

# A Randomized Controlled Trial of Low-Dose Recombinant Human Growth Hormone in the Treatment of Malnourished Elderly Medical Patients\*

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## ABSTRACT

High-dose recombinant human GH (rhGH) has been shown to improve the nutritional status of malnourished older adults. It is uncertain whether low-dose rhGH is effective and whether its effect on nutritional status will lead to any improvement in physical function. There is also no data on the outcome after a short course of rhGH treatment. The objectives of this study were to determine the efficacy of low-dose rhGH treatment for 4 weeks in malnourished elderly patients, its effect on physical functions, and the intermediate term outcome after a 4-week rhGH treatment. The study design was a randomized, placebo-controlled, double-blind trial conducted in a university teaching hospital. The patients were 19 medically stable malnourished elderly subjects. Intervention in the rhGH group was as follows: rhGH (Saizen, Serono, Switzerland) 0.09 IU/kg body weight (BW) 3 times weekly were given together with appropriate dietary intervention as prescribed by the dietitian. In the placebo group, equal volumes of normal saline per kilogram BW were given 3 times weekly together with the dietary intervention.

The baseline demographic, anthropometric, nutritional, and hematological variables, measures of physical function, and insulin-like growth factor I levels in both groups were comparable. Compared with the placebo group, the GH-treated group showed a more rapid gain in

BW (after 3 weeks,  $+1.27 \pm 0.36$  vs.  $-0.28 \pm 0.37$  kg;  $P = 0.008$ ), total lean body mass (change after 3 weeks by bio-impedance analysis,  $+1.45 \pm 0.36$  vs.  $-0.37 \pm 0.48$  kg;  $P = 0.009$ ) and a faster improvement in 5-m walking time (decrease after 4 weeks,  $23.79 \pm 9.41$  vs.  $0.45 \pm 4.62$  sec;  $P = 0.047$ ). The hemoglobin level rose more in the rhGH than the placebo groups (change at 8 weeks,  $+0.84 \pm 0.34$  vs.  $-0.42 \pm 0.29$  g/dL;  $P = 0.012$ ). Serum albumin level also showed a greater delayed increase in the rhGH group than in the placebo group (change at 8 weeks,  $+5.1 \pm 0.8$  vs.  $1.6 \pm 1.2$  g/dL;  $P = 0.023$ ). There was no statistically significant difference for other nutritional variables. There was a greater rise in the mean serum insulin-like growth factor I level at 4 weeks in the GH than in the placebo groups ( $197 \pm 58$  vs.  $54 \pm 26$  U/L;  $P = 0.034$ ). The improvement in the rhGH group gradually diminished on follow-up and became statistically insignificant 8 weeks after stopping rhGH treatment. There were no GH-related adverse effects.

Low-dose rhGH was an effective and safe adjuvant to dietary augmentation for stable malnourished elderly subjects. It led to a faster gain in total lean body mass, which was associated with greater improvement in walking speed when compared with dietary intervention alone. There were no apparent side effects. (*J Clin Endocrinol Metab* 86: 1913–1920, 2001)

**M**ALNUTRITION IS common in elderly people with chronic diseases. The prevalence of protein-energy under-nutrition in the elderly medical patients has been reported to be 17–44% (1–4). Undernourished elderly not only have an increased chance of mortality, but are at increased risk of impaired immune function, infections, impaired muscle function, falls, and deterioration of functional status (5–10).

Clinical management principally includes the treatment of the underlying cause and nutritional intervention. The standard treatment approach in nutritional repletion is by increasing the protein and energy intake in the diet, and nutritional supplementation has been shown to be an effective

means of providing additional nutrients on top of the usual diet (11).

Aging is associated with decreased GH secretion and dynamic response (12). The beneficial effects of GH replacement in GH-deficient children and adults have been well reported (13). GH is a potent protein anabolic agent. Several studies of 1–3 weeks duration using moderate doses of recombinant human GH (rhGH) in postoperative subjects and malnourished elderly [rhGH 0.3 IU/kg body weight (BW) daily] have shown promising positive results in nitrogen balance and weight gain, with no accompanied adverse effect (14–16). Low-dose rhGH replacement (rhGH 0.09 IU/kg BW 3 times per week) for 6 months in healthy elderly men also improved body composition (17). However, side effects such as edema of the lower limbs, diffuse arthralgia, hand stiffness, gynecomastia, and carpal tunnel syndrome were common (17–21). These side effects subsided after the reduction of GH dose by 25–50% (17).

There are no published data on the efficacy of low-dose rhGH in the treatment of protein-energy malnourished elderly patients. It is uncertain whether any beneficial effect on

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physical function outcomes can be obtained after rhGH in malnourished elderly patients. The lack of benefit in physical function in a previous trial of low-dose GH replacement in healthy older men (17) did not necessarily imply that functional improvement would not occur with GH treatment for frail malnourished older adults. Finally, no data are available regarding the longer-term outcome after a 4-week short course treatment of rhGH in these patients.

The objectives of the present study were to evaluate the efficacy of low-dose rhGH in elderly subjects with protein-energy malnutrition, its effect on physical function, and the intermediate-term outcome after a 4-week rhGH treatment course.

