Acromegaly : treatment and follow-up : the Leiden studies

Biermasz, N.R.

10

Long-term maintenance of the anabolic effects of GH on the skeleton in successfully treated patients with acromegaly

Nienke R. Biermasz, Neveen A.T. Hamdy, Alberto M. Pereira, Johannes A. Romijn and Ferdinand Roelfsema

Department of Endocrinology and Metabolic Diseases, Leiden University Medical Centre, Leiden, The Netherlands

Eur J Endocrinol 2005; 152: 53-60

ABSTRACT

INTRODUCTION: The anabolic actions of growth hormone (GH) are well documented. In acromegaly, the skeletal effects of chronic GH excess have been mainly addressed by evaluating bone mineral density (BMD). Most data were obtained in patients with active acromegaly, and apparently high or normal BMD was observed in the absence of hypogonadism. Data on BMD are not available after successful treatment of acromegaly. Whether the positive effect of GH excess on bone mass is maintained in the long term after clinical and biochemical cure of acromegaly remains to be established.

PATIENTS AND METHODS: In a cross-sectional study design, lumbar spine and femoral neck BMD was measured in 79 acromegalic patients cured or well controlled on octreotide treatment (45 male and 34 female patients; mean age 57±1 years). Successful treatment (by surgery, radiotherapy and/or use of octreotide) was defined as normal age-adjusted IGF-I. Mean time after biochemical remission was 10.2±7 years.

RESULTS: Normal or increased BMD was observed at the femoral neck and lumbar spine in both men and women in remission after treatment for acromegaly. Similar results were obtained in patients in remission for 5 years or longer. Osteoporosis was present in 15% of the patients, with similar prevalence in men and women. There was no relationship between BMD and duration or severity of GH excess before treatment, gonadal status and presence of pituitary hormone deficiencies. Pituitary irradiation was a strong negative predictor of bone mass at the femoral neck. Long-term bone loss was observed only at the femoral neck.

CONCLUSION: Our data suggest that the anabolic effect of GH on trabecular and cortical bone remains demonstrable after remission of acromegaly, although it may not be maintained at cortical sites in the long term. In the present study, the lack of effect of gonadal status on BMD may be explained by the presence of only mild hypogonadism and by our policy of prompt hormonal replacement therapy for severe hypogonadism. The negative effect of pituitary irradiation on femoral neck BMD remains intriguing, although it is probably related to some degree of the diminished GH secretion frequently observed after this form of treatment.

INTRODUCTION

The anabolic actions of growth hormone (GH) on many organ systems, including bone, are well documented. As a result of GH excess, patients with active acromegaly demonstrate an increase in bone turnover as evidenced by elevated biochemical markers of bone resorption and formation, whereas low bone turnover prevails in GH deficiency (GHD). Earlier case reports based on radiological investigations suggested that a number of patients with acromegaly may have osteoporosis (1). Later investigation by dual energy X-ray absorptiometry (DXA) established the presence of a high cortical bone mass and of a normal trabecular bone mass in patients with active acromegaly, although the number of patients studied was limited (2). Recently, Scillitani et al. reported, irrespective of severity of disease, increased lumbar spine bone mineral density (BMD) in eugonadal patients, but diminished BMD at this predominantly trabecular site in hypogonadal patients in a large population of mainly active acromegalic patients (3). In contrast, BMD was found to be higher at the femoral neck in patients with active disease than in patients with controlled disease, irrespective of gonadal status (3). These data are in keeping with those from other studies, suggesting that cortical bone mass is increased and trabecular bone unaffected in patients with high circulating GH concentrations (4). Whether this positive effect of GH excess on bone mass is maintained in the long term after clinical and biochemical remission of active acromegaly remains to be established. To address this question, we measured BMD in a cross-sectional design in our large series of acromegalic patients in remission as defined by a normal serum insulin-like growth factor (IGF)-I concentration for age. We further addressed the relationship between BMD and duration of active disease, therapeutic modality, duration of remission, current serum IGF-I and GH concentrations, and gonadal status.

