achieved sufficient acceleration in growth velocity to attain a SDS more positive than $-2.00$ and were above the 5th percentile for chronological age on the growth curve.

In addition to the increase in growth velocity, the patients exhibited an increment in weight and an increase in the midarm muscle circumference, indicating that rhGH produced an anabolic effect. The salutary effect of rhGH was achieved without any adverse impact on glucose tolerance or calculated creatinine clearance; however, two patients required initiation of dialysis at 18 and 30 months after initiation of rhGH treatment. Despite the acceleration in growth velocity, the bone age did not increase more than the increase in chronologic age, indicating that growth potential was preserved.

The magnitude of the increment is illustrated in Figure 1, which represents acceleration in growth velocity during a 3-yr period of rhGH treatment. Improvement on the percentile curve from below the 5th percentile for chronological age to the 50th percentile during 3 yr of rhGH treatment, despite a gradual decline in renal function that necessitated the initiation of dialysis, demonstrates the marked therapeutic efficacy of rhGH. After discontinuation of rhGH, when the patient reached the 50th percentile for midparental height, and after successful renal transplantation, the patient has remained in the 50th percentile on the growth curve despite discontinuing rhGH. This patient therefore exemplifies the potential of rhGH treatment to maximize the possibility of children with CRF reaching their optimal inherent height potential.

Rees et al. (60) recently reported confirmatory results in six prepubertal children with preterminal CRF. The height SDS increased from $-2.9$ to $-2.1$ after 1 yr of daily rhGH treatment. Overnight GH profiles were normal before treatment; however, the IGF-I levels were below the normal range before treatment and increased to normal values after treatment. The mean calculated GFR was 18 mL/min/1.73m² before treatment and remained unchanged. Although the parents reported that the children had an improvement in appetite, this impression was not confirmed by dietary assessment. The improvement in growth rate despite unchanged energy and protein intake suggested an increase in the efficiency of food utilization with rhGH. Those authors (60) concluded that the magnitude of improvement in growth rates after rhGH treatment obviated the need for subsequent controlled trials.

Similarly, Tonshoff et al. (61,62) have recently reported their initial results on the use of rhGH in nine children with CRF, eight of whom were undergoing dialysis (eight continuous ambulatory peritoneal dialysis and one hemodialysis). Seven patients completed 1 yr of treatment, two patients completed 9 months of treatment, and one patient completed 6 months of treatment. The height velocity increased from 4.4 cm/yr before treatment to 8.0 cm/yr (actual plus annualized) after treatment ($P < 0.005$). No acceleration in bone age or increase in glucose intolerance was noted despite the increase in growth velocity. Sm bioactivity, IGF-I, IGF-II, and IGF-binding protein levels increased after rhGH treatment; however, the increment in IGF-I levels was greater than the increment in the IGF-binding protein levels. Those authors (61,62) hypothesized that the net increase in unbound IGF-I could explain the normalization in the Sm activity and that the acceleration in growth velocity could be attributed to the increased concentration of circulating IGF-I.
The only other reported data on the use of rhGH in children with preterminal CRF are the data in the report of Wilson et al. (63) of two severely growth-retarded children with cystinosis. During 1 yr of rhGH treatment, the growth velocity was 9.0 and 9.3 cm/yr; however, data were not available regarding the growth velocity during the year before treatment and no information was presented detailing the precise degree of renal functional impairment. The patients were 10 and 11 1/2 yr of age at the initiation of rhGH treatment, and those authors (63) stated that the progression of renal failure was not altered by rhGH treatment.

In addition to the eight dialysis patients reported by Tonshoff et al. (61,62), Fine et al. (64) recently reported the results of rhGH treatment in five growth-retarded children undergoing continuous ambulatory peritoneal dialysis (CCPD). Three of the five children manifested an acceleration in growth velocity after 6 to 12 months of thrice weekly rhGH treatment. The lack of a uniform effect in this small group of patients may be related to dosage schedule which was thrice weekly and not daily.

Effective absorption of intraperitoneal (i.p.) rhGH (65) has led to preliminary studies with daily i.p. rhGH during the diurnal dwell in patients undergoing CCPD (66).