## Patients and Methods

### Study design, setting, and subjects

This was a double-blind randomized controlled study conducted in the Division of Geriatric Medicine, University Department of Medicine of the Queen Mary Hospital (Hong Kong, China). The protocol was approved by the Ethics Committee of the University of Hong Kong. All 884 patients who attended our Queen Mary Hospital Geriatrics Assessment Clinic and Geriatrics Inpatient Unit from March 1998 to July 1999 were consecutively assessed for eligibility for the study. Eighty-five elderly patients who had low BW by height (<80%) were screened. Subjects were recruited if they were 70 yr of age or older, less than 80% ideal BW for height (height-weight tables for elderly persons in Hong Kong; Ref. 22), had a body mass index less than 19 kg/m<sup>2</sup>, a serum albumin level less than or equal to 38 g/L (normal reference range, 43–55 g/L), and a prealbumin level less than or equal to 0.18 g/L (normal reference range, 0.18–0.42 g/L).

Exclusion criteria were as follows: any malignancy within the past 5 yr, a known history of diabetes mellitus or fasting glucose level greater than or equal to 7.0 mmol/L (23), active infections including tuberculosis, end-stage organ failure (e.g. renal), metabolic causes for weight loss including hyperthyroidism and Addison's disease, a diagnosis of acromegaly, uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >105 mm Hg), a history of carpal tunnel syndrome, corticosteroid use (within the previous year), or fixed contractures of lower limbs, which could hinder the assessment of walking.

The primary endpoints were total lean body mass (LBM) and 5-m walking time. Secondary endpoints were BW, arm muscle circumference (AMC), handgrip strength, and serum albumin level.

### Randomization and blinded assessment

Eligible subjects, who had given written informed consent, were randomized to receive either rhGH or placebo. A random number table was used to generate the randomization codes, which were put into individually sealed envelopes and drawn in consecutive order. All subjects, the two research nurses, as well as the clinicians, who were involved in the assessment and clinical treatment, were blinded to the subjects' group assignment. The interrater reliabilities of anthropometric measurements between the two research nurses were assessed in 10 subjects. The intraclass correlation coefficients (*r*) for the measurements of height, BW, midarm circumference (MAC), triceps skin fold (TSF), left hand grip strength, right hand grip strength, bio-impedance readings for body compositions, and 5-m walking time were 0.99, 0.99, 0.99, 0.99, 0.94, 0.94, 0.94, and 0.99, respectively (all *P* values <0.001, two-tailed).

### Baseline, weekly assessment for the first 4 weeks and subsequent posttreatment observational follow-up for 26 weeks

All subjects were assessed at baseline and then at weeks 1, 2, 3, 4, 8, 12, and 26. At the baseline visit, complete history and physical examination were performed and the principal medical diagnosis and comorbid medical diseases were recorded. Dietary intake of protein and cal-

ories was evaluated at baseline and after 4 weeks, based on a 3-day food diary and analyzed by our dietitians.

BW was measured with a digital weight scale with the patient wearing standard hospital pajamas. Standing height without shoes was measured with a stadiometer. MAC and TSF were measured on the left arm at the midpoint between the acromion and olecranon processes, using a plastic tape measure. TSF was measured at the same level along a vertical fold posteriorly, using Harpenden calipers (British Indicators Limited, West Sussex, UK). The mean values derived from 3 measurements of TSF and MAC were used in the analysis. AMC in cm was calculated from the following formula: MAC – TSF × 3.14. Body composition was measured by bioelectric impedance analysis (BIA; Bio-Analogs, Beaverton, OR), using tetrapolar leads over the right wrist and right ankle and with an excitation current of 800 microamperes at 50 kilohertz. The impedance value measured was used to calculate the total body lean mass and fat mass. BIA has been shown to be a reliable method in monitoring of LBM [*i.e.* fat-free mass (FFM)] during clinical management of malnutrition and GH replacement in GH deficiency states in hypopituitary adults (24–27). Beshyah *et al.* (27) have compared the results of several methods of body composition reassessments (*i.e.* total body potassium, bioimpedance analysis, and dual-energy x-ray absorptiometry) in hypopituitary adults before and during GH treatment. In our study, we also assessed LBM change before and after GH treatment. In the study of Beshyah *et al.* (27), there was a significant correlation between the values of LBM (*i.e.* FFM) obtained by DEXA and BIA. The correlation coefficients (*r*) were 0.9 (*P* = 0.001) for all subjects and 0.83 (*P* = 0.001) for nonobese subjects. For nonobese subjects, there was no significant difference between the mean values of LBM (*i.e.* FFM) obtained from DEXA and BIA.

Hand grip strength (kilograms-force) for right and left hands was measured at each visit with the Jamar hand dynamometer (Sammons Preston, Bolingbrook, IL). The subject sat on a firm chair with his arm flexed at 90 degrees at the elbow. Three measurements at 1-min intervals were obtained and the mean value was calculated. During every visit, the 5-m walking time (seconds) along a 5-meter straight path marked with a small rope on the floor, was assessed, using a stop-watch. The subjects were asked to walk as fast as possible during assessments. Usual walking aids (*e.g.* stick, walker) were allowed if required.

