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Original Article

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Growth hormone induces anabolism in malnourished maintenance haemodialysis patients

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Abstract

Background. Growth hormone (GH) promotes anabolism in patients undergoing maintenance haemodialysis (MHD). However, no studies have examined the effects of GH on protein anabolism in MHD patients using full nitrogen-balance techniques. This study tested the hypothesis that recombinant human GH (rhGH) will induce an anabolic response, as assessed by long-term classic nitrogen-balance techniques, in malnourished MHD patients.

Methods. Six adult MHD patients with protein–energy malnutrition underwent nitrogen-balance studies in a general clinical research centre for 28–35 days each. Patients were maintained on a constant dialysis regimen and protein and energy intakes that were similar to their dialysis regimen and diet prior to hospitalization. The first 14–21 hospital days constituted a baseline phase; during the subsequent 8–21 days, patients were given daily subcutaneous injections of rhGH (0.05 mg/kg body weight/day).

Results. During treatment with rhGH, serum insulin-like growth factor-I (IGF-I) increased by ~225% ($P = 0.002$), nitrogen balance became strongly positive (+2.35 g/day; $P = 0.034$ *vs* baseline) and there was a reduction in serum urea nitrogen (−32%; $P = 0.001$). Two patients who became acutely ill and had the lowest dietary protein intakes developed a much smaller rise in serum IGF-I levels and increase in nitrogen balance when they received the rhGH treatment. In the remaining four responders, the decrease in nitrogen output was sustained throughout the entire period of treatment with rhGH. There was no change in body weight during the baseline or treatment phases of the study.

Conclusions. Injections of rhGH induce a strong and sustained anabolic effect, as indicated by positive nitrogen balance, in MHD patients with protein–energy malnutrition. This response was attenuated in two patients who were acutely ill with low protein intakes, suggesting that they may have developed partial resistance to GH.

Keywords: growth hormone; haemodialysis; insulin-like growth factor-1; kidney disease; malnutrition; protein anabolism

Introduction

It is well documented that growth hormone can promote anabolism in both healthy individuals and people with a variety of illnesses [1,2]. The anabolic effects of growth hormone appear to be largely, if not entirely, due to insulin-like growth factor-I (IGF-1) [1,3]. Growth hormone stimulates the production and secretion of IGF-I in a variety of organs, primarily liver but also in bone, muscle and kidney as well as other organs [1]. In individuals with chronic kidney failure, growth hormone may stimulate anabolism, improving utilization of ingested proteins or infused amino acids and lowering serum urea nitrogen (SUN) levels for a given quantity of dietary protein intake [4–10]. However, there are no studies of the effects of growth hormone on adults with advanced chronic kidney failure using full nitrogen-balance techniques.

The present study was undertaken to examine in greater detail the anabolic response to growth hormone in six patients undergoing maintenance haemodialysis (MHD). Because it was anticipated that benefits of growth hormone treatment for adult patients with advanced chronic renal failure might be largely limited to individuals with evidence for protein–energy malnutrition (PEM), only patients with clear

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evidence of PEM were studied. Patients underwent full nitrogen-balance studies in a general clinical research centre both before and after they received daily injections of recombinant human growth hormone (rhGH). The results indicate that, in general, growth hormone does induce a strongly anabolic response in MHD patients with PEM. However, this dramatic anabolic response was not universal and individuals who suffered from acute catabolic illness or perhaps have low nutrient intakes or are more debilitated may not mount as strong an anabolic response to growth hormone injections.

