Excessive Dietary Protein and Suboptimal Caloric Intake Have a Negative Effect on the Growth of Children With Chronic Renal Disease Before and During Growth Hormone Therapy

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Although diet and nutrition are an integral part of the management of individuals with chronic renal failure (CRF), little has been written on the effect of nutrition on the growth response to growth hormone (GH) in CRF. We studied the GH axis and nutritional status of 31 prepubertal children aged 8.7 ± 0.5 years with a height standard deviation score (SDS) of −3.2 ± 0.2 (mean ± SEM) with CRF. Sixteen CRF patients on hemodialysis and 15 on peritoneal dialysis were studied. Forty-four age-matched normal short children without GH deficiency served as controls. Spontaneous 12-hour GH and stimulated GH values were significantly higher and GH binding protein (GHBP) was significantly lower in the CRF patients than in the normal short children. Both before the initiation of GH therapy and after the first year of treatment, the growth velocity (SDS) was inversely correlated with dietary protein intake and positively correlated with caloric intake. GH was administered at a dosage of 28 and 21 IU/m^2/wk to the CRF group and the normal short children, respectively, divided into seven daily doses. The growth response of the normal short children was significantly greater than that of the CRF patients. GH therapy induced a smaller increment in GHBP and IGF-I in the CRF patients versus the normal short children (8.8 ± 2.2 and 10.2 ± 2.7 *v* 24.8 ± 1.3 and 27.6 ± 2.5 nmol/L, respectively, $P < .01$). The 1-year growth velocity of the CRF children was most closely correlated with dietary protein and caloric intake. The nutritional status of CRF patients is concluded to be a major factor in growth both before and during GH therapy.

GROWTH RETARDATION is a frequent complication of chronic renal failure (CRF).[1-6] Although several factors contribute to impaired growth in uremia,[1,7,8] treatment aimed at alleviating these factors has generally been disappointing. Thus, attention has turned to the role of growth hormone (GH) as a cause of growth retardation in patients with CRF, as well as in renal replacement therapy. These patients exhibit a normal to high GH level and normal to high GH response to pharmacological stimulation tests.[9-13] The level of GH binding protein (GHBP),[14,15] an indirect measure of the GH receptor level, is low and insulin-like growth factor-I (IGF-I) may be normal or low.[13,16,17] It is now common knowledge that the best way to prevent early growth failure in children with renal disease is by using the specified nutrition and an appropriate buffer, activated vitamin D and calcium-containing phosphate binders, as needed.[18] Previous reports on clinical GH trials in CRF have not analyzed or reported the effect of nutrition on the growth response to GH. The present study was undertaken to evaluate the relative importance of nutrition in CRF patients during GH therapy. The results were compared with those from a group of short children without renal disease who were treated with GH.

SUBJECTS AND METHODS

Study Population

The study group consisted of a total of 75 (60 males) prepubertal children: 31 (23 males) had CRF (creatinine clearance, 6.4 to 30 mL/min/1.73 m^2), of whom 16 were on hemodialysis and 15 on peritoneal dialysis. CRF patients were continuously monitored for electrolytes, acid-base balance, and parathyroid hormone (PTH) levels. Calories, vitamin D, calcium, bicarbonate, and erythropoietin were supplemented as suggested by Sedman et al[18] throughout the study, and the actual intake of the patients was monitored. The other 44 children were normal short children referred to the pediatric endocrine clinic for short stature. The normal short children were of normal birth weight for gestational age and free of chronic diseases, nutritional or gastrointestinal problems, or dysmorphic syndromes, all exhibiting a maximal GH response to a provocative test >10 μcg/L. The final height prediction for the short normal children was not significantly different from the target height (standard deviation score [SDS], −2.3 ± 0.3 *v* −2.5 ± 0.3, respectively). The two groups of patients were matched for age. Height was measured using a Harpenden stadiometer. The height SDS was determined according to National Center for Health Statistics growth charts.[19] Pubertal status was evaluated according to Tanner's[20] criteria. The participation of all the children conformed with institutional standards and with approved protocols for research involving human subjects. Written informed consent was obtained for each participant from his/her legal guardian. Pertinent clinical and laboratory data are listed in Table 1.

Study Protocol

Spontaneous GH secretion[21-23] and the GH response following GH provocative tests (with clonidine, insulin, or arginine)[23] were determined as previously described, except that the spontaneous blood collection period was 8 PM to 8 AM.[21-23] Bone age was determined according to the method of Greulich and Pyle.[24] All participants were seen in-clinic at 3-month intervals.

