

Limited effects of growth hormone replacement in patients with GH deficiency during long-term cure of acromegaly

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Abstract The aim of this study was to assess the effects of replacement with recombinant human growth hormone (rhGH) in patients with GH deficiency (GHD) after treatment of acromegaly. Intervention study. Sixteen patients (8 men, age 56 years), treated for acromegaly by surgery and radiotherapy, with an insufficient GH response to insulin-induced hypoglycaemia, were treated with 1 year of rhGH replacement. Study parameters were assessed at baseline and after 1 year of rhGH replacement. Study parameters were cardiac function, body composition, bone mineral density (BMD), fasting lipids, glucose, bone turnover markers, and Quality of Life (QoL). During rhGH replacement IGF-I concentrations increased from -0.4 ± 0.7 to 1.0 ± 1.5 SD ($P = 0.001$), with a mean daily dose of 0.2 ± 0.1 mg in men and 0.3 ± 0.2 mg in women. Nonetheless, rhGH replacement did not alter cardiac function, lipid and glucose concentrations, body composition or QoL. Bone turnover markers (PINP and β crosslaps) levels increased ($P = 0.005$ and $P = 0.021$, respectively), paralleled by a small, but significant decrease in BMD of the hip. The beneficial effects of rhGH replacement in patients with GHD during cure from acromegaly are limited in this study.

Keywords Growth hormone deficiency · Growth hormone replacement · Acromegaly

Introduction

Growth hormone deficiency (GHD) in adults is characterized by an adverse cardiovascular metabolic profile, altered body composition (reflected in reduced muscle strength and mass, and visceral obesity), decreased bone mass, decreased cardiac function and decreased quality of life (reviewed in [1]). Treatment with recombinant human growth hormone (rhGH) ameliorates symptoms and signs of the GHD syndrome in the short [2] and in the long-term [3, 4]. GHD is a well-known sequel of pituitary radiotherapy, e.g. for non-functioning adenomas, adrenocorticotrope hormone- or prolactin-secreting adenomas [5]. Remarkably, GHD can also be induced by treatment of active acromegaly. We have documented a diminished GH increase to insulin-induced hypoglycemia during long-term follow-up in 36% of the patients with acromegaly after postsurgical radiotherapy [6].

Almost all randomized controlled studies on the efficacy of rhGH replacement in adult GHD have excluded patients previously treated for acromegaly. Nonetheless, two intervention studies have reported on the effects of rhGH replacement in patients with GHD after previous treatment of acromegaly. In a subanalysis of acromegalic patients with GHD extracted from the large KIMS database, 6 months of rhGH replacement had no significant beneficial effects in the acromegalic patients [7]. In addition, a recent study compared the effects of 2 years of rhGH replacement on body composition, muscle strength, bone mass and metabolic parameters between ten patients previously treated for acromegaly and ten patients treated for non-functioning

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pituitary disease [8]. At baseline, patients with acromegaly had decreased muscle endurance and increased LDL concentrations compared to the other patients, but after 2 years of rhGH replacement there were no differences between both groups [8].

The aim of this study was to evaluate 1 year of rhGH replacement on heart function, quality of life, glucose and lipid metabolism, body composition and bone mass and turnover in order to extend the exploration whether GH replacement is beneficial in acromegalic patients with GHD during long-term biochemical cure.

Patients and methods

Patients

We enrolled 16 acromegalic patients (8 men and 8 women), who developed GHD after combined pituitary surgery and radiotherapy in the study. Inclusion criteria were previous treatment for acromegaly by surgery and/or radiotherapy and an insufficient GH increase to insulin-induced hypoglycemia (short-acting insulin 0.05–0.1 U/kg body weight, blood samples drawn at 0, 20, 30, 45, 60 and 90 min; nadir glucose levels below 2.2 mmol/l) [9]. The increase in GH concentrations was considered insufficient, when the peak GH response was below 3 µg/l [10].

Fifteen patients had been treated with primary surgery and secondary conventional radiotherapy mean interval after radiotherapy 18 years (range 4–29 years). The other patient was diagnosed with pituitary apoplexy of a GH producing adenoma. Because GH concentrations remained elevated, he underwent surgery and subsequently developed complete anterior pituitary failure. Clinical details were published previously [11].