PATIENTS AND METHODS

Patients

We studied 79 consecutive patients with acromegaly in remission, routinely followed up at the outpatient clinic of the Department of Endocrinology of the Leiden University Medical Centre. Remission (after surgery, radiotherapy or during medical treatment) was defined by a normal age-adjusted serum IGF-I concentration. At the time of assessment, all patients had to have been in remission for at least 1 year, and none of the patients had been treated with a bisphosphonate or other antiresorptive therapy except for hormone replacement therapy as required to correct deficiencies.

Informed consent was obtained from all patients, and the study was approved by the Medical Ethical Committee of the Leiden University Medical Centre.

Study parameters

Disease duration. Disease duration was calculated from the date of estimated onset of symptoms to the date of normalisation of serum IGF-I concentration after trans-sphenoidal surgery, after treatment with a somatostatin analogue or after pituitary irradiation. A normal IGF-I had to be subsequently maintained up to the time of the study.

Disease activity. In the untreated state, disease activity was assessed by measuring serum GH and glucose-suppressed GH and IGF-I concentrations. At the time of the study, disease activity was assessed by measuring serum IGF-I concentrations expressed as age-adjusted SD scores. GH status was further evaluated by measuring random and glucose-suppressed serum GH concentrations.

Duration of remission. The duration of remission was defined as the time elapsed between normalisation of IGF-I concentrations and BMD measurements.

Evaluation of hormone deficiencies. Eugonadism was defined as normal testosterone concentration in men and by the presence of a normal menstrual cycle at preoperative and all postoperative evaluations in women. Hypogonadism was defined by a testosterone concentration below 10 nmol/l in males and by a low serum oestradiol concentration and the absence of a menstrual cycle in females. For the purpose of this study, no distinction was made between hypergonadotrophic or hypogonadotrophic hypogonadism. Adequately treated hypogonadism was defined as gonadal hormone replacement therapy instituted within a year of onset of hypogonadism, and these patients were not considered hypogonadal in terms of this study. Cortisol and thyroid hormone deficiencies were defined as the need for chronic replacement therapy supported by appropriate diagnostic stimulation tests.

Biochemical assays

Serum IGF-I concentrations were determined by a RIA available from 1985 onward (Incstar; Stillwater, MN, USA) with a detection limit of 1.5 nmol/l and an inter-assay coefficient of variation (CV) below 11%. Normal values were expressed as age-related S.D. scores derived from normal values in 137 healthy controls (5). Serum GH concentrations were measured before 1992 by RIA (Biolab, Serona, Coissins, Switzerland) calibrated against WHO International Reference Preparations (IRP) 66/21 (detection limit 0.5 mU/l; interassay CV of <5%). From 1993 onward, a sensitive immunofluorometric assay (IFMA) was used (Wallac, Turku, Finland), specific for the 22 kDA GH protein, calibrated against WHO IRP 80/505 (detection limit 0.03 mU/l; interassay CV 1.6–8.4% of 0.25–40 mU/l). Normal values for serum GH and glucose-suppressed GH concentrations (after an oral load of 75 mg) were respectively <5 and <2.5 mU/l for the RIA, and <5 and <1 mU/l for the IFMA, as established in healthy controls in our own laboratory (6). After surgery and radiotherapy, the combination of glucose-suppressed

serum GH of <1 mU/l, serum GH of <5 mU/l and normal IGF-I for age was used to define remission. During medical treatment, serum GH of <5 mU/l and normal IGF-I for age were used to indicate controlled disease (7–9). For the present study, we chose serum IGF-I concentration as the criterion for inclusion and for calculation of the time from remission. Both surgically and/or irradiated cured patients and patients with controlled disease during somatostatin analogue treatment were collectively referred to as 'in remission'.