At each visit, serum albumin, prealbumin, transferrin, hemoglobin, white cell count, absolute lymphocyte count, neutrophil count, renal and liver function tests, serum calcium and phosphate, fasting lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol), and plasma glucose were measured. Serum TSH, free T<sub>4</sub>, free T<sub>3</sub> (if indicated), and morning cortisol (0900 h) were performed at baseline. HbA<sub>1c</sub> and a 75-g oral glucose tolerance test was performed at baseline and the end of 4 weeks. A fasting serum sample for insulin-like growth factor I (IGF-I) was obtained at 0900 h at baseline and the end of 4 weeks (24 h after rhGH injection). IGF-I was measured by RIA in acid-ethanol extracted EDTA plasma samples with commercial kits (Nichols Institute Diagnostics, San Juan Capistrano, CA). The intraassay coefficient of variation was 3%, and the interassay coefficient of variation was 8.4%.

### Monitoring adverse effects

All outcome and adverse effect parameters were monitored at every follow-up visit, noting especially GH-related adverse effects such as glucose intolerance, carpal tunnel syndrome, hypertension, hyperlipidemia, gynecomastia, edema, arthralgia, arthritis, and hand stiffness (17, 20, 21). All deaths and their causes were confirmed from hospital records and death registry.

### Dietary treatment for both groups

Dietary requirement was calculated according to the ideal BW to meet the individual needs of energy and protein. All subjects were encouraged to eat as much as possible, but none was able to take an adequate amount of food (as indicated from the dietary assessment of their usual daily intake of protein and energy). Enercal-plus, containing 360 kilocalories (Kcal) and 14 g protein per 240 mL, was used as nutritional supplement. The daily amount required for each subject was calculated by our dietitians with reference to the dietary deficit, and closely monitored by community nurses who made home visits 3 times per week.

### GH or placebo injections

In the GH group, subjects were given sc rhGH (Saizen, Serono, Switzerland) 0.09 IU/kg (0.03 mg/kg) 3 times per week (17) for 4 weeks. In the placebo group, an equal volume of normal saline per kg, BW was given three times weekly for 4 weeks. Neither the nurse who prepared the injections nor the ones who administered the injections were involved in the assessment of the subjects. The injection vials of identical appearance were labeled as either GH A or GH B.

### Sample size calculation

Based on data from Papadakis *et al.* (17) and using total LBM as the outcome variable, the number required in each group would be 7 (estimated effect size = 2.1% higher increase in lean mass in rhGH vs. placebo groups;  $\alpha = 0.05$ , power = 0.95) (28).

Assuming a corresponding improvement in muscle function, the estimated statistical power for the 5-m walking time would be 0.95. This would decrease to 0.8, still acceptable, if the effect size was 20% less for this functional measure. To allow for up to 3 cases of withdrawal or loss to follow-up, 10 subjects in each group were recruited.

### Statistical analyses

An intention to treat analysis was used for all randomized subjects. Baseline characteristics between the two groups were first analyzed. Differences in responses to the two treatments in the two groups were then analyzed. Continuous variables were analyzed by Student's unpaired *t* tests and categorical variables were analyzed by the Fisher's exact test. Within group differences were analyzed by paired *t* tests for continuous variables. Data were expressed as mean  $\pm$  SEM. Statistical significance was taken to be *P* less than 0.05 (two-tailed). Multivariate analysis was performed using analysis of covariance (ANCOVA) for baseline variables with *P* less than 0.1. Statistical analyses were performed using SPSS for Windows (version 7.5; SPSS, Inc., Chicago, IL).

### Results

From March 1998 to July 1999, 85 elderly medical patients who had low BW by height (<80%) were screened. Of the 35 subjects who fulfilled all of the inclusion and exclusion criteria, 15 refused to participate. Their reasons were either fear of venesection or unwillingness to attend the follow-up visits frequently. There were no statistically significant differences in age and sex between the excluded subjects and the study's subjects. The 20 subjects recruited gave written informed consent and were randomized to receive either rhGH ( $n = 10$ ) or placebo ( $n = 10$ ) treatment. One subject in the GH group was subsequently excluded from analysis because the baseline prealbumin level became normal although the screening value was low. (Fig. 1, trial profile).

As shown in Table 1, there was no statistically significant difference with respect to demographic, nutritional, biochemical, serum IGF-I level, and physical function parameters (*i.e.* 5-m walking time and hand grip strength) between the two study groups. The principal diagnoses were chronic obstructive pulmonary disease, dementia, previous stroke, transient ischemic attack, Parkinson's disease, hypertension, and nutritional anemia (because of the small numbers for the two groups in each category, statistical comparison was not performed). Clinically, there was no progression of the principal medical disease during the course of the study.

