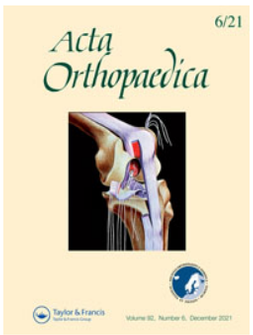

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Positive effects of short-term growth hormone treatment on lean body mass and BMC after a hip fracture

A double-blind placebo-controlled pilot study in 20 patients

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Background **A catabolic state develops after a hip fracture, with loss of muscle and bone tissue. Growth hormone (GH) treatment has been shown to exert anabolic effects during other catabolic states. We investigated whether GH given postoperatively to elderly hip fracture patients could increase serum insulin-like growth factor-I (IGF-I) and reduce the loss of lean body mass and bone mineral content (BMC) without considerable side effects.**

Patients and methods **We randomized 20 patients operated on for a hip fracture to a double-blind placebo-controlled 4-week study with daily subcutaneous injections of GH or placebo. The patients were followed for another 2 months after termination of GH treatment.**

Results **Serum IGF-I and the IGF-I binding protein 1 (IGFBP-1) were measured by specific radioimmunoassay (RIA) technique. BMC and lean body mass were assessed by dual-energy X-ray absorptiometry and quantitative computed tomography. Serum IGF-I increased significantly during GH treatment, which also preserved lean body mass and BMC without serious adverse events.**

Many patients are unable to resume their previous living habits after a hip fracture (Berglund-Rödén et al. 1994). Previous studies have shown an apparent link between clinical outcome and nutritional status in elderly orthopedic patients (Lumbers et al. 1996), and that one-half of patients with hip fracture are malnourished on admission (Akner and Cederholm 2001). The inflammatory reaction in response to the injury/surgical stress often leads to energy expenditure and production of catabolic substances. A prolonged catabolic state develops which is characterized by hypermetabolism, enhanced insulin resistance and nitrogen loss (Weissman 1990). The consequences are loss of BMD (bone mineral density), of weight and of lean body mass at least during the first 6 months after hip fracture (Karlsson et al. 1996, Hedström et al. 1999). Malnutrition and muscle weakness increase the propensity for falls (Vellas et al. 1990), and low BMD is associated with an increased fracture rate (Cummings et al. 1993).

Growth hormone (GH) exerts anabolic effects on bone (Brixen et al. 1993) and skeletal muscle (Fryburg and Barret 1993). The capacity of GH to increase nitrogen retention and to stimulate bone metabolism suggests that it would be useful in situations where otherwise there is an acute loss of bone and muscle mass. GH has also been used to promote anabolism in a variety of clinical catabolic situations (Vara-Thorbeck et al. 1993, Petersen et al. 1994). The anabolic effects of GH may be mediated by GH directly or by insulin-like growth factor-I (IGF-I) and modified by the binding proteins IGFBP-1 to 6. Circulating IGF-I levels generally correlate well with GH secretion in healthy well-nourished patients having normal responsiveness. IGFBP-1 concentration is mainly

insulin-regulated and its production is inhibited by insulin. Low caloric intake and low protein content in the diet are usually accompanied by decreased IGF-I and increased IGFBP-1 levels, partly as a result of decreased insulin levels.

Few studies have evaluated the use of GH after hip fracture, but there have been reports of an increased rate of return to the prefracture living situation in patients operated on for a hip fracture after short-term GH therapy (Van der Lely et al. 2000). This has also been shown after abdominal surgery (Vara-Thorbeck et al. 1993).

We investigated whether GH given postoperatively could increase the levels of serum IGF-I in elderly patients with hip fracture and reduce the loss of lean body mass and BMC after a hip fracture without major side-effects.

Patients and methods

Patients

We randomized 20 patients (15 women) operated on for a hip fracture and fulfilling the criteria for inclusion and exclusion to the study. The 7 patients with femoral neck fractures were operated on with 2 parallel screws and those 13 with trochanteric fractures with a sliding nail-plate or intramedullary fixation. Patients over 65 years of age without cognitive impairment, free-living, previously ambulant with a femoral neck or trochanteric fracture were included. Those who had been treated with GH during the last 12 months, who had had severe illness during the last 6 months, major surgery within 1 month, glaucoma or insulin-treated diabetes mellitus were excluded. Patients were also excluded if they had current or previous malignant disease, severe liver or renal disease (ASAT, ALAT > 1.8 ukat/L, s-creatinine > 200 µmol/L), known or suspected alcohol abuse or were suspected to be non-cooperative.