Additional hormone replacement therapy was kept stable for at least 3 months prior to study inclusion, and was only adjusted thereafter when necessary. The purpose, nature, and possible risks of the study were explained to all subjects and written informed consent was obtained. The study protocol was approved by the ethics committee of the Leiden University Medical Center.

Study design

Study parameters were assessed both at baseline and after 1 year of rhGH replacement. The following variables were measured: fasting concentrations of lipoproteins, glucose, and IGF-I, body composition, bone turnover markers and bone mass, echocardiography, and Quality of Life parameters.

Growth hormone vials of 1 ml were manufactured and provided by Novo Nordisk Pharma, Denmark. Growth

hormone replacement dose was started at 0.2 mg/day and, subsequently, titrated in the first 12 weeks of the study to obtain an IGF-I concentration within the age- and gender-adjusted reference range, according to Growth Hormone Research Society guidelines [10].

The mean age of the patients was 56 years (range 34–75 years). The interval between radiotherapy and the start of the study was 18 years (range 4–29 years). TSH deficiency was present in five patients, ACTH deficiency in nine patients, and LH-FSH deficiency in eight patients (see Table 1).

Body composition

Body weight and height, waist circumference, hip circumference, systolic and diastolic blood pressure (SBP and DBP, respectively) were measured. Waist-hip (WH) ratio was calculated. Body weight was measured to the nearest 0.1 kg, and body height was measured barefoot to the nearest 0.001 m. Lean body mass and fat mass were measured with DXA (Hologic 4500; Hologic Inc., Waltham, MA, USA).

Markers for bone turnover and bone mass

The following serum markers of bone turnover were measured: N-terminal propeptides of type I collagen (PINP), as a marker for bone synthesis, and β -crosslaps as a marker for bone resorption. Bone mineral density (BMD) was measured by DXA (Hologic 4500; Hologic Inc., Waltham, MA, USA). Sites measured were the lumbar

Table 1 Clinical characteristics of the 16 patients with growth hormone deficiency after acromegaly

Age (year)	Gender	Substitution therapy
65	Male	None
65	Male	None
59	Male	Thyroxine, Testosterone, Hydrocortisone
75	Female	Hydrocortisone
66	Female	None
62	Female	Hydrocortisone
66	Female	Thyroxine, Estradiol, Hydrocortisone
40	Female	Thyroxine, Estradiol, Hydrocortisone
43	Male	Testosterone
56	Male	Thyroxine, Testosterone, Hydrocortisone
48	Male	Thyroxine, Testosterone, Hydrocortisone
51	Female	None
34	Female	Hydrocortisone
74	Male	Testosterone
45	Male	Testosterone
50	Female	Hydrocortisone

spine (L1-L4) and the femoral neck (left and right). Mean BMD of the left and right femoral neck was calculated. Mean *T* and *Z* scores were calculated for total left and right hip using the NHANES reference values. The CV of BMD measurements was 1% and the machine was cross-calibrated at regular interval.

Echocardiography

Echocardiography was performed while the patients were in the left lateral decubitus position using a commercially available system (Vingmed Vivid-7, General Electric-Vingmed, Milwaukee, WI, USA). Standard parasternal (long- and short-axis) and apical views (2-, and 4-, and long-axis) were obtained. M-mode images were obtained from the parasternal long-axis views for quantitative assessment of LV dimensions (inter-ventricular septum thickness (IVST), posterior wall thickness (PWT), LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), fractional shortening (FS) and LV ejection fraction (LVEF)) [12].

The following parameters of diastolic function were obtained: diastolic transmitral peak velocities (*E* and *A* wave) and the *E/A* ratio. Quantitative diastolic data were derived from tissue Doppler imaging (TDI). For TDI analysis, the digital cine loops were analyzed using commercial software (Echopac 6.1; General Electric-Vingmed). The sample volume (4 mm²) was placed in the LV basal portion of the septum (using the 4-chamber views). The following parameters (mean values calculated from three consecutive heartbeats) were derived: early diastolic velocity (*E'*), late diastolic velocity (*A'*) and the *E'/A'* ratio. The severity of valvular regurgitation was assessed by two independent expert readers blinded to the clinical data on a qualitative scale of trace, mild, moderate, or severe, using previously described methods [13, 14]. Left ventricular mass (LVM) was calculated by the cube formula, and using the correction formula proposed by Devereux et al. [15]: $0.8 \times \{1.04 [(LVEDD + PWT + IVST)^3 - LVEDD^3]\} + 0.6$. The data were assessed by two independent observers, blinded for the clinical data of the patients.