### Mortality and causes of death

Four subjects in the placebo group died of pneumonia at 5.4, 11.7, 12, and 23.7 weeks of follow-up. There was no death in the GH group. However, the difference in mortality was

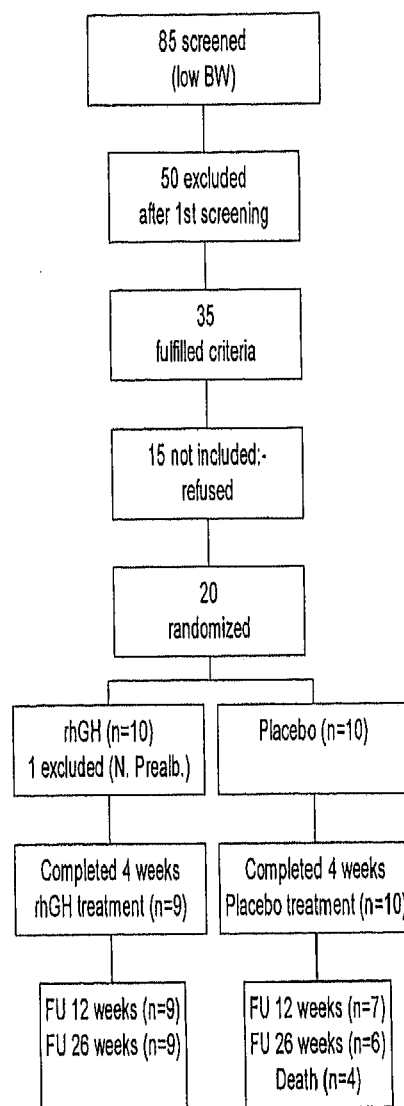


FIG. 1. Trial profile.

not statistically significant ( $P = 0.087$ , two-tailed; Fisher's exact test). One subject in the GH group defaulted the week-26 follow-up. Because at week 26, the sample size of 6 subjects in the placebo group fell short of the minimum sample size of 7 required for adequate statistical power, data of week 26 were omitted in subsequent presentation.

### Effects of rhGH

**BW and body composition.** The GH-treated group showed a faster increase in BW than the placebo group. The difference in weight gain was significant by the end of week 3 [mean difference 1.55 kg; 95% confidence interval (CI) 0.45, 2.64 kg;  $P < 0.01$ ]. In the placebo group, weight gain started gradually from week 4 onward (Fig. 2A).

Total LBM increased rapidly in the GH group, whereas that of the placebo group showed a mild decrease during weeks 2, 3, and 4 before showing a gradual small rise. (Fig.

TABLE 1. Baseline characteristics of study subjects

	GH (n = 9)	Placebo (n = 10)	P value
Sex (Female)	66.7%	30%	0.18
Age (yr)	83.7 ± 2.2	84.9 ± 3.1	0.75
No. of comorbid diseases	3.56 ± 0.50	3.60 ± 0.34	0.94
BW (kg)	33.6 ± 2.2	35.7 ± 2.5	0.55
Body mass index (kg/m <sup>2</sup> )	16.4 ± 0.7	15.1 ± 0.9	0.28
TSF (mm)	5.38 ± 0.65	5.24 ± 0.68	0.89
MAC (cm)	17.95 ± 0.60	17.97 ± 0.79	0.99
AMC (cm)	16.27 ± 0.54	16.32 ± 0.66	0.96
Total body fat mass (kg)	3.44 ± 0.77	2.15 ± 0.62	0.21
Total body lean mass (kg)	30.26 ± 2.5	33.55 ± 2.33	0.35
Right handgrip strength (kg-f)	8.66 ± 2.36	12.34 ± 1.94	0.24
5-m walking time (sec)	59.99 ± 13.83	31.15 ± 6.71	0.09
Serum albumin (g/L)	32.8 ± 1.1	32.0 ± 1.4	0.67
Serum transferrin (g/L)	1.47 ± 0.08	1.77 ± 0.18	0.15
Serum prealbumin (g/L)	0.148 ± 0.012	0.131 ± 0.010	0.28
Hemoglobin (g/dL)	10.90 ± 0.54	11.73 ± 0.36	0.21
Lymphocyte (10 <sup>9</sup> /L)	1.34 ± 0.19	0.97 ± 0.15	0.14
Fasting glucose (mmol/L)	4.81 ± 0.26	4.69 ± 0.14	0.68
Calorie intake (Kcal/day)	904 ± 90	1034 ± 96	0.34
Protein intake (g/day)	34.5 ± 2.9	40.6 ± 3.4	0.19
IGF-I at baseline (U/L)	229 ± 60	179 ± 28	0.45

Mean ± SEM, except for sex (%).

2B) The differences in total LBM gain were statistically significant by the end of week 3 (mean difference 1.82 kg; 95% CI 0.52, 3.11 kg;  $P < 0.01$ ). Analyses by percent changes in BW and LBM showed similar positive results, with significantly greater increases in weight gain ( $P = 0.013$ ) and LBM gain ( $P = 0.016$ ) in the GH vs. placebo groups at week 3. There was no significant difference between the two groups regarding the change in total body fat mass at any time point.

There were no significant differences concerning the changes in AMC, MAC, and TSF between the two groups ( $P = NS$  at all time points).