Subjects and methods

Subjects

This study was performed in the General Clinical Research Center at Harbor-UCLA Medical Center and was approved by the Institutional Human Subjects Committee. All patients gave signed informed consent. Six patients entered and completed this study (Table 1). The eligibility criteria for participation in the study included a diagnosis of protein and/or energy malnutrition, treatment with haemodialysis for ≥3 months and aged 18–75 years. Protein and/or energy malnutrition was diagnosed by the presence of at least two of the following: (i) evidence for muscle wasting by clinical appraisal or by decreased mid-arm muscle circumference; (ii) body weight ≤90% of desirable body weight or a serum albumin of ≤3.7 g/dl; and (iii) an inadequate dietary protein and/or energy intake prior to entering the study (i.e. a protein intake of ≤1.0 g/kg actual body weight per day and/or an energy intake of ≤30 kcal/kg actual body weight per day). Dietary protein intake was determined from a 3 day dietary diary kept by the patient and a dietary interview with the research dietician during the screening period before the patient was accepted into the study.

Patients were excluded from the study if their renal creatinine clearance was >5.0 ml/min or if they had insulin-dependent or insulin-independent diabetes mellitus, any illness requiring hospitalization, the presence of cancer except basal cell carcinoma, severe liver, lung or heart failure, vasculitis, psychosis or if they were not clinically stable.

Table 1. Characteristics of the subjects at onset of study[a]

Number (male/female)	3/3
Age (years)	59.5 ± 10.7
Duration of haemodialysis (months)	20.7 ± 35.1 (range: 3–92)
SUN (mg/dl)[b]	66.9 ± 20.0
Serum creatinine (mg/dl)[b]	11.0 ± 1.3
Serum albumin (g/dl)[b]	3.46 ± 0.93
Body weight (kg)[c]	51.5 ± 12.5
Relative body weight (%)[c]	70.2 ± 9.1
Desirable body weight (%)[c]	81.2 ± 10.3
Mid-arm muscle circumference (percentile)[c]	26.5 ± 2.7
Triceps skinfold (percentile)[c]	25.7 ± 9.3
Subscapular skinfold (percentile)[c]	18.3 ± 10.4
Body fat (%)[c]	Male: 20.2 ± 2.0 Female: 22.7 ± 7.2

Values are expressed as means ± SD ($n = 6$).
[a]Data were obtained at onset of the baseline phase.
[b]Data obtained pre-dialysis on the morning of a haemodialysis treatment.
[c]Data obtained on the day after a haemodialysis treatment.

Study design

Patients were studied in the General Clinical Research Center at Harbor-UCLA Medical Center for a total of 28–35 days. Throughout the entire study, each patient's haemodialysis regimen was kept constant and similar to his/her pre-study dialysis treatment. Each patient was fed a constant diet that was calculated to provide a daily dietary protein and energy intake similar to his/her diet prior to entering the study. For each patient, the daily intake of both energy and protein was divided into portions of approximately two-eighths, two-eighths, three-eighths and one-eighth for consumption at breakfast, lunch, supper and the evening snack, respectively. Dietary fat, sodium and potassium intakes were designed to be similar to the patient's pre-study intake. The diets were prepared using metabolic kitchen protocols that have been employed in previous studies. Any requests to change food intake were strongly discouraged after the first 3–4 days of the study. All patients were given one tablet per day of a multivitamin containing folate (Nephrovite®; R & D Laboratory, Santa Monica, CA, USA) and an oral iron supplement. Patients often received other medicines typically prescribed for chronic haemodialysis patients, including antihypertensive medications, erythropoietin, phosphate binders and various other agents. No patient was started or stopped on erythropoietin therapy during the study or within several weeks before commencing the study.

The first 2 weeks of the study were considered a baseline phase during which baseline (control) data were collected. One individual (patient 1) had a 3 week baseline phase. During the treatment phase, usually beginning on day 15 and ending on day 36, patients continued to undergo the same constant dietary and dialysis regimen, except that each day the patients received one subcutaneous injection of rhGH (0.05 mg/kg body weight) in the abdominal wall, at 08.00, after blood drawing. Nitrogen balances were measured continuously in each patient for the entire metabolic study using previously described techniques [11]. Total nitrogen was measured in a 24 h pooled collection of the patient's daily food intake, prepared in duplicate for analysis at least five times during the study in each patient, in each haemodialysate outflow, in urine collected daily or, for oliguric patients with <500 ml urine output per day, in 7-day urine pools, and in faeces collected during the same 7-day pools. Nitrogen balances were calculated for each of the 7-day collection periods and were adjusted for changes in body urea nitrogen as described previously [11]. Blood for measurement of serum urea, creatinine, albumin, growth hormone and IGF-1 was obtained in the post-absorptive state after an overnight fast, before any injection or medicinal intakes, between 07.45 and 08.00 at the beginning of each 7-day period and at the end of the last period.