Quality of life

Quality of life was assessed using four different validated health-related quality of life questionnaires

Hospital anxiety and depression scale (HADS): The HADS consists of 14 items pertaining to anxiety and depression. Each item is measured on a 4-point scale. Scores for the anxiety and depression subscale range from 0 to 21 and for the total score from 0 to 42. A high score points to more severe anxiety and depression [16].

Multidimensional fatigue index (MFI-20): The MFI-20 contains 20 statements to assess fatigue [17]. Five different dimensions of fatigue (four items each) are calculated from these statements; (1) general fatigue; (2) physical fatigue; (3) reduced activity; (4) reduced motivation and (5) mental fatigue. Every statement is measured on a 5-point scale; scores vary from 0 to 20. Higher scores indicate higher experienced fatigue.

Nottingham health profile (NHP): The NHP is frequently used in patients with pituitary disease to assess general well-being and QoL. The survey consists of 38 yes/no questions, which are subdivided in 6 scales assessing impairments, i.e. pain (8 items), energy level (3 items), sleep (5 items), emotional reactions (9 items), social isolation (5 items) and disability/functioning, i.e. physical mobility (8 items) [18, 19]. Subscale scores are calculated as a weighted mean of the associated items and are expressed as a value between 0 and 100. The total score is the mean of the six subscales.

Quality of life-assessment of growth hormone deficiency in adults (QoL-AGDHA): This disease specific quality of life questionnaire has been developed specifically for the detection of deficits in needs achievements in areas which have shown to be commonly affected in adults with GHD [20]. The questionnaire comprises 25 items, which are summed to form a total score. Higher numerical scores (to a maximum of 25) denote poorer quality of life.

Assays and dynamic tests

Growth hormone reserve was evaluated by the insulin tolerance test in fasting conditions (short-acting insulin 0.05–0.1 U/kg body weight, blood samples drawn at 0, 20, 30, 45, 60 and 90 min; the nadir glucose concentration should drop below 2.2 mmol/l) [9]. The increase in GH concentration was considered insufficient, when the peak GH concentration was below 3 µg/l [10].

Serum IGF-I concentration was measured with the Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, USA). The intra-assay variation was 5.0 and 7.5% at mean serum levels of 8 and 75 nmol/l, respectively. IGF-I levels are expressed as standard deviation-scores (SDS), using lambda-mu-sigma (LMS) smoothed reference curves based on measurements in 906 healthy individuals [21, 22].

IGFBP-3 was measured using an immunometric technique on an IMMULITE Analyzer (Diagnostic Products Corporation, Los Angeles, USA). The lower limit of detection was 0.02 mg/l and inter-assay variation was 4.4 and 4.8% at 0.91 and 8.83 mg/l. A Hitachi P800 auto analyzer (Roche, Mannheim, Germany) was used to quantify serum concentrations of glucose, total cholesterol and TG. HDL was measured with a homogenous enzymatic assay (Hitachi 911, Roche, Mannheim, Germany). LDL

cholesterol concentrations (LDL) were calculated using the Friedewald formula. C-crosslinking terminal telopeptide of type I collagen (β -crosslaps) and procollagen type I aminoterminal propeptide (PINP) by chemoluminescence immunoassay with the Modular Analytics E-170 system (Roche Diagnostics, Almere, The Netherlands).

Statistics

Statistical analysis was performed using SPSS for Windows, version 14.0 (SPSS Inc. Chicago, Illinois, USA). Results are scored as the mean \pm standard deviation (SD), unless specified otherwise. The data were analyzed with the paired samples Student's *t*-test. Statistical significance was set at $P < 0.05$.

Results

IGF-1 and IGFBP-3 concentrations

One year of rhGH replacement increased IGF-I SD scores and IGF-BP3 levels (baseline IGF-I SD score: -0.4 ± 1.7 and 1.0 ± 1.5 at 1 year, $P < 0.001$; baseline IGFBP-3: 4.2 ± 1.2 mg/l and 5.2 ± 1.4 mg/l after 1 year, $P < 0.001$).