**Functional status.** The GH group showed a greater reduction in 5-m walking time (*i.e.* walked faster) than the placebo group, with the difference being significant at the end of week 4 (mean difference -23.3 sec; 95% CI -46.3, -0.42 sec;  $P < 0.05$ ). (Fig. 2C) ANCOVA for the change in 5-m walking time between the two groups at week 4, adjusted for the baseline 5-m walking time, showed that it was independent of the baseline 5-m walking time ( $P = 0.012$ , adjusted ANCOVA model).

Because the 5-m walking time could not be tested in one subject at week 4 (because of pneumonia), another analyses with last observation carried forward (from week 3) for this subject were also performed. The GH group showed a similar greater reduction in 5-m walking time than the placebo group ( $P = 0.044$ ).

The mean gains in right or left hand grip strength were not significantly different between the two groups.

**Serum albumin, prealbumin and transferrin as biochemical measures of protein status.** There was a delayed rise in serum albumin level, which was significantly higher in the GH than the placebo group at the end of 8 weeks (mean difference 3.56 g/L; 95% CI 0.55, 6.57 g/L;  $P < 0.03$ ) (Fig. 3A). No difference in the changes of serum transferrin and prealbumin levels was seen between the two groups.

**Hemoglobin and lymphocyte count.** A rise in hemoglobin was seen only in the GH group. The difference in the increment in hemoglobin level between the two groups was statistically significant at 8 weeks (*i.e.* mean difference 1.27 g/dL; 95% CI 0.32, 2.21 g/dL;  $P < 0.02$ ) (Fig. 3B). There was no difference in the changes in lymphocyte count between the two groups.

#### Change in daily protein and calorie intake

The daily intakes of protein and calorie at week 4 were higher than their baseline values in the GH but not the placebo groups. There was no statistically significant difference in the magnitude of increase in protein or calorie intakes between the 2 groups during the 4-week treatment period (Table 2). The overall mean week 4 protein and calorie intakes were 79.3% and 73.3%, respectively, of the recommended amounts.

#### IGF-I responses to dietary and rhGH treatments

The baseline serum IGF-I values (mean, 204 U/L; range, 25–629 U/L) of the 19 subjects were all below the normal youthful range (25–75th percentile of young adult population = 792–1458 U/L) (17). The serum IGF-I levels at week 4 were statistically higher than their baseline levels in the GH but not the placebo groups, and the rise in serum IGF-I level was significantly greater in the GH group (Table 3). Even in the GH-treated subjects, IGF-I levels at week 4 (range, 229–1242 U/L) were still all within the normal youthful range.

#### Adverse effects

No GH-related adverse effects such as edema, arthralgia, hand stiffness, hypertension, carpal tunnel syndrome, gynecomastia, hyperlipidemia, or glucose intolerance were observed in the GH-treated subjects. There were no significant differences between the two groups in lipid profile, HbA<sub>1c</sub>, and liver and renal functions tests. There were also no sig-