These data on the use of rhGH in the treatment of growth-retarded children with preterminal CRF and those with end-stage renal disease undergoing dialysis are certainly encouraging. Confirmation of the salutary results with controlled studies should lead to the uniform use of rhGH in growth-retarded children with renal insufficiency.

**rhGH ADMINISTRATION TO GROWTH-RETARDED RENAL ALLOGRAFT RECIPIENTS**

Pennisi et al. (67), in 1979, evaluated Sm bioactivity and GH concentration in 10 growth-retarded, well-nourished pediatric allograft recipients. The Sm activity was clearly subnormal in 3 of 10 recipients, and there was a significant correlation between Sm activity and creatinine clearance. Serial determinations of Sm activity over a 24-h period after administration of prednisone demonstrated that Sm activity decreased to subnormal values at 6 and 12 h and returned to normal values by 24 h. Insulin-induced hypoglycemia failed to produce a significant (>7 ng/mL) rise in the plasma GH concentration in four of eight recipients. The mean 24-h GH concentrations tended to be lower in three of four poor responders. However, there was no correlation between the GH values and (1) growth velocity during the preceding year, (2) prednisone dosage, or (3) creatinine clearance.

Those authors (67) concluded that growth failure in pediatric allograft recipients receiving daily prednisone may result from (1) partial GH deficiency, (2) reduced Sm activity resulting from diminished allograft function, and (3) decreased Sm levels after daily prednisone administration.

In 1988, Rees et al. (68) performed overnight GH profiles in 17 adolescent renal allograft recipients with short stature and/or maturational delay receiving alternate day corticosteroid therapy. Decreased GH secretion was present in 8 of 17. However, there was no correlation between height velocity during the previous 6 months and (1) area of GH under the curve, (2) mean GH concentration, or (3) GH mean peak amplitude. Similarly, there was no correlation between either the steroid dose or GFR and growth velocity or any GH parameters. All concentrations of IGF-I were within normal limits for age and sex. Those authors (68) suggested that corticosteroid treatment was responsible for maturational and growth delay in pubertal renal allograft recipients and recommended either excluding corticosteroids from the immunosuppressive regimen or using rhGH in those recipients with stable renal function who were manifesting slow pubertal growth.

Tejani et al. (69), in 1989, studied the L-DOPA-stimulated GH response in 21 recipients who were either receiving daily prednisone or who had discontinued prednisone and were receiving cyclosporine monotherapy. In 4 of 21 recipients who were receiving >5 mg of prednisone daily, the peak-stimulated GH levels were <10 ng/dL. Treatment with rhGH thrice weekly for 3 to 6 months resulted in accelerated growth velocity in three of four; however, the precise growth data were not included in that report.

Jabs et al. (70), in 1990, evaluated plasma GH concentrations during sleep and after arginine and L-DOPA stimulation in eight poorly growing renal allograft recipients. Maximum GH concentration was inadequate both after pharmacologic stimulation and during sleep in four of eight recipients. In an additional two of eight, there was inadequate responses during sleep despite normal responses to pharmacologic stimulation. Plasma IGF-I levels were normal for age in all eight recipients. Those authors (70) concluded that abnormalities of GH secretion occur frequently in poorly growing recipients of successful renal transplants and that the usefulness of rhGH therapy should be investigated.

David-Neto et al. (71) studied nocturnal spontaneous GH secretion and Sm levels (RIA) before and after converting 15 pediatric renal allograft recipients from an azathioprine/prednisone to a azathioprine/cyclosporine regimen. Insulin-induced hypoglycemia-stimulated GH response was normal before conversion and the discontinuation of prednisone. GH nocturnal spontaneous secretion was inversely correlated with the prednisone dosage. In 6 of 15, the
GH nocturnal spontaneous secretion increased significantly after prednisone withdrawal. After conversion to azathioprine/cyclosporine and prednisone withdrawal, the growth rate increased significantly.

Lastly, as mentioned previously, Schaefer et al. (19) studied pulsatile spontaneous GH secretion in 40 pubertal transplant recipients. GH peak amplitude was correlated with height velocity in the transplant recipients, and a strong inverse relationship was observed between the GH peak amplitude and steroid dosage in the transplant recipients. Those authors (19) concluded that pubertal growth failure despite successful transplantation appears to be due to corticosteroid-induced GH hyposecretion.