Cardiovascular risk parameters and body composition

During rhGH replacement lipid profiles did not change. In addition, blood pressure (systolic and diastolic) and fasting glucose concentrations did not change (Table 2). Mean lean body mass increased by almost 4 kg and total fat mass

Table 2 Metabolic and antropometric parameters before and after 1 year of rhGH replacement

	Before	After	<i>P</i> -value
Total cholesterol (mmol/l)	6.0 ± 1.0	5.7 ± 1.2	0.317
TG (mmol/l)	1.8 ± 1.0	2.1 ± 1.3	0.222
HDL-cholesterol (mmol/l)	1.4 ± 0.5	1.4 ± 0.4	0.597
LDL-cholesterol (mmol/l)	4.1 ± 0.8	3.9 ± 1.0	0.250
Glucose (mmol/l)	4.6 ± 0.6	4.7 ± 0.5	0.138
SBP (mm Hg)	138 ± 17	135 ± 10	0.222
DBP (mm Hg)	87 ± 9	88 ± 8	0.924
Waist circumference (cm)	102.8 ± 11.4	103.6 ± 12.5	0.599
WH ratio	0.9 ± 0.1	0.9 ± 0.1	0.921
LBM (kg)	57.1 ± 13.0	61.7 ± 13.4	0.102
Fat mass (kg)	34.8 ± 16.0	31.3 ± 14.7	0.367

TG triglycerides; HDL high-density lipoprotein; LDL low-density lipoprotein; SBP systolic blood pressure; DBP diastolic blood pressure; WH ratio waist-to-hip ratio; LBM lean body mass

decreased by approximately 3 kg, but these differences did not reach statistical significance.

Bone parameters

RhGH replacement increased plasma concentrations of bone turnover markers (PINP and β -crosslaps) in all patients (Table 3; Fig. 1). During rhGH replacement bone mass at the lumbar spine remained unchanged in all patients, but decreased significantly at the femoral neck by 4% (Table 3; Fig. 1).

Cardiac parameters and quality of life parameters

During rhGH replacement there were no significant changes in cardiac parameters or QoL parameters (Tables 4, 5).

Discussion

In this prospective study, we evaluated the effect of rhGH treatment on a range of relevant parameters in GHD patients, previously treated for acromegaly. During rhGH replacement IGF-I concentrations increased into the

Table 3 Bone markers and biochemical parameters of bone turnover before and after 1 year rhGH replacement

	Before	After	<i>P</i> -value
PINP (ng/ml)	29.1 ± 19.5	44.3 ± 33.4	0.005
β crosslaps (ng/ml)	0.2 ± 0.1	0.3 ± 0.2	0.021
BMD lumbar spine (g/cm^2)	1.1 ± 0.2	1.1 ± 0.2	0.640
BMD femoral neck (g/cm^2)	0.85 ± 0.17	0.81 ± 0.15	<0.001
<i>T</i> score total hip	-0.30 ± 1.5	-0.24 ± 1.4	0.434
<i>Z</i> score total hip	0.26 ± 1.6	0.37 ± 1.5	0.125

PINP N-terminal propeptides of type I collagen; BMD bone mineral density

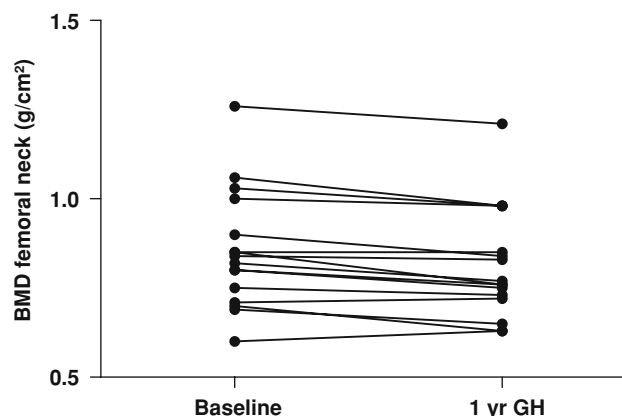


Fig. 1 Bone mineral density decreased in all patients during 1 year rhGH replacement ($n = 16$, $P < 0.001$)