Laboratory Methods

Radioimmunoassay. The GH level was measured with a double-antibody radioimmunoassay (RIA) kit (HGHK-2; Sorin, Vercelli, Italy) and IGF-binding protein 3 (IGF-BP3) by an immunoradiometric kit (Diagnostic System Laboratories, Webster, TX). The IGF-I RIA kit (Incstar, Stillwater, MN) consists of acid separation on microcolumns.

Radioreceptor assay. IM9 GH radioreceptor assay (RRA) was performed on a 12-hour plasma pool of 10 CRF patients on peritoneal dialysis and 12 normal short children as detailed by Bistritzer et al.[25]

Plasma GHBP. A GH-binding assay based on dextran-coated

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Table 1. Clinical and Laboratory Data for the Children With CRF and the Normal Short Children (mean ± SEM)

Parameter	CRF	NSC
No. of subjects	31	44
Age (yr)	8.7 ± 0.54	8.4 ± 0.6
BA:CA	0.8 ± 0.04	0.7 ± 0.04
Height (SDS)	−3.19 ± 0.2	−2.8 ± 0.20*
Growth velocity (SDS)	−2.3 ± 0.3	−0.8 ± 0.3
Growth velocity before GH therapy (cm/yr)	3.6 ± 0.3	4.9 ± 0.2
BMI (kg/m²)	19.5 ± 0.5	15.5 ± 0.3
Creatinine clearance (mL/min/1.73 m²)	15.7 ± 1.2*	119 ± 1.1
GH max (μg/L)	30.1 ± 2.2*	18.7 ± 2.6
12h-GH (μg/L)	8.13 ± 0.9*	2.5 ± 0.6
IGF-BP3 (mg/L)	6.2 ± 0.35	2.0 ± 0.05*

Abbreviations: BA/CA, bone age to chronological age ratio; BMI, body mass index; GH max, maximal GH response to stimulation; NSC, normal short children.

*$P < .01$.

charcoal separation was used to measure plasma GHBP as previously described.[26] Binding results were corrected for endogenous GH bound to plasma GHBP, based on the plasma GH level in each sample. GHBP results are given as a percent of a normal adult control pool.

Nutritional evaluation. Thirty-one CRF patients and 44 normal short children underwent nutritional evaluation by a dietitian before and during the year of GH therapy. The individual nutritional needs of each patient were calculated, and the appropriate recommendations were made at each visit for all patients in both groups. The actual dietary intake was analyzed on the basis of detailed food records kept for 3 days before each of the 3-monthly clinical visits. The food composition was analyzed by a computer program based on local food tables. Results of the analysis are reported as percent recommended daily allowance.[27]

Statistical Methods

Student's t test, least-squares linear regression, multiple linear regression, and ANOVA were performed using the Sigmastat program.[28] The data are presented as the mean ± SEM.

RESULTS

Clinical and laboratory data for the groups are presented in Table 1. There were no significant differences in the creatinine clearance, growth velocity before and after 1 year of GH therapy, GH response to GH provocative tests, spontaneous GH secretion, and IGF-I and IGF-BP3 levels between patients on peritoneal dialysis versus hemodialysis. All results were therefore combined as one CRF group. There was no significant change in the bone age to chronological age ratio during the year of GH therapy in either group.

12-Hour Integrated GH Concentration

The mean 12-hour integrated GH concentration (12h-GH) of CRF patients was significantly higher than that of the normal short children ($P < .01$; Table 1). These levels were positively correlated with the pretreatment growth velocity (SDS) of the normal short children ($r = .532$, $P < .01$, $n = 44$), as previously reported.[29,30] No such correlation was found in the CRF group.

GH Stimulation Testing

The maximal GH response to provocative stimulation was significantly higher ($P < .001$) in the CRF group.

RRA:RIA Ratio of 12h-GH Samples

GH levels measured by IM9 receptor assay (RRA) were compared with those determined by RIA in 10 CRF patients and 12 normal short children. The ratios were 0.88 ± 0.07 and 0.9 ± 0.08, respectively.

IGF-I and GHBP

IGF-I levels of the CRF group and the normal short children were not significantly different before initiation of GH therapy. The ΔIGF-I:12h-GH ratio, which represents the ratio between the IGF-I increment during the year of GH therapy and plasma GH levels, was higher in the normal short children versus CRF patients ($P < .01$). GHBP in the CRF group was lower than in the normal short children ($P < .01$).

IGF-BP3

IGF-BP3 levels in CRF patients were significantly higher than in the normal short children (Table 1).