The study was approved by the local ethics committee and was performed in accordance with the Helsinki declaration.

Study design

Treatment consisted of recombinant human growth hormone (Genotropin, Kabi-Pharmacia) 0.1 IU/kg body weight (although the maximum daily dose was 8 IU), (n = 11), or an equivalent placebo volume (n = 9) injected subcutaneously once daily. The study was withdrawn for a period after reports of serious adverse events in another GH study with high doses to critically ill patients who required intensive care (Takala et al. 1999). The study continued after one year but with a lower daily dose, 0.04 IU/kg body weight. The mean GH dose administered was 5.8 IU/day (range 1.6–8 IU). The duration of treatment was 21–28 days, depending of the length of the hospital stay. The patients started to eat on the first postoperative day. Treatment was started mean 4 (2–5) days postoperatively, depending on the general condition of the patient. The study was performed during the hospital stay, with a follow-up 3 months after surgery.

Fasting blood samples were collected by venipuncture in the morning on three occasions: within 24 h of admission, on the last day of treatment and 3 months after surgery.

We examined the participants after 3 days and after 1, 2, 3 and 4 weeks of treatment to determine whether any side effects had developed. They were specifically examined regarding the presence of edema, arthralgia and carpal tunnel syndrome. Laboratory measurements and clinical assessments were performed to ensure that the treatment had no ill effects; blood glucose, blood pressure and weight were checked. In cases of edema, if this was not improved by diuretics within 48 h the dose was reduced by 50%. If fasting B-glucose was 7 mmol/L or higher, or patients had signs of (or reported) side effects that were potentially attributable to growth hormone, the dose was reduced by 50%.

Dual energy X-ray absorptiometry (DXA) and muscle strength measurements were performed before the start of treatment, at the end of the treatment period (21–28 days) and 2 months after termination of treatment. Quantitative computed tomography (QCT) measurements were performed before treatment and 2 months after its termination.

Measurements

Body composition. Estimates of body composition (total body tissue including lean body mass, fat mass and bone mineral content (BMC, g) and areal bone mineral density (BMD, g/cm^2) were acquired

by whole body DXA using a Lunar DPX-L Scanner (Lunar Corp. Madison, WI, USA). We used the manufacturer's reference population for calculation of an individual T-score for BMD-DXA, i.e. the difference, expressed in standard deviations (SD) from a gender-specific population of young adults. The precision error of the method has been shown to be 0.5% for total body BMC (Lunar Corp.) and the coefficient of variation (CV) for the total BMC in our measurements was 1%. The CV for soft-tissue measurements have been reported elsewhere (Slosman et al. 1992).

QCT (General Electric Pace Plus, Milwaukee, WI) was used for volumetric BMD (g/cm^3) and BMC measurements of the proximal tibia, distal femur and the middle femur. The femurs were scanned 20 and 5 cm above the distal limit of the lateral femoral condyle and the tibias were scanned 2 cm below this reference point. We chose 3 circular regions of interest in the cortical bone in the middle femur. The mean BMD value of these regions was estimated as the volumetric BMD at this location. By tracing around the distal femur and proximal tibia, the area and bone density in that region were determined. We calculated the BMC as the bone mineral density multiplied by the bone volume at the location in question.

The cross-sectional area of the thigh muscle was also measured 20 cm proximal to the distal limit of the lateral condyle. There is a difference in X-ray attenuation between fat, bone and muscle and by using thresholds for each tissue, the computer calculates the tissue volumes. To elucidate whether the muscles had gained normal muscle tissue or intracellular fluid in the GH-treated group, we measured the attenuation in the muscles before treatment and 2 months after the end of treatment. The precision error has earlier been estimated as 2% for bone mineral density in the middle femur, 4% and 5% for the distal femur and the proximal tibia, respectively, and 3% for muscle volume of the middle femur (Neander et al. 1997). These values are similar to those found by others (Karantanas et al. 1991).

Triceps skinfold (TSF), which reflects subcutaneous fat mass (Symreng 1982), was determined with a caliper before the start of treatment, on the last day of treatment and 2 months after termination of treatment.

Body mass index (BMI) was calculated according to the formula weight/height^2 (kg/m^2).