Table 4 Cardiac parameters before and after 1 year rhGH replacement

	Before	After	<i>P</i> -value
LVEDD (mm)	51.6 ± 5.8	47.0 ± 15.5	0.165
LVESD (mm)	34.3 ± 4.4	32.6 ± 7.5	0.222
IVST (mm)	12.2 ± 3.4	12.4 ± 3.9	0.704
PWT (mm)	10.2 ± 1.6	10.0 ± 1.3	0.594
FS (%)	35.1 ± 6.7	37.0 ± 6.1	0.319
LVEF (%)	63.5 ± 8.4	66.3 ± 7.5	0.244
<i>E</i> (mm/s)	0.5 ± 0.2	0.5 ± 0.1	0.745
<i>A</i> (mm/s)	0.6 ± 0.2	0.6 ± 0.1	0.789
<i>E/A</i> ratio	1.0 ± 0.3	0.9 ± 0.3	0.589
<i>E'</i> (cm/s)	0.6 ± 0.2	0.5 ± 0.3	0.629
<i>A'</i> (cm/s)	0.7 ± 0.1	0.6 ± 0.4	0.300
<i>E'/A'</i> ratio	0.8 ± 0.4	0.9 ± 0.3	0.589
LVM (g)	233 ± 64	215 ± 105	0.307

LVEDD left ventricular end-diastolic diameter; *LVESD* left ventricular end-systolic diameter; *FS* fractional shortening; *LVEF* left ventricular ejection fraction; *IVST* inter-ventricular septum thickness; *PWT* posterior wall thickness; *LVM* left-ventricular mass

age- and gender-adjusted normal range, but neither cardiac parameters, nor any of the cardiovascular risk parameters or quality of life parameters changed during rhGH treatment. Bone turnover markers increased during rhGH replacement, which was associated with a decrease of bone mineral density at the femoral neck of 4%, whereas the bone mass of the lumbar spine remained unchanged. These data indicate that the effects of rhGH treatment of GHD patients previously treated for acromegaly are limited.

Data on the manifestations of GHD after treatment for acromegaly are limited. Two previous studies reported several clinical manifestations in this particular patient

group [7, 8]. The first study compared patients with GHD after treatment for acromegaly and Cushing's disease with patients with GHD due to other etiologies [7]. No differences in body mass index, waist-hip ratio, serum lipid concentrations, bone mineral density (at the lumbar spine and femoral neck), or IGF-I SD score were found in patients with GHD after acromegaly compared with patients with GHD due to other etiologies [7]. In the second study, muscle strength, bone mass and metabolic indices were compared between ten patients previously treated for acromegaly and ten patients treated for non-functioning pituitary disease [8]. Although there were no differences between both groups after 2 years of rhGH replacement, at baseline, patients with acromegaly had a decreased muscle endurance and increased LDL concentrations compared to the other patients, which points towards differences in their response to the treatment [8]. However, body fat decreased and lean body mass increased in that study in the patients with non-functioning pituitary disease, whereas it did not change in the same number of patients with GHD after acromegaly simultaneously studied [8], in agreement with our findings.

In adult patients with GHD, rhGH replacement increases bone mineral density [23], left ventricular mass and stroke volume [24], lean body mass [1], and quality of life [25], whereas it improves the serum lipid profile [26]. These effects are apparent within 6–12 months and are maintained during continued treatment with rhGH in the long-term [4, 24, 26–29]. However, it appears that these abnormalities associated with GHD in adults are not always reversed completely solely by rhGH replacement [29, 30] and that some patients might benefit more from combined treatment of rhGH with, for instance, lipid-lowering agents and bisphosphonates [31, 32].

Table 5 Quality of life parameters at baseline and after 1 year rhGH replacement in patients with GHD after previous treatment for acromegaly

		Before	After	<i>P</i> -value
QoL NHP	Energy	55.2 ± 38.2	41.8 ± 35.4	0.125
	Pain	19.4 ± 21.8	14.1 ± 18.8	0.278
	Emotional reaction	12.0 ± 16.4	13.2 ± 20.0	0.603
	Sleep	13.6 ± 26.9	14.1 ± 24.4	0.913
	Physical mobility	20.1 ± 20.8	16.0 ± 23.7	0.258
	Social isolation	12.0 ± 17.1	10.6 ± 17.1	0.586
QoL MFI-20	General fatigue	15.4 ± 4.5	14.2 ± 4.7	0.154
	Physical fatigue	12.9 ± 5.2	13.2 ± 5.2	0.747
	Reduction in activity	11.4 ± 4.9	11.8 ± 4.9	0.625
	Reduction in motivation	10.8 ± 4.4	10.1 ± 4.5	0.415
	Mental fatigue	9.3 ± 4.6	9.8 ± 4.3	0.650
QoL HADS	Anxiety	4.6 ± 2.4	4.9 ± 2.3	0.453
	Depression	6.0 ± 4.4	6.1 ± 4.3	0.933
	Total score	10.6 ± 5.0	11.0 ± 5.3	0.674
QoL-AGDHA		7.6 ± 6.1	7.7 ± 5.9	0.880