Anthropometry

Anthropometry was performed on each patient at the beginning of study as described previously [11]. Relative body weight was calculated as the patient's weight × 100 divided by the median weight of normal individuals of the

same height, gender, frame size and age range as the patient as determined from the NHANES II data [11]. Skinfold thickness measurements were performed in triplicate at four different locations, i.e. biceps, triceps, subscapular and suprailiac. Fat mass was determined from these values as described previously [11].

Measurements

Serum urea, creatinine, albumin and other standard laboratory parameters were measured in the hospital clinical laboratory at Harbor-UCLA Medical Center. Albumin was assayed by the bromcresol green method. Total nitrogen was measured by pyrochemiluminescence with an Antek Nitrogen Analyzer Model 401 (Antek Instruments, Inc., Houston, TX, USA). Serum growth hormone was measured in duplicate by immunoradiometric assay at the Genentech Corporation using a polyclonal rabbit antibody. Serum total IGF-I was measured in duplicate by radioimmunoassay using a polyclonal rabbit antibody after acid–ethanol extraction, as described previously [12].

Statistical analyses

Data were analysed by analysis of variance (ANOVA) and paired *t*-tests when applicable. The nitrogen-balance data were analysed by Student's paired *t*-tests. For statistical comparisons of the baseline and treatment phases, the first 7 days of baseline were excluded from analysis in order to allow for equilibration on the diet and dialysis regimens. All days of rhGH treatment were included for the comparison with baseline. Data are expressed as means ± SD.

Results

The characteristics of the six patients are shown in Table 1. Three patients were women. Mean age was 59.5 ± 10.7 years. Three patients were Hispanic, two were Caucasian and one was Asian. The mean duration of their haemodialysis therapy was 20.7 months (range: 3–92 months). The patients showed much evidence of PEM. At the onset of the study (i.e. beginning of baseline), their serum albumin averaged 3.46 g/dl (range: 2.3–5.0 g/dl) and their relative body weight was 70.2% (range: 60–85%). Serum IGF-1 was 165 ± 80 ng/ml (normal: 250–300 ng/ml). Patient 1, who was a small man (body weight: 50.0 kg), had a pre-study dietary energy and protein intake of 44.4 kcal/kg/day and 1.45 g/kg/day, respectively. Excluding patient 1, the pre-study energy and protein intakes of the other five patients averaged 26.4 ± 4.1 kcal/kg/day and 0.97 ± 0.11 g/kg/day, respectively. Serum bicarbonate, obtained 1 or 2 days after a haemodialysis treatment, was 26.0 ± 2.8 mEq/l (range: 23–29 mEq/l).

Although all patients appeared clinically stable when they entered the study, two individuals became acutely ill during the trial. Patient 3, a 56-year-old Japanese American woman weighing 35.4 kg, with a height of 1.49 m, body mass index of 16.0 kg/m^2, relative body weight of 62%, serum albumin of 2.65 g/dl and pre-haemodialysis serum bicarbonate of 23 mEq/l, developed a recurrence of pancreatitis several days after commencing the balance study. Her serum amylase rose to 938 mU/ml. Since this patient was able to continue eating her food and agreed to continue to participate in the study, nitrogen balances were continued. Patient 4 was a 71-year-old Hispanic female weighing 45.6 kg, with a serum albumin of 2.5 g/dl and relative body weight of 71%. On commencing the balance study, she complained of vague pains in both knees which did not appear to be red, hot or swollen. Her white blood cell count was 9100×10^9/l with 70% polymorphonuclear leukocytes and she was afebrile. The aspirate of the synovial fluid in her knee showed a white cell count of 5500×10^9/l with 77% neutrophils and cultures of the aspirate were negative. Her serum C3 was 31 mg/dl (normal: 70–176 mg/dl), C4 was <8.0 mg/dl (normal: 12–36 mg/dl), rheumatoid arthritis latex fixation titre was 80 (normal: <80) and four erythrocyte sedimentation rates obtained from day 15 through day 24 of the study were 93, 76, 125 and 120 mm/h, respectively. She was diagnosed as having an active collagen-vascular disease, probably rheumatoid arthritis.