Muscle force. We measured isometric muscle force with a portable electronic dynamometer (Myometer, Penny and Giles Transducers Ltd., Dorset, UK). The instrument consists of a hand-held force transducer, an electronic display and an amplifier unit. The peak force value was presented in kg. The operating range was 0–35 kg and the accuracy given by the manufacturer was ± 0.3 kg. The muscle group tested was the quadriceps muscle and the site of application of resistance was the anterior aspect of the lower leg, just above the malleoli. The muscle force measurement was performed 3 times on each leg and the maximum value was recorded. The standard error of a single determination made by the same observer has been found to be 9% of the muscle force (Bäckman and Öberg 1989). One physiotherapist did all muscle measurements, and 3 patients could not be measured when she was not available.

Assays. Blood samples were analyzed for hemoglobin concentration, sedimentation rate, total leukocyte count, blood platelet count, glucose, HbA1c, albumin, creatinine, urea, sodium, potassium, calcium and phosphate. Liver function was assessed by measuring levels of serum aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), total bilirubin and alkaline phosphatases (ALP). Thyroid function was checked before and after treatment by measurement of serum thyroid stimulation hormone, triiodothyronine and thyroxin (free/total).

Fasting blood samples were collected for assays of IGF-I and IGFBP-1. After centrifugation, the sera were frozen at –70 °C pending use. IGFBPs were separated from IGF-1 by acidified ethanol extraction prior to assay. Including the extraction step, the intra-assay and inter-assay coefficients of variation were 4 and 8%, respectively. The normal ranges of IGF-I concentration at different ages are based on earlier studies on 448 healthy subjects (Hilding et al. 1999). The mean concentration at 20 years of age was 277 µg/L, with a range of 159–481 µg/L, and at 84 years of age the mean was 100 µg/L with a range of 57–173 µg/L.

The concentrations of IGFBP-1 were determined by a specific radioimmunoassay (RIA) technique. The intra-assay and inter-assay varia-

Table 1. Characteristics of patients at the start of the study (n = 20). Mean (SD)

	GH group (n = 11)	Placebo group (n = 9)
Age (years)	83 (7)	85 (3)
Weight (kg)	61 (12)	55 (6)
Height (m)	1.65 (0.09)	1.63 (0.06)
Triceps skinfold (mm)	12.3 (3.2)	10.7 (5.6)
Strength, operated leg (Nm)	5.3 (2.6)	6.0 (2.9)
Strength, uninjured leg (Nm)	10.5 (4.1)	10.5 (5.1)
S-calcium (mmol/L)	2.14 (0,2)	2.17 (0.09)
S-phosphate (mmol/L)	1.0 (0,17)	1.2 (0.14)
S-albumin (g/L)	37.6 (5.2)	37.3 (5.9)
S-ALAT (< 0.6 ukat/L)	0.71 (0.68)	0.79 (0.68)
S-ASAT (< 0.6ukat/L)	1.17 (0.52)	1.37 (1.37)
S-TSH (0.1-5.0 mU/L)	1.17 (0.68)	1.53 (1.36)
B-HbA1c (< 5.2 %)	4.5 (0.32)	4.1 (1.16)
S-ALP (0.8-3–8 ukat/L)	3.9 (1.89)	5.2 (2.95)
BMI (kg/m^2)	22.8 (4.5)	20.4 (1.8)
Total body BMD (g/cm^2)	0.93 (0.13)	0.92 (0.08)
Total body BMD (T score)	–2.65 (1.39)	–2.66 (0.8)

tions were 3 and 10% respectively. The mean and range of IGFBP-1 in healthy subjects aged 20–66 years were 34 and 12–91 µg/L, respectively (Hall et al. 1988).

Statistics

We used Student's t-test for parametric independent groups. For nonparametric tests, the Wilcoxon rank sum test was used to compare groups of patients (statistics software: JMP 3.1). A p-value less than 0.05 was considered statistically significant. Two-sided tests were used.

Results

Patients

Half of the patients had a BMI < 21.5, serum albumin < 36 g/L, serum IGF-I below –2 SD for age, and TSF < 12 mm. 13 patients had a total body BMD 2.5 SD below the mean for a young reference population, indicating osteoporosis (Table 1). 2 patients were lost from the study: 1 patient from the control group died of myocardial infarction shortly after surgery and 1 patient from the GH group was discharged from hospital after 5 days and the treatment could not continue. 18 patients completed the treatment period. 3 patients had their dose reduced by 50% because of suspected side effects, and these subjects were analyzed by intention to treat analysis. 2 patients could not undergo measurements 2 months after termination of treatment, as 1 had developed a psychosis and the other had become bedridden and could not participate.