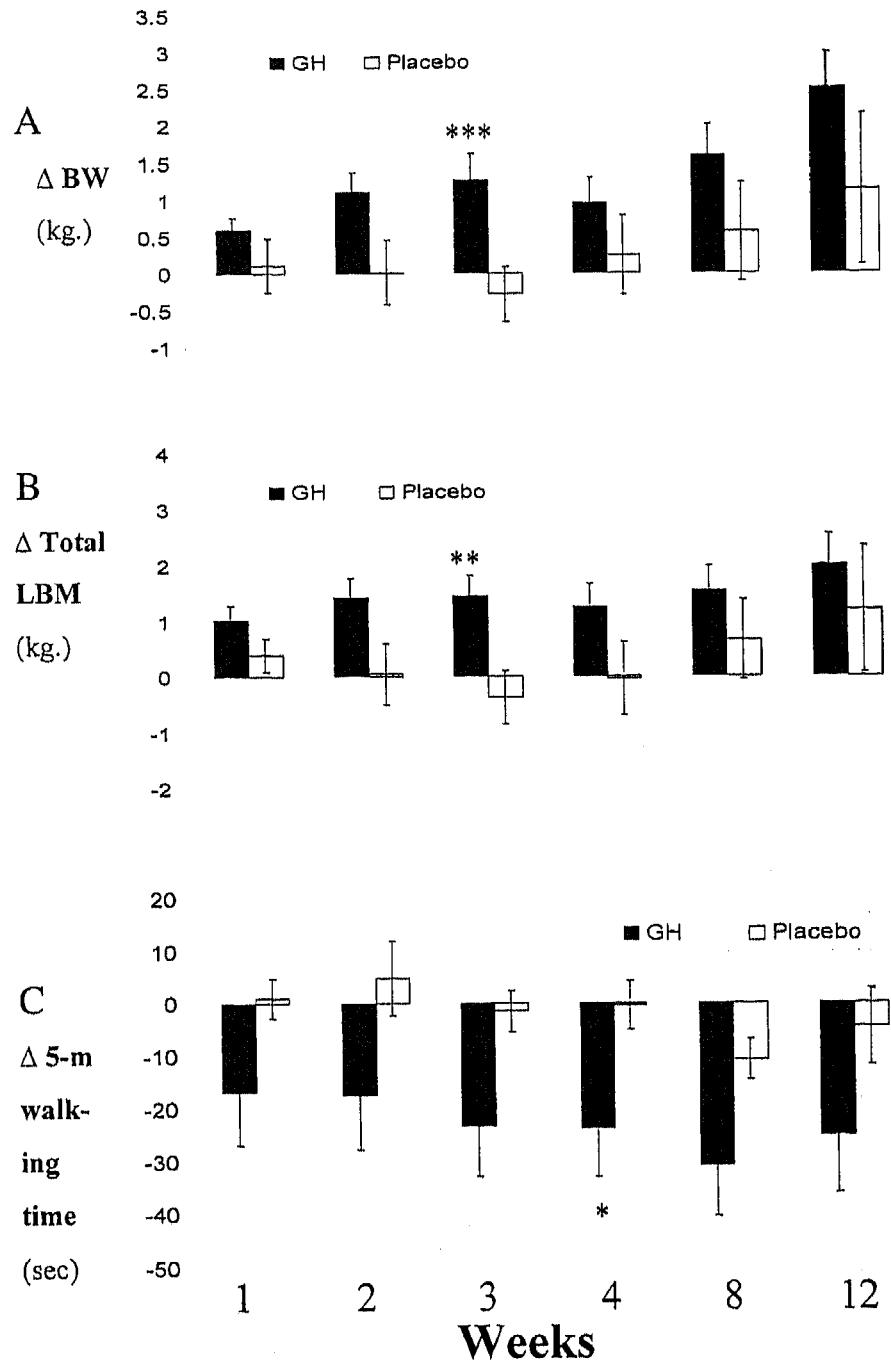


FIG. 2. Mean change in BW (A), total LBM (B), and 5-m walking time (C) in rhGH and placebo-treated patients. GH,  $n = 9$ ; placebo,  $n = 10$  except for week 4 ( $n = 9$ ) in C, week 8 ( $n = 9$ ), and week 12 ( $n = 7$ ) in A-C. \*,  $P = 0.047$ ; \*\*,  $P = 0.009$ ; \*\*\*,  $P = 0.008$  vs. placebo;  $\Delta$ , mean change, mean  $\pm$  SEM; ■, rhGH; □, placebo.

nificant differences in the fasting glucose levels between the two groups at all time points except week 2. A small decrease in the mean fasting glucose level was seen in the GH vs. placebo groups (GH:placebo, mean fasting glucose levels,  $-0.5 \pm 0.1$  mmol/L vs.  $0.1 \pm 0.1$  mmol/L;  $P = 0.003$ ).

#### Discussion

In the present study, low-dose rhGH treatment was shown to be an effective therapy when used as an adjunct to dietary

augmentation in malnourished elderly patients. It gave rise to faster increases in BW, total LBM, hemoglobin level, and serum albumin level in the GH than the placebo groups, despite similar dietary augmentation. It also led to a greater improvement in the 5-m walking time. The improvement in the rhGH group persisted for 4 weeks after stopping this short course of treatment. The improvement in LBM and walking speed were in agreement with the findings of increased protein synthesis observed after rhGH in healthy