Total serum alkaline phosphatase activity was measured with automated techniques: normal laboratory reference range is 40–120 U/l. Osteocalcin was measured by RIA (Incstar), with a detection limit of 0.2 µg/l and an interassay CV of 7–9.5%. Reference ranges for males are 3.2–12.2 µg/l and for females 2.7–11.5 µg/l. Urinary hydroxyproline was measured from 24-h urine collected while on a gelatin-restricted diet by the method of Prockop and Udenfriend (10) and expressed as hydroxyproline/creatinine ratio. Normal values are 8–30 µmol/mmol.

BMD measurements

BMD was measured by DXA (Hologic 4500; Hologic Inc., Waltham, MA, USA). Sites measured were the lumbar spine (L1–L4), the femoral neck, Ward's triangle and the trochanteric, intertrochanteric and total hip areas.

The Hologic 4500 used in our study was equipped with reference values based on the National Health and Nutrition Examination Survey from 1988 to 1991 (NHANES) (11, 12). The reference values from the NHANES survey are compatible with those of Dutch control populations (13). The CV of BMD measurements was 1%, and the machine was cross-calibrated at regular intervals.

The mean of the left and right femoral neck measurements were used for analysis. BMD was also expressed as T scores and Z scores. The WHO consensus definitions were used for the diagnosis of osteoporosis (T score –2.5) and osteopenia (T score between –2.5 and –1).

Statistics

Statistical analysis was performed with Systat 10.0 (Systat Software, Richmond, CA, USA) using bivariate correlation, ANOVA and regression analyses. Descriptive data were expressed as mean±S.E.M. (range) unless otherwise stated. Univariate stepwise regression analysis was used to explore the effects of various factors on BMD. A P value of <0.05 was considered significant.

RESULTS

Patient characteristics

Forty-five male and 34 female patients in remission after treatment for acromegaly, with a mean age of 57±1 years, were studied. Primary treatment was trans-sphenoidal pituitary surgery in the majority of patients (n = 73), followed in a minority by pituitary irradiation as

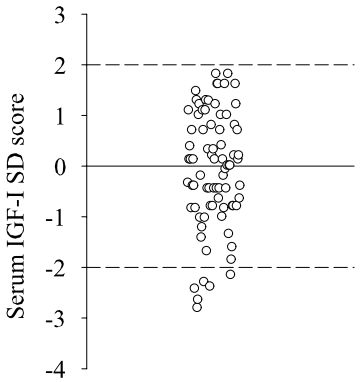

Figure 1. Scatter plot of individual IGF-I S.D. scores in 79 patients in remission after treatment for acromegaly.

required (n = 18), somatostatin analogue treatment (n = 9) or both radiotherapy and somatostatin (n = 7) to achieve remission as defined by normal age-adjusted IGF-I concentrations. Three patients achieved normal IGF-I concentrations by primary treatment with somatostatin analogues, and three by primary pituitary irradiation followed by somatostatin analogue treatment in one of the patients. Twenty patients were thus still being treated with somatostatin analogues at the time of analysis, and 28 had eventually been treated with primary or subsequent pituitary irradiation.

The mean duration of active disease was 13.5±1.1 years, and the mean duration of follow-up after remission was 10.2±7 years. Before start of treatment, mean serum GH concentration was 103±16 mU/l (range 4–600 mU/l), and mean IGF-I concentration was 61±4 (range 25–154) nmol/l. At the time of analysis, mean serum GH was 1.76±0.19 mU/l and mean IGF-I S.D. score was –0.07±0.12 (Fig. 1). As per inclusion criterion, none of the 79 patients had an elevated serum IGF-I S.D. score for age; 76 had GH concentrations of <5 mU/l. Six patients had a serum IGF-I score less than –2 S.D. In total, 59 of the 79 patients (75%), 32 male and 27 female patients, had been in remission for 5 years or more at the time of analysis.