Adverse events

In no patient was the study discontinued because of clinical laboratory results, and none of the laboratory abnormalities noted were considered to be related to study drug treatment. 2 patients developed soft edema of the feet, and 1 developed hypertension. The 2 patients with edema were being treated with GH and the one with hypertension with placebo. The treatment dose was reduced to 50% of the initial dose and the edema disappeared, but the patient with hypertension had to discontinue placebo after 14 days. No patients showed elevated blood glucose or developed carpal tunnel syndrome.

Hormonal response

The IGF-I levels were similar in the 2 groups at baseline. There was a significant increase in serum level of IGF-I on the seventh day after starting GH treatment (p = 0.002), while the IGF-I level was unchanged in the control group (Table 2). IGF-I remained higher in the GH group than in the placebo group during the treatment period. Two months after termination of treatment, there was no difference in IGF-I levels between groups. IGFBP-1 was significantly lower in the GH group after 1 week of treatment (Table 2).

Measurement of body composition

The GH-treated group did not lose lean body mass during treatment, while the placebo group lost a significant amount of lean body mass (p = 0.004) (Table 3). There was no significant difference in muscle volume or attenuation value (QCT) between the groups.

At the end of the treatment period, total tissue loss (mineralized tissue, fat and lean body mass) was 8% in the placebo group and 4% in the GH group (p = 0.05). Total body fat mass, as measured by DXA, decreased significantly during the treatment period in both groups.

Table 2. IGF-I and IGFBP-1 before start of treatment, during treatment, after treatment (21-28 days) and 2 months after termination of treatment. P-value between groups. Mean µg/L (SD)

	Before start of treatment			After 1 week of treatment			After 4 weeks of treatment			After 2 months		
	GH group	Placebo group	p	GH group	Placebo group	p	GH group	Placebo group	p	GH group	Placebo group	p
IGF-I	59 (24)	66 (25)	0.6	206 (102)	80 (32)	0.005	243 (98)	103 (48)	0.004	100 (52)	114 (59)	0.7
IGFBP-1	63 (20)	53 (32)	0.5	32 (13)	60 (29)	0.04	35 (21)	61 (29)	0.2	89 (35)	55 (30)	0.1

Table 3. Changes from baseline in total BMC, fat mass, lean body mass and total body tissue after treatment (21–28 days) and 2 months after termination of treatment. Mean differences between groups were tested by a two-sided t-test (SD)

	DXA values on admission		Difference after 4 weeks of treatment			Difference 2 months after termination of treatment		
	GH group (n = 11)	Placebo group (n = 8)	GH group (n = 10)	Placebo group (n = 8)	p	GH group (n = 7)	Placebo group (n = 8)	p
BMC (g)	1869 (571)	1789 (323)	27	–31	0.04	51	–79	0.01
Lean body mass (g)	39887 (6242)	38113 (5595)	–646	–3246	0.03	–3164	–2856	0.5
Fat mass (g)	20279 (8222)	16021 (4620)	–1225	–934	0.5	–803	–1830	0.2
Total body tissue (g)	60186 (11856)	54159 (7279)	–1871	–4193	0.04	–3967	–4709	0.5

The GH-treated group lost subcutaneous fat in the triceps region (TSF) during treatment (p = 0.02) and the loss persisted 2 months after termination of treatment (p = 0.01), while the subcutaneous fat did not change significantly in the placebo group.

Measurement of BMC

The placebo group lost total body BMC during treatment, but the GH group did not (Table 3). Two months after termination of treatment, the significant difference remained and the placebo group had lost 4.4% of total BMC (p = 0.01) while total BMC was unchanged in the GH treated group.

QCT measurements could only be performed in 11 patients, 7 from the placebo group and 4 from the GH group. The other patients had metal implants which made the measurement impossible. The placebo group lost significantly more BMC in the distal femur in both the operated (p = 0.05) and the unoperated leg (p = 0.003) compared to the GH treated group. There was no difference in change-over time between groups in the tibia or proximal femur BMC.

Table 4. Changes from baseline in quadriceps strength (Nm) after treatment (21–28 days) and 2 months after termination of treatment. Mean differences between groups were tested by a two-sided t-test (SD)

	GH group	Placebo group	p
Operated leg			
after treatment (n = 15)	3.0 (2.3)	1.1 (2.4)	0.2
2 months after termination of treatment (n = 12)	5.7 (2.5)	4.2 (3.0)	0.4
Uninjured leg			
after treatment (n = 15)	2.4 (3.1)	2.0 (3.4)	0.8
2 months after termination of treatment (n = 12)	3.8 (3.9)	1.9 (4.1)	0.4

Muscle force

We found no significant difference in the quadriceps force between groups (Table 4).