In addition to the four recipients reported by Tejani et al. (69), the only patients reported in the literature to have been treated with rhGH after renal transplantation are 1 patient, reported by Van Dop et al. (72), who had no evidence of GH deficiency but who had a growth rate of only 2 cm/yr when receiving 9 mg/m² of prednisone on alternate days and who grew 8.7 cm in 12 months of rhGH treatment. 12 patients (six prepubertal and six pubertal) reported by Rees et al. (60), and 5 patients recently reported by Fine et al. (73). Four of the five latter recipients manifested an increment in growth velocity after rhGH treatment; however, the magnitude of the increment was not as great as that obtained after rhGH treatment of the patients with CRF. Similar results were observed by Rees et al. (60). In both of the latter two reports, there was no significant decline in GFR or increase in the number of episodes of graft dysfunction after rhGH treatment.

The most recent data from the North American Pediatric Renal Transplant Cooperative Study (74) on 1,284 renal transplants performed in 1,244 pediatric recipients <18 yr of age between 1987 and 1990 indicates that growth failure persists in the majority of recipients despite successful transplantation in the cyclosporine era. The data cited above would seem to implicate perturbations in GH secretion resulting primarily from the concomitant use of corticosteroid therapy as a significant contributing factor to the growth failure. Further studies designed to determine the efficacy of rhGH treatment in this patient group seem justified.

Recent studies by Kaufmann et al. (75) implicated the hypothalamus as the site of glucocorticoid-induced inhibition of GH secretion. The serum GH response to GHRH was tested in seven normal individuals before and after 4 days of prednisone (20 mg, three times a day). After prednisone administration, the GH response to GHRH was markedly depressed. Those authors (75) concluded that the short-term administration of glucocorticoids decreases GHRH-induced GH secretion to a degree indistinguishable from basal secretion. Although the precise mechanism of the inhibition was not delineated, those authors proposed a local increase in somatostatin inhibitory activity.

CONCLUSIONS

Plasma GH levels are elevated in patients with CRF (7–9). Whether the elevated levels result from impaired renal clearance of GH (22) or from GH hypersecretion (23) remains to be determined; however, there do not appear to be any clinical consequences attributable to these elevated GH levels (8–10,15–18). In contrast, by current methodologies, serum IGF levels are not abnormal in uremia (32,33); however, serum IGF binding-protein levels are elevated (34).

Both endogenous (38) and exogenous (43) GH results in increases in GFR and RPF. It is likely that the increased GFR/RPF are mediated by IGF-I (46). Although short-term rhGH administration does not result in an increase in GFR in uremic adults (48), it is of concern that long-term rhGH treatment could produce hyperfiltration (76) with resultant glomerulosclerosis and accelerated decline in renal function.

Uremic rats given supraphysiologic doses of GH manifest an acceleration of growth velocity compared with uremic control animals (49–51). The mechanism responsible for the improvement in growth velocity has not been delineated, but fluctuation in the IGF-1 levels has not been implicated (51). Reduction in the protein intake to 8% does not abrogate the beneficial affect of GH on growth velocity (52). These animal data led to preliminary studies with rhGH to improve the growth velocity of growth-retarded children with CRF.

Children with CRF manifest growth retardation. Multiple factors have been implicated (77); however, correction of acidosis, prevention of renal osteodystrophy, reversal of electrolyte imbalances, and provision of adequate caloric intake rarely result in an accelerated growth velocity. Treatment with rhGH of growth-retarded children with CRF has resulted in a significant improvement in growth velocity (56–64).

Unfortunately, growth retardation frequently persists despite successful transplantation in the cyclosporine era (74). A major factor contributing to the growth failure is corticosteroid-induced GH hyposecretion (19). Preliminary data on a small number of recipients indicate that rhGH treatment can produce an increase in growth velocity after renal transplantation without adjustments in the immunosuppressive regimen (60,69,72,73).

Obviously, corroborative controlled studies are required to confirm these preliminary results; however, it appears that one of the onerous facets (growth retardation) of CRF in children may be eliminated, to some extent, in the future with the availability of rhGH treatment.
REFERENCES