Thirty-four of the 45 male patients were eugonadal (n = 27) or had adequately supplemented hypogonadism (n = 7) for a mean duration of 9±3 years. The other 11 males had been hypogonadal for at least 1 year during the course of follow-up, eight being still hypogonadal and the other three being supplemented for 3–4 years at the time of the studies. These 11 patients were considered hypogonadal for the present analysis. Nineteen female patients were oestrogen depleted as a result of natural menopause (n = 17) or as a result of (treatment for) acromegaly (n = 2). Four menopausal patients had received pituitary irradiation and showed subnormal levels of luteinising hormone and follicle-stimulating hormone. Two out of 15 pre-menopausal women, without a history of oestrogen depletion had received oestrogen replacement therapy for hypogonadism for 10 and 20 years respectively.

Thirty-one patients demonstrated pituitary hormone deficiencies in one or more axes.

Eighteen of these required thyroid, and 19 corticosteroid, replacement therapy. None of the patients was treated by recombinant human (rh) GH replacement.

Bone turnover parameters

Mean serum alkaline phosphatase activity was 76.8±3 U/l. Mean serum osteocalcin concentration was 2.28±0.24 µg/l, and mean 24-h urinary hydroxyproline/creatinine ratio was 15.7±1 µmol/mmol (Table 1). Although parameters of bone turnover were within the normal laboratory reference range in all patients, oestrogen-depleted women had higher mean serum alkaline phosphatase activity and osteocalcin concentrations than oestrogen-replete women and men.

Table 1. Biochemical markers of bone turnover and GH status in male and female cured acromegalic patients grouped according to gonadal status.

	Male patients		Female patients		Reference values
	Eugonadal	Hypogonadal	Oestrogen-replete	Oestrogen-deplete	
	n=34	n=11	n=15	n=19	
Age (years)	56.0 ± 2.0	60.5 ± 2.8	47.1 ± 2.6[1]	65 ± 2.0[1]	
Serum					
IGF-I SD-score	-0.15 ± 0.18	0.44 ± 0.4	-0.47 ± 0.36	0.09 ± 0.19	-2 - +2
GH (mU/L)	1.6 ± 0.2	3.0 ± 0.9	1.7 ± 0.3	1.4 ± 0.3	<5
Alkaline Phosphatase (U/L)	76.1 ± 4.1	70.1 ± 8.4	62.4 ± 3.8[2]	92.3 ± 7.0[2]	40-120
Osteocalcin (µg/L)	1.6 ± 0.2	2.0 ± 0.6	1.3 ± 0.6	2.9 ±0.6	<5
Urine					
calcium/creatinine ratio (mmol/mmol)	0.34 ± 0.03	0.45 ± 0.07	0.39 ± 0.08	0.52 ± 0.07	<0.4
hydroxyproline/creatinine ratio (µmol/mmol)	15.6 ± 1.5	15.4 ± 2.7	17.5 ± 2.5	14.4 ± 1.5	8-30

Data shown as mean ± SEM. There was no difference were observed between hypogonadal and eugonadal male patients. Significance of differences between oestrogen-replete and oestrogen-deplete female patients: [1] $P < 0.001$; [2] $P = 0.002$.

BMD measurements

BMD measurements at the lumbar spine and femoral neck are shown for the whole population in Table 2 and separately for male and female patients in Fig. 2. In men, mean BMD at the lumbar spine was 1.07±0.03 g/cm^2, with corresponding T score and Z score of –0.28±0.22 and + 0.31±0.23 respectively (range of Z score –3.43 to +3.15; P = 0.19 vs zero). Mean BMD at the femoral neck was 0.88±0.02 g/cm^2, T score –0.90±0.19 and Z score +0.52±0.17 (range of Z score –1.97 to + 3.97; P = 0.005 vs zero). Six male patients (13%) had osteoporosis (one at the lumbar spine, four at the femoral neck and one at both sites). The characteristics of patients with and without osteoporosis at the lumbar spine or femoral neck are given in Table 3. Only age and duration of remission were significantly different between patients with and without osteoporosis.