Discussion

Our group of elderly hip fracture patients showed low IGF-I levels, albumin levels and BMI on

admission, and signs of malnutrition, which is similar to what others have found in hip fracture patients (Akner and Cederholm 2001). This pre-fracture state, together with the catabolic state that develops postoperatively, probably contributes to the poor clinical outcome. Few earlier studies have addressed the effect of GH treatment on IGF-I levels and on body composition after a hip fracture.

There are known differences in GH responsiveness, at least in GH-deficient adults, and it has been shown to be dependent on both dose (Murray et al. 1999) and gender (Johansson et al. 1999). In our group of elderly postoperative hip fracture patients, GH treatment increased serum levels of IGF-I significantly.

We found a preserving effect of GH treatment on BMC, despite the shortness of the treatment period. The BMC change over time and differences between groups persisted and was even more evident 2 months after termination of treatment. A small increase in spinal BMD has been reported after GH therapy in healthy elderly men (Rudman et al. 1990), while GH alone or added to other therapies for osteoporosis has had varied effects (Holloway et al. 1994, Sääf et al. 1999, Gillberg et al. 2002, Landin-Wilhelmsson et al. 2003). The patients in the present study were older, they had a more recent fracture and received higher GH levels than in earlier studies. The discrepancies between different study results may also be explained by variations in nutritional status, the severity of the osteoporosis, duration of GH treatment, the state of bone turnover and in whether BMC or BMD were followed and measured. If the GH treatment mainly increases periosteal bone formation as has been suggested (Bravenboer et al. 1997), this could contribute to an initial reduction in areal bone density, as newly formed bone has a lower mineral density than older bone, but still increase the projected area (Meunier et al. 1997). This is compatible with the finding in experimental animals that GH increases cortical thickness and has the potential to increase bone size (Andreassen et al. 1995). An increased remodeling volume might explain the initial (0-6 months) reduction in total body BMD that has been described in some studies on GH-deficient adults (Degerblad et al. 1995, Välimäki et al. 1999).

We found that GH had a preserving effect on total body tissue and a lipolytic effect on the subcutaneous fat measured in the triceps region, although there was no difference in total body fat mass between groups. One explanation could be topographical variations in responsiveness of fat to GH therapy, which may be gender-dependent in healthy elderly (Münzer et al. 2001).

The placebo group lost 9% of lean body mass postoperatively, and this postoperative loss was prevented in the GH-treated group. Recently, Weissberger et al. (2003) reported a similar positive effect on lean body mass after short-term GH treatment in elderly patients undergoing a total hip replacement. The preserving effect of GH on lean body mass in the present study lasted during the 4 weeks of treatment but had disappeared 2 months after discontinuation of treatment, in agreement with other recent reports (Lange et al. 2001). This observed reduction in lean body mass after termination of treatment could be due to a persistent catabolic state. We also considered the question of whether GH had increased the extracellular fluid volume, an effect that could confound the measurement of lean body mass with DXA. However, after calculations of total body water and intracellular fluid, both GH and IGF-I have been shown to produce a real increase in lean body mass measured with DXA in elderly women (Thompson et al. 1995).

Even if GH treatment has a preserving effect on lean body mass, the effect on "functional" muscle strength is unproven. We found no differences between groups regarding the thigh force in this small study. Although limited data are available from catabolic situations, improved hand grip strength in the postoperative period has been reported after GH treatment during the first postoperative week (Jiang et al. 1989). Some indications of a favorable effect of GH treatment on muscle strength in healthy elderly have been reported, mainly in the lower limb girdle muscles (Weissberger et al. 2003), whereas one earlier study on healthy elderly men showed no improvement in hand grip muscle strength (Papadakis et al. 1996). In adult GH deficiency due to pituitary disease, where the effects of GH on muscle strength have been studied more thoroughly, results have also been less impressive than the observed positive

effects on lean body mass and muscle mass (Jorgensen et al. 1989, Johannsson et al. 1997). This may reflect the inherent imprecision of current strength-testing methods, which are dependent on uncontrollable factors such as patient cooperation and well-being.

Takala et al. (1999) reported an increased relative risk of death after GH therapy among acutely critically ill intensive care patients, but much higher GH doses were given than in the present study. No serious adverse events occurred in the present study on relatively healthy patients without severe diseases or conditions other than hip fracture, and with treatment not started until 2–5 days after surgery.

In conclusion, short-term postoperative administration of GH to elderly patients with hip fractures appears to improve BMC and to preserve lean body mass.

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