Effect of GH Therapy

12h-GH levels were negatively correlated with the 1-year increment in growth velocity (SDS) following GH therapy in the normal short children ($r = -.523$, $P < .01$), as previously reported.[30] No such correlation was found in the CRF group.

Table 2. Changes in Growth Velocity, IGF-I, GHBP, PTH, and Alkaline Phosphatase During 1 Year of GH Therapy in Short Children With CRF Versus Normal Short Children (mean ± SEM)

Parameter	CRF			NSC		
	No.	Pretreatment	1 yr	No.	Pretreatment	1 yr
Growth velocity (SDS)	31	−2.3 ± 1.5*	−1.37 ± 2.1†	44	−1.7 ± 1.3*	3.4 ± 3.1
IGF-I (nmol/L)	31	8.2 ± 0.8	18.45 ± 1.0†	44	7.8 ± 2.6*	29.8 ± 7.4†
GHBP (%)	31	43.9 ± 2.7	53.5 ± 1.6	44	62.3 ± 2.1*	92 ± 1.4
Serum AP (IU/L)	31	251.6 ± 8.3	370 ± 32.6	44	205 ± 27*	274 ± 50†
pH	31	7.3 ± 0.01	7.31 ± 0.13	44	7.35 ± 0.02	7.34 ± 0.08
PTH (pg/mL)	31	209.1 ± 31.9	202.1 ± 27.9	44	20 ± 5†	19 ± 5†
Calories (%RDA)	31	74.7 ± 2.9†	83.3 ± 3.7†	34	98.5 ± 4.5	105 ± 5.0
Protein (%RDA)	31	180.5 ± 12.3	169 ± 15.8	34	85.2 ± 10.5†	90 ± 10.0†

Abbreviations: AP, alkaline phosphatase; RDA, recommended daily allowance; NSC, normal short children.

*Significantly lower than after 1 year of GH therapy ($P < .01$).

†Significantly lower than the corresponding group ($P < .01$).

Pretreatment growth velocity expressed as the SDS was negatively correlated with the 1-year growth velocity in GH-treated normal short children ($r = -.329$, $P < .03$), as previously reported[30]; again, no correlation was found in the CRF group.

The increase in GHBP following 1 year of GH treatment was low in CRF patients compared with the normal short children (8.8 ± 2.2 *v* 24.8 ± 1.3, $P < .01$). During GH therapy, IGF-I levels increased. However, the increase in the CRF group was significantly lower than in the normal short children (10.2 ± 1.2 *v* 27.6 ± 2.5, $P < .01$). The mean serum alkaline phosphatase level was significantly higher in the CRF group versus the normal short children. In both groups, alkaline phosphatase increased during GH therapy. Alkaline phosphatase was negatively correlated with blood pH ($r = .380$, $P = .035$), whereas no correlation was found with PTH ($r = .313$, $P = .086$); at the same time, PTH was negatively correlated with blood pH ($r = .536$, $P = .0019$). By linear regression, no correlations were found between the pretreatment growth velocity (SDS) and IGF-I, caloric intake, and protein intake. When multiple linear regression analysis was applied, a significant correlation was found:

$$VSD_0 = -3.05 + 0.0184\,CAL - 0.00365\,protein (r = .509, P < .01),$$

where VSD_0 is growth velocity in SDS units before initiation of GH therapy, CAL is the mean 3-day caloric intake, and protein is the mean of 3-day protein intake. At the end of the first year of GH treatment, a similar correlation was obtained.

Growth velocity (SDS) was positively correlated with caloric intake and negatively correlated with protein intake:

$$VSD_{12} = -0.0261 + 0.0380\,CAL_{12} - 0.00683\,protein_{12} (r = .515, P < .01),$$

where VSD_{12} is growth velocity in SDS units after 12 months of GH therapy, CAL_{12} is the mean 3-day caloric intake after 12 months of GH therapy, and $protein_{12}$ is the mean of 3-day protein intake after 12 months of GH therapy. The study design does not allow segregation of the excess dietary protein from the suboptimal caloric intake. However, the weighted *P* value of the regression for calories and protein was .0392 and .08 before GH therapy versus .0397 and .107 after 1 year of GH therapy, respectively, results that may imply a greater importance for suboptimal caloric intake than for the excessive protein load.