During the treatment phase, when daily rhGH injections were given, serum growth hormone levels, obtained in the morning before the day's 08.00 rhGH injection, did not increase (Table 2). Serum growth hormone was also measured serially for 24 h on one occasion in each patient after a single injection of rhGH (Figure 1). The serum growth hormone levels rose rapidly and T_{max} occurred 2 or 6 h after injection. After reaching peak values, serum growth hormone decreased rapidly. Immediately before the next rhGH injection at 08.00 the next day, serum growth hormone

Table 2. Serum values and dietary parameters during the study

	Mean of baseline phase[a] (8–21 days)	Mean of rhGH treatment phase[a] (0–21 days)
SUN (mg/dl)[b]	66.9 ± 20.0	49.9 ± 12.8[c]
Serum creatinine (mg/dl)[b]	6.53 ± 2.7	6.58 ± 2.5
Serum growth hormone (ng/ml)[b]	1.32 ± 0.80	1.54 ± 0.98
Serum IGF-I (ng/ml)[b]	160.0 ± 80	360.5 ± 242.5[d]
Serum albumin (g/dl)[b]	3.47 ± 0.83	3.70 ± 0.48
Body weight (kg)	51.2 ± 12.1	52.0 ± 12.7
Dietary energy intake (kcal/kg/day)	30.0 ± 8.8	30.0 ± 8.8
Dietary protein intake (g/kg/day)	1.07 ± 0.23	1.07 ± 0.23

Values are means ± SD ($n = 6$).
[a]Data for this table were collected in the baseline phase at days 8–21 for patient 1 and days 8–14 for patients 2–6. Data were collected in the treatment phase at days 0–8 for patient 1, days 0–14 for patient 5 and days 0–21 for patients 2–4 and 6.
[b]Data obtained pre-dialysis the morning of a haemodialysis treatment.
Significant difference *vs* baseline: [c]$P = 0.001$ and [d]$P = 0.002$, ANOVA; data from the first week of baseline were deleted from patient 1 for repeated measures.

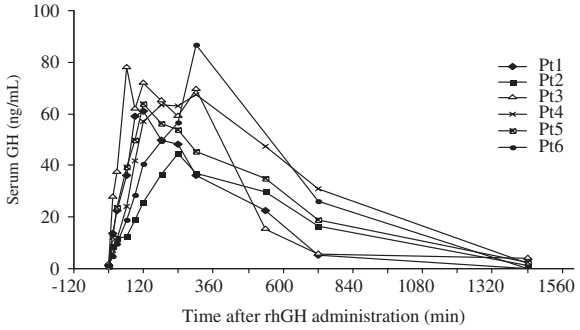

Fig. 1. Serum growth hormone concentrations (GH), measured periodically over 24 h, in six MHD patients before and after they received their first subcutaneous injection of rhGH (0.05 mg/kg). Note that serum growth hormone peaked between 2 and 6 h after the subcutaneous administration and that serum growth hormone returned to baseline values before patients received their next rhGH injection at time 1440 min (i.e. 24 h later).