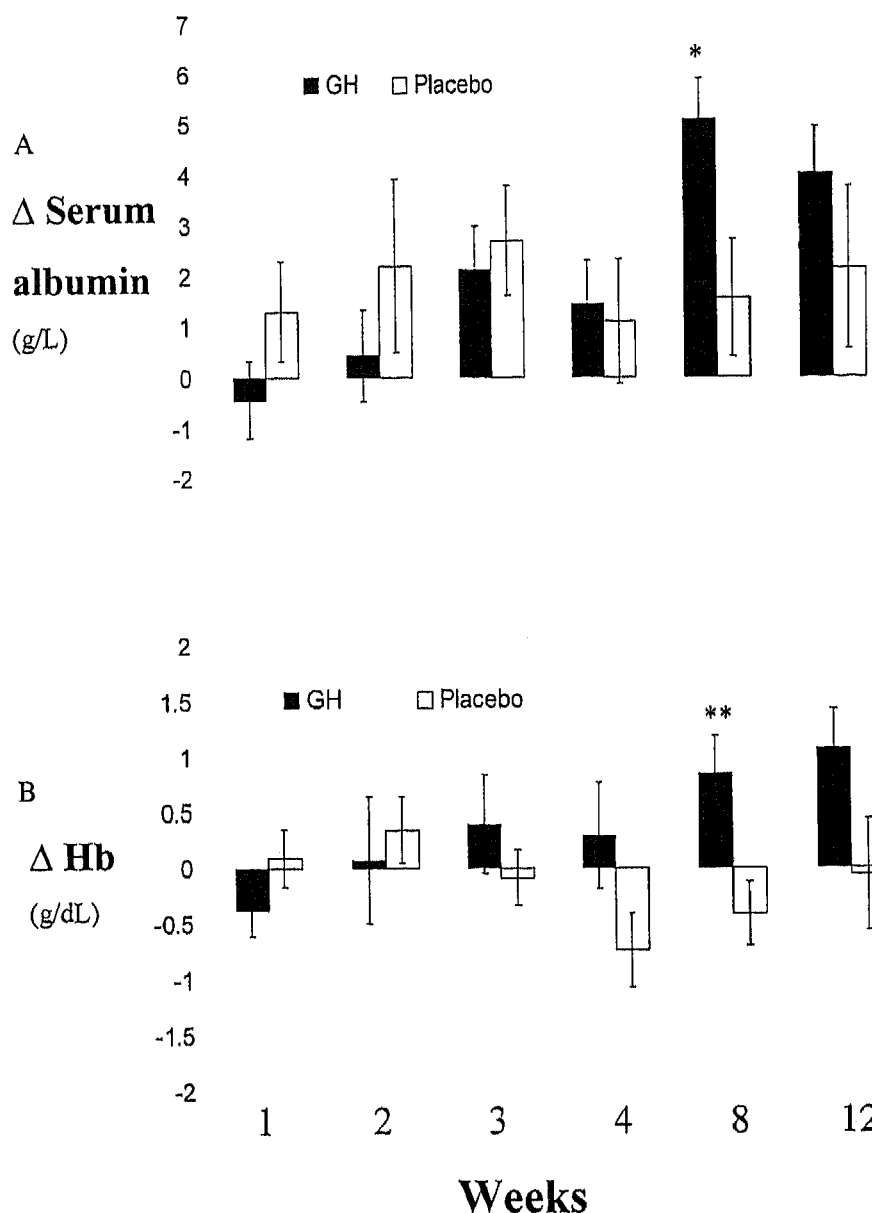


FIG. 3. Mean change in serum albumin level (A), hemoglobin level in rhGH (B), and placebo-treated patients. GH,  $n = 9$ ; placebo,  $n = 10$  except for weeks 8 ( $n = 9$ ) and 12 ( $n = 7$ ). \*,  $P = 0.023$ ; \*\*,  $P = 0.012$  vs. placebo;  $\Delta$ , mean change, mean  $\pm$  SEM; ■, rhGH; □, placebo.

subjects (29), and the improvement in muscle strength and maximal exercise performance after GH treatment in GH-deficient adults (30).

Protein-energy malnutrition in the elderly commonly leads to generalized wasting of muscle mass, weakness of limbs, and decline in physical function. Immobility, falls, injuries, decreased immunity, and proneness to infection are important consequent complications (5–10). Correcting malnutrition effectively and rapidly is important from a clinical perspective.

Dietary intervention with nutritional supplementation alone has been shown to be effective in improving the anthropometric measurements and activities of daily living outcomes of healthy elderly persons recovering from pneumonia (31), but may not be practical for frail malnourished elderly patients. Very often, they cannot take in the required

amount of calories and protein. In our study, the mean total intake of protein and calories after dietary supplementation were still below the prescribed quantity calculated according to their ideal BWs.

Moderately high-dose rhGH (*i.e.* 0.3IU/kg BW, 7 days/week) has been reported to improve protein anabolism and BW gain in malnourished elderly patients (16). In our study, we found that even low-dose rhGH (0.09 IU/kg BW 3 times/week) plus dietary intervention was more effective than dietary intervention alone in enhancing the BW and total LBM, which was accompanied by an improvement in muscle function as measured by the 5-m walking time. Our rhGH dosage was based on the replacement regimen used by Papadakis *et al.* (17), who observed an increase in lean mass and decrease in fat mass in healthy elderly men after 6 months of rhGH treatment at this

TABLE 2. Daily protein and calorie intakes at baseline and week 4

	GH (n = 9)	Placebo (n = 10)	P value
Protein intake (g/day)			
Baseline	34.5 ± 2.9	40.6 ± 3.4	0.19
Week 4	46.5 ± 4.4 <sup>a</sup>	49.1 ± 5.1 <sup>b</sup>	0.7
Increase (week 4 vs. baseline)	12.0 ± 5.1	8.5 ± 6.5	0.68
Calorie intake (Kcal/day)			
Baseline	904 ± 90	1034 ± 96	0.34
Week 4	1205 ± 103 <sup>c</sup>	1300 ± 115 <sup>d</sup>	0.55
Increase (week 4 vs. baseline)	301 ± 95	265 ± 133	0.84

Within group differences (paired *t* test) are noted below.

<sup>a</sup> GH, *P* = 0.048.

<sup>b</sup> Placebo, *P* = 0.22.

<sup>c</sup> GH, *P* = 0.013.

<sup>d</sup> Placebo, *P* = 0.77.

TABLE 3. Serum IGF-1 levels at baseline and week 4

Serum IGF-1 levels (U/L)	GH (n = 9)	Placebo (n = 10)	P value
Baseline	229 ± 60	179 ± 28	0.45
Week 4	426 ± 105 <sup>a</sup>	233 ± 33 <sup>b</sup>	0.086
Increase (week 4 vs. baseline)	197 ± 58	54 ± 26	0.034

Within group differences (paired *t* test) are noted below.