DISCUSSION

GH secretion in patients with CRF varies widely from normal to high; this is true for both spontaneous GH secretion and the GH response to provocative stimulation tests.[9-13] Elevated random GH plasma levels[9] and an increased response to known GH stimuli such as hypoglycemia or arginine infusion have been reported in most uremic children.[9,10] Increased spontaneous plasma GH levels were reported in 34% of CRF patients.[13] Dysregulation of GH secretion at the level of the hypothalamus and pituitary was suggested by the lack of suppression of, or even a paradoxical increase in, plasma GH after glucose loading.[11,12]

Derangement in the GH axis was found in some CRF patients; however, in 66% of these children, normal 24-hour GH secretion was found, albeit with wide variation.[13] By deconvolution analysis, Tonshoff et al[31] demonstrated an increased half-life together with an increased production rate of GH in some patients with CRF. It has thus been suggested that the growth retardation of many CRF patients is not the result of abnormal GH secretion.[13] The pretreatment growth velocity (SDS) was highly correlated with the 12h-GH in normal short children, as previously reported[29,30,32]; no such correlation was found in the CRF group. The growth velocity of the CRF patients was lower than expected, taking into account the 12h-GH levels. In view of the prevailing high GH levels, serum IGF-I levels are inadequately low, and this might indicate a state of GH insensitivity as suggested previously.[13,16,17] Plasma levels of GHBP, the circulating extracellular domain of the GH receptor, are reduced in renal failure.[14,15] In addition, IGF-I bioactivity is reduced in CRF patients, and the inhibitory effect of IGF-I in CRF serum can be attributed to an excess of high-affinity IGF-BPs in CRF patients.[16,17,33]

During GH therapy, the lower growth response at a GH dose 25% higher than that given to the normal short children and the small increment of GHBP and IGF-I induced by GH imply peripheral resistance to GH therapy.

The nutritional status is known to have an effect on the GHBP level.[34,35] Both caloric intake and GHBP were lower in CRF patients before and after 1 year of GH therapy compared with the nonuremic group. We therefore speculate that the resistance to GH is induced by the lower number of GH receptors as reflected by the lower GHBP levels of the CRF patients, and is expressed by the small increase in GHBP and IGF-I levels in these patients during GH therapy.

Serum GHBP activity probably represents only part of GH receptor activity. The slightly decreased basal level of GHBP in CRF patients reported by our group and others[14,15] does not exclude transmembrane or intracellular receptor defects. Indeed, Tonshoff et al[36] demonstrated a reduction in hepatic GH receptor gene expression in uremic Sprague-Dawley rats, and a reduced production of GH receptor transcript in response to GH therapy. In contrast to our patients, who had low GHBP levels, the rats had a low GHBP level before GH therapy. Similar to our patients, GH therapy had little effect on the rats' GHBP. GH is known to induce IGF-I generation in target tissues. Although normal, IGF-I was relatively low for the respective endogenous GH reserve as measured by 12h-GH. In addition, the IGF-I increment during 1 year of GH therapy was relatively low in CRF patients as compared with the normal short children group. To exclude the possibility of the lower IGF-I production being caused by a "bio-inactive" GH molecule, we tested the serum binding of GH to the IM9 receptor. The RRA:RIA ratio of CRF patients was not different from that of the normal short children. As demonstrated in rats,[37-40] in a small number of children with classic GH deficiency,[41] and in normal short children,[42] GH therapy increases GHBP levels. This phenomenon probably represents upregulation of the GH receptor by GH therapy, which cannot be achieved in CRF. An increase in alkaline phosphatase in healthy children is usually an indicator of growing bone. In CRF children, the positive correlation with PTH and the negative correlation with blood pH suggest that the increased alkaline phosphatase may be the result of acidosis and secondary hyperparathyroidism. Both before GH therapy and after 1 year of treatment, caloric intake appeared to be

positively correlated with growth velocity, whereas dietary protein intake was negatively correlated with growth. These observations are not surprising: CRF patients are known to suffer from poor appetite and major feeding difficulties. These patients are therefore unable to comply with the nutritional instructions given. Despite the fact that the patients were closely supervised with respect to their dietary needs as suggested in the literature,[18] repeated monitoring at each trimonthly visit disclosed that some of the patients were unable to comply with the dietary instructions.

This is the first report on the effect of nutrition on the growth response to GH in CRF patients. It appears from this study that adequate nutritional support is important in CRF patients not only under basal conditions but also during GH therapy. A lack of adequate nutrition affects the growth response of these patients. Since the nutritional intake of the patients was not by design but by their preference, it is difficult to segregate the effect of suboptimal caloric intake from the effect of the protein overload. Statistically, it seems that the effect of the suboptimal caloric intake is stronger than that of the excessive protein load.

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