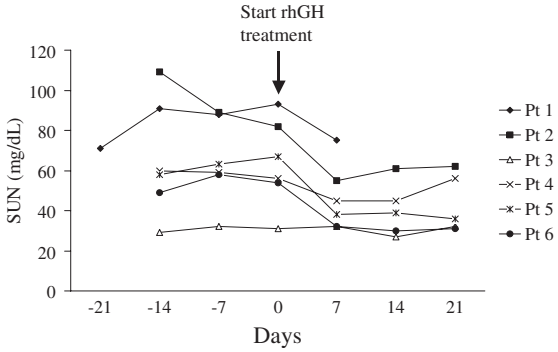

Fig. 3. SUN concentrations in six MHD patients, taken the morning before the dialysis session and before and during the administration of rhGH (0.05 mg/kg/day) for 8–21 days (change in SUN after starting rhGH injections: $P = 0.001$, ANOVA for repeated measures). To convert to Système International (SI) units, multiply SUN values by 0.357.

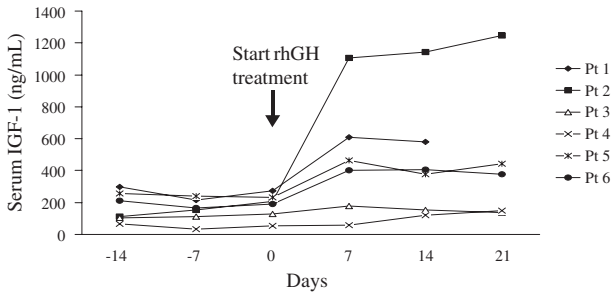

Fig. 2. Serum levels of IGF-I in six MHD patients before and during the administration of rhGH (0.05 mg/kg/day) for 8–21 days (change in serum IGF-I after starting rhGH injections: $P = 0.002$, ANOVA for repeated measures).

concentrations were not different from the previous day's pre-injection values.

Serum IGF-1, measured in blood drawn at about 07.45, rose rapidly and significantly ($P = 0.002$) after commencing the daily rhGH injections (Figure 2 and Table 2). The rise was particularly great in patients 1, 2, 5 and 6. There was, at most, a minimal rise in serum IGF-1 in patients 3 and 4, which appeared to be transient in patient 3 and delayed in patient 4 (Figure 2). A comparison of the magnitude of rise in serum growth hormone (Figure 1) and serum IGF-I (Figure 2) indicates a lower serum IGF-I: serum growth hormone ratio in patients 3 and 4 in comparison to the other four patients.

The baseline and treatment phases of the study averaged 15.2 ± 2.9 and 17.3 ± 5.3 days of duration, respectively. During the 2 or 3 weeks of the baseline phase, SUN decreased slightly from 69.6 ± 20.0 mg/dl (24.8 ± 7.1 mmol/l) to 67 ± 20 mg/dl (23.9 ± 7.1 mmol/l) (P = NS) (Figure 3). During the first week of rhGH treatment, SUN decreased in every patient, by 3–26 mg/dl (1.1–9.3 mmol/l). By the end of the first week of rhGH therapy, SUN had fallen significantly to 52 ± 14 mg/dl (18.6 ± 5.0 mmol/l) (end of baseline *vs* end of first rhGH treatment week; $P = 0.01$) and SUN fell further by the end of the second week of rhGH treatment to 47 ± 11 mg/dl (16.8 ± 3.9 mmol/l) (end of baseline *vs* end of second week of treatment; $P = 0.007$). The change in SUN between the end of the first and second weeks of rhGH treatment averaged 3.2 mg/dl (1.1 mmol/l) [range: 0–22 mg/dl (0–7.0 mmol/l)] and was not statistically significant. SUN at the end of the rhGH treatment was 43.4 ± 14.5 mg/dl (15.5 ± 5.2 mmol/l), which constituted a 32% decrease below the concentrations at the end of baseline. Thus, most of the reduction in SUN after starting rhGH occurred during the first week of treatment. It is pertinent that the smallest decrease in SUN, between the onset of rhGH therapy and the completion of the study, occurred in patients 3 and 4. SUN values in these individuals decreased by only 1 and 7 mg/dl (0.36 and 2.5 mmol/l), respectively, during the course of their rhGH treatment.