<sup>a</sup> GH, *P* = 0.01.

<sup>b</sup> Placebo, *P* = 0.07.

dosage. However, no improvement in physical function was observed (17), probably because the subjects were all healthy elderly men whose physical function abilities were likely to be around the maximum for their age. In contrast, our subjects were frail malnourished elderly patients whose physical function abilities were below the maximum for their age. The mean 5-m walking time in our subjects was over 30 sec, much higher than the value of below 10 sec for elderly persons from Hong Kong (32). Similarly, previous studies have shown that only the frail and near-frail, but not the healthy, elderly benefited from an improvement in functional status after exercise training (33). Therefore, the intervention window corresponded to the phase of physical function of frailty or near-frailty. This improvement of lower extremity function after GH treatment in malnourished elderly was an important finding, which has not been reported previously.

In this study, a 4-week duration was chosen because a previous study had used GH for 3 weeks successfully and without adverse effects (16). Their rhGH dosage was about 10 times the dose of GH used for the present study. Based on the fact that the difference between the rhGH and placebo groups diminished after stopping the GH treatment at 4 weeks and became statistically insignificant at 12 weeks, a longer duration of rhGH treatment might produce additional benefit. However, the optimal duration of rhGH treatment would need another study in the future.

In our study, it should be noted that all baseline IGF-I levels were very low in both groups of subjects. They were much below the lower limit of the normal youthful range. Low serum IGF-I levels in our subjects might be largely due to protein energy malnutrition although age-related GH deficiency could not be excluded (12). The small rise in IGF-I level in the placebo group suggests that the increased dietary protein and calorie intake was able to stimulate some endogenous release of IGF-I. In the GH-treated group, an additional endogenous secretion of IGF-I was elicited by rhGH administration, leading to the

greater increase in muscle mass, also increased strength and walking speed in the treated subjects. Previous studies have also shown that rhGH improved protein use and increased muscle mass and strength in the elderly (29, 30, 34). The greater rise in serum albumin in the GH group also reflected a positive effect of rhGH on body protein status.

Patients with protein-energy malnutrition often had mild normochromic normocytic anemia due to a hypoproliferative bone marrow (35). In our study, a delayed rise in hemoglobin level was observed in the GH-treated group. To our knowledge, no previous study has reported a similar beneficial effect of rhGH on anemia associated with protein-energy malnutrition in the elderly. In contrast, an elevation in hemoglobin level was reported in children with short stature who were treated with rhGH for 6 months (36). There was no additional benefit in terms of lymphocyte count after GH treatment, consistent with previous observations that GH had no effect on T cell number or proliferative responses (37).

In this study, GH treatment for medically stable malnourished elderly patients was safe. There were no GH-related adverse effects including fluid retention, arthralgia, hand stiffness, hypertension, carpal tunnel syndrome, gynaecomastia, hyperlipidemia, or glucose intolerance. Cohn *et al.* (20) have previously shown that GH-related adverse effects were more likely to occur if the posttreatment serum IGF-I levels were above the normal youthful range. In our study, the IGF-I levels in our GH-treated patients were all within the normal youthful range, accounting for the absence of GH-related adverse effects. In summary, there was a marked benefit to risk ratio. All these findings would support of the use of a short course rhGH as an adjuvant treatment in the frail malnourished elderly patients.

The major limitation of the present study was its small sample size. Four subjects died of pneumonia between 5 and 26 weeks of follow-up in the placebo group, a mortality rate comparable with that of 18.9% calculated in a recent review

on malnourished adults (11). No subject died in the GH group. However, the difference in mortality rates between the two groups was not statistically significant, probably because the sample size was too small for assessing the difference in mortality. Our sample size was calculated on the basis of expected changes in total LBM, and was not empowered to assess the mortality outcome.

The clinical use of GH in the elderly has been a very controversial subject. We now have evidence not to use GH in critically ill patients. Takala *et al.* (38) have reported a good study which demonstrated an increased mortality with the use of GH in critically ill adults. Because of the failure to improve physical function and the presence of adverse effects despite an improvement in body composition (17), the use of GH in the healthy elderly routinely is also not recommended. GH-related adverse effects are often related to the dose or the prolonged duration of GH treatment (20, 21). Our preliminary study shows that the frail but clinically stable malnourished elderly is the patient subgroup which can benefit from a 4-week course of low-dose GH therapy. A larger study with a longer duration of rhGH treatment should be conducted in the future to determine the optimal duration of rhGH treatment in elderly with malnutrition. It is likely that intermittent courses or depot preparation of rhGH (39) may produce and maintain these beneficial effects. Another study may be needed in the future to look at these approaches. Furthermore, additional physical functional measures should also be studied.

In conclusion, we have shown that 4 weeks of low-dose rhGH therapy was an effective and safe treatment when used as a dietary adjunct to dietary intervention in stable malnourished frail elderly medical patients. Whether GH treatment can lead to a decreased mortality remains to be confirmed in a larger study with a longer duration of rhGH treatment.

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