HADS, NHP, MFI-20, QoL-AGDHA higher scores: more impairment

In our study, parameters of both bone resorption and bone formation increased, paralleled by a net decrease in bone mineral density at the femoral neck, in agreement with the observed increase in bone turnover found during 2 years of rhGH replacement in these patients by Norrman et al. [8]. In this latter study, however, no treatment differences in the response of bone mineral density between patients previously treated for acromegaly and patients previously treated for non-functioning pituitary disease were found [8]. It is important to note, however, that there are several small differences with our study. The patients in the study of Norrman et al. were included between 1991 and 1997. Hence, the initial dose previously applied before the consensus statement of the Growth Hormone Research Society in 1998 was first based on weight in some patients, but was subsequently gradually lowered when the weight based dose regime was abandoned. In addition, almost all patients studied (90%) were female [8]. These differences could explain the discrepant effects of rhGH replacement found on bone mineral density between the present study and the study by Norrman et al. [8].

The decrease in BMD found in our study could point towards a different response to rhGH replacement in patients previously exposed to persistently increased GH concentrations. Alternatively, this observation may indicate that the possible beneficial effect of rhGH replacement on bone in these patients is insufficient to compensate the ongoing bone loss after previous GH excess in these specific patients. In active acromegaly, bone mineral density is increased [33] and this favorable effect seems to persist after successful biochemical cure [34]. However, in patients with biochemical cure of acromegaly, radiotherapy was an independent negative predictor of bone mineral density at the femoral neck [34]. Almost all patients in our cohort had been treated previously by radiotherapy. On the other hand, in patients with adult-onset GHD due to other etiologies, some, but not all, studies have found a decreased bone mass at the lumbar spine (reviewed in [1]). Replacement with rhGH in those patients seems to modestly increase bone mineral density after 1 year [27]. However, the lack of the increase in BMD, usually seen during rhGH replacement but absent in our specific patients, is in accordance with the only other study performed in patients with GHD after treatment of acromegaly [7]. Further longer-term studies are needed to clarify this issue.

Body composition did not change during rhGH replacement, whereas it has been consistently found to be altered by rhGH replacement in patients with GHD due to other diseases (an increase in lean body mass and a decrease in body fat [1]). However, the trends seen in our study point towards similar changes in body composition in patients previously treated for acromegaly. Interestingly,

body fat decreased and lean body mass increased in the study of Norrman et al. [8] in the patients with non-functioning pituitary disease, whereas it did not change in the same number of patients with GHD after acromegaly simultaneously studied. Replacement with rhGH did not improve QoL parameters. Various aspects of QoL seem to improve slightly during rhGH replacement in adults with GHD due to other diseases [25]. Therefore, it is likely that other factors in our patients with GHD after treatment for acromegaly explain the lack of effect on QoL during rhGH replacement, such as persisting joint related complaints [35] and/or unfavorable late effects of previous radiotherapy [36].

Considering the beneficial effects of rhGH replacement in patients with GHD due to other causes than acromegaly, substitution in this particular subgroup is warranted. We did not find many marked beneficial effects of rhGH replacement in these patients. Higher, non-physiological, doses of rhGH could possibly result in detectable changes in the targeted parameters, as has been extensively documented in patients with GHD not pre-exposed to acromegaly. In clinical practice, however, current treatment guidelines from the Growth Hormone Research Society, advocate to titrate rhGH dose to target IGF-I concentrations within the normal age-related reference range, to ensure a therapeutic dose also in those patients with severe GHD, and avoid side effects of rhGH replacement.

In conclusion, the effects of rhGH replacement in patients with GHD after treatment for acromegaly seem to be limited. The observed effect on bone resorption and in bone mineral density might be affected by ongoing bone loss despite rhGH replacement seen in acromegaly after radiotherapy, or by the response to rhGH of bone after previous long-term exposure to GH excess. Larger long-term studies in this specific patient group are warranted to clarify the issue whether the effects of rhGH replacement in GHD might be altered by previous acromegaly. However, these patients will most probably become increasingly rare since the introduction of effective drug treatment for acromegaly.

Disclosure summary The authors have nothing to disclose.

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