The decrease in SUN with rhGH administration cannot be due to changes in urine excretion. Patients 2 and 4 had no urine output at any time during the study. In patients 1, 5 and 6, urine total nitrogen fell during the first week of rhGH treatment by 0.21, 0.31 and 0.50 g/day, respectively; patient 3 showed a slight increase in urine total nitrogen of 0.19 g/day. After the first week of rhGH treatment, urine total nitrogen decreased further in patients 1, 5 and 6. In patient 3, urine total nitrogen stabilized during the second week of rhGH therapy and then fell by 0.21 g/day in the third week. The serum albumin and creatinine concentrations and body weights did not change during the course of study (Table 2).

The nitrogen-balance data are shown in Table 3 and Figure 4. Nitrogen intake, which was constant throughout the study in any given patient, averaged 8.91 ± 2.04 g/day in the six patients, which is equivalent to a dietary protein intake of 55.7 ± 12.8 g/day or 1.10 ± 0.48 g/kg/day. Nitrogen balance, adjusted for changes in body urea nitrogen (see 'Subjects and methods'), varied from slightly positive to moderately negative in the six patients during the second and

Table 3. Adjusted nitrogen balances (g N/day) in MHD patients undergoing rhGH treatment

Patient	1	2	3	4	5	6	Mean ± SD
Nitrogen intake (g/day)							
Average daily intake	9.03	12.35	6.23	7.68	9.43	8.76	8.91 ± 2.04
Period							
Nitrogen balance (g/day)							
Baseline phase							
I (7 days)	+0.49	+3.10	+0.50	+0.71	+1.13	+0.70	+1.11 ± 1.00
II (7 days)	−1.24	+1.65	+0.41	+0.35	+0.59	+0.27	+0.34 ± 0.93
III (7 days)	−0.02	–	–	–	–	–	–
Treatment phase[a]							
IV (7 days)	+3.99	+3.19	+1.02	+0.89	+2.97	+1.46	+2.25 ± 1.30
V (7 days)	–	+5.18	+0.32	+0.82	+3.06	+2.07	+2.29 ± 1.94
VI (7 days)	–	+3.57	+0.30	+0.84	–	+1.67	+1.60 ± 1.43

Values are the mean of 7 days within each nitrogen-balance period, except for period IV in patient 1, which lasted 8 days.
[a]Difference between the mean of the last baseline period and the mean of all rhGH treatment periods: $P = 0.03$, $n = 5$.

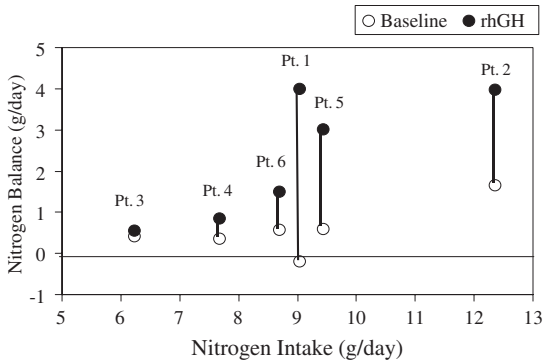

Fig. 4. Nitrogen balances adjusted for changes in body urea nitrogen and averaged for all periods during baseline (before commencing rhGH injections, open circles) and also during treatment (after commencement of daily injections of rhGH (0.05 mg/kg/day) for 8–21 days, closed circles) in six malnourished MHD patients. The measured total nitrogen intake (g/day) during both baseline and treatment phases is also shown. For more detail, refer to Table 3; difference between baseline and rhGH treatment phases, $P = 0.021$ by Student's paired *t*-test.

(for patient 1) third periods of the baseline phase and averaged +0.40 ± 0.75 g/day during the second and third baseline periods. Mean nitrogen balance became abruptly and significantly more positive during the first rhGH treatment period and remained significantly more positive throughout each week of growth hormone treatment. Nitrogen balance during rhGH treatment averaged 2.35 ± 1.53 g/day (nitrogen balance during treatment *vs* baseline phases; $P = 0.034$) and became more positive in each patient during rhGH treatment. It may be estimated that between 0.50 and 1.0 g of nitrogen were lost each day from the body from such unmeasured outputs as respiration, growth of integumentary structures (epidermis, nails and hair), sweat, flatus and the regeneration of proteins, peptides and amino acids lost from blood drawn [13]. If either of these amounts of nitrogen are added to the total nitrogen output, the average nitrogen balance would not differ from zero during the baseline phase and still would be significantly more positive than zero and greater than the baseline nitrogen balances during the treatment phase.

In patients 1, 2, 5 and 6, adjusted nitrogen balance became strikingly positive and averaged +3.18 ± 1.07 g/day throughout the rhGH treatment phase. After commencing rhGH treatment, nitrogen balance became only slightly more positive in patients 3 and 4, who were acutely ill and had the lowest nitrogen intakes (Table 3 and Figure 4). Indeed, the increased positivity of nitrogen balance in patient 3 was transient and lasted only for the first of the patient's three balance periods during rhGH treatment (Table 3). Patients 3 and 4 were the individuals who displayed only a minimal rise in serum IGF-I concentrations and a small decrease in SUN levels.

Discussion

The results of this study confirm that rhGH treatments can rapidly induce positive protein balance in MHD patients who have PEM. Malnourished MHD patients living in a research ward, who were eating a constant protein diet, were given daily subcutaneous injections of rhGH (0.05 mg/kg/day) for 8–21 days. They quickly experienced a reduction in total nitrogen output, a decrease in SUN and a more positive nitrogen balance. The reduction in total nitrogen output can be ascribed primarily to the fall in the nitrogen output in dialysate. Since throughout the course of the study the dietary protein intake and haemodialysis regimen were kept constant, renal function was negligible, urine nitrogen excretion generally did not rise and patients were clinically stable, the fall in SUN with rhGH treatment must reflect a decrease in urea nitrogen appearance. The nitrogen content of spent haemodialysate is largely composed of urea nitrogen.

Hence, the fall in dialysate total nitrogen must largely reflect a decrease in dialysate urea nitrogen.

These nitrogen-balance studies support the findings of previous investigators who examined the metabolic effects of rhGH in MHD [4,5,7–9] or chronic peritoneal dialysis (CPD) [6,9] patients. Ziegler *et al*. [4] reported that five well-nourished MHD patients displayed a decrease in SUN and phosphate during rhGH treatment. Schulman and colleagues [5] described a reduction in protein nitrogen appearance (PNA) and an increase in serum albumin in MHD patients who were receiving intradialytic parenteral nutrition and rhGH. Ikizler and associates [6] gave rhGH to CPD patients and observed a reduction in SUN, potassium, phosphorus and also albumin. Garibotto *et al*. [7], measuring muscle protein metabolism, showed an increase in protein synthesis in malnourished MHD patients. Iglesias *et al*. [9] reported decreased SUN and body fat mass and improved anthropometry in both malnourished MHD patients and CPD patients. Shinobe and co-workers [8] also observed a rapid drop in SUN and PNA and an increase in serum albumin and haematocrit. Hansen *et al*. [10], using dual X-ray photon absorptiometry, showed a decrease in body fat and increase in lean body mass in malnourished MHD adults. These findings are similar to the anabolic response to rhGH treatment of most patients with chronic or acute illnesses who generally did not have renal disease [2,14].

The mechanism by which rhGH engenders an anabolic response involves the elaboration of IGF-I. IGF-I induces many anabolic processes that result in growth in children and more positive nitrogen balance in adults [1,3,15]. IGF-1 enhances intracellular transport of glucose and amino acids, stimulates protein synthesis, suppresses protein degradation and stimulates bone growth and enlargement of many organs [1,3,15].

An unusual and potentially clinically relevant observation from this study was the discrepant responses to rhGH in individual patients. After commencement of the rhGH injections, four patients demonstrated a major reduction in SUN levels and a large increase in the positivity of nitrogen balance (patients 1, 2, 5 and 6). Each of these four individuals also displayed a rather large rise in serum IGF-I (Figure 2). In contrast to this response to rhGH injections, patients 3 and 4 displayed, at most, only a minimal rise in serum IGF-I, a very small decrease in SUN and a small and, in the case of patient 3, only transient increase in the positivity of nitrogen balance. The ratio in sera of IGF-I to growth hormone in patients 3 and 4 was much lower than in the other four patients (Figures 1 and 2). These observations, taken together, suggest that patients 3 and 4 were resistant to the stimulatory actions of growth hormone on IGF-I secretion. Moreover, these considerations are consistent with the thesis that a rise in IGF-I levels is necessary for rhGH treatment to induce an anabolic response in protein metabolism. It is pertinent that there was a rapid rise and short half-life of serum growth hormone in all six of our MHD patients following the injection of rhGH, which was similar to the kinetics of rhGH described in normals (Figure 1) [16].

The cause of the impaired rise in serum IGF-I may be the episode of acute pancreatitis experienced by patient 3 after commencement of the study and the inflammatory illness in patient 4. Of the six individuals studied, patients 3 and 4 also displayed the greatest degree of PEM, as indicated by their reduced dietary energy and protein intakes, their low serum albumin levels and their low body mass.

These findings of a reduced rise in serum IGF-I and impaired anabolic response with rhGH treatment have been observed in some studies of severely ill patients [14]. In experimental as well as in human studies, starvation, sepsis, acidosis, malnutrition and inflammation have been associated with a reduction in serum IGF-1 concentrations and the major IGF binding protein (BP) in serum, IGFBP-3, or a reduced rise in IGF-1 levels in response to rhGH injections [14,17–19].

Thus, although some studies, including the present research, indicate that the anabolic effects of rhGH on protein balance may be attenuated or abolished in acutely ill or poorly nourished individuals, many studies have demonstrated that rhGH will induce an anabolic response in patients with acute catabolic illnesses [14], some of whom showed evidence of substantial malnutrition. The explanation for these differences in the serum IGF-1 and anabolic response to rhGH injections is not clear, but might be related to the concentrations or reactivity of pro-inflammatory cytokines or other toxins in septic and/or inflamed patients [17]. Thus, it could be argued that individuals who have inflammatory or catabolic illnesses or very low nutrient intakes and who might benefit from an anabolic hormone may be given rhGH, but the anabolic response should be monitored because some of these patients may not respond to such treatment.

A limitation of this study is that there was no control group. However, patients had been on a constant diet and dialysis regimen and had been living in the protected environment of a general clinical research centre for 2–3 weeks before rhGH injections were started. Then, concurrently with the onset of rhGH treatment, there was a sudden increase in the positivity of nitrogen balance and fall in SUN levels in patients 1, 2, 5 and 6. These observations strongly suggest that their more positive nitrogen balance and fall in SUN were due to the rhGH injections.

It is possible that a greater treatment dose or a longer duration of treatment with rhGH might have induced a greater rise in serum IGF-1 levels and a more positive anabolic response in patients 3 and 4. Also, it should be recognized that, at present, rhGH treatment has not been shown to improve morbidity, mortality or quality of life in acutely ill or malnourished adults with renal failure [4–6,10,19], although large-scale studies to examine these potential effects of rhGH have not been carried out. Although the patients in the present study were not critically ill and could readily

be medically managed in a hospital research ward, care must be taken when considering giving rhGH to severely ill patients; rhGH treatment has been observed to increase mortality in sick intensive care unit patients [20]. Further studies will be helpful to elucidate the mechanisms by which some sick individuals develop a rise in serum IGF-1 and a strongly anabolic response to rhGH and others do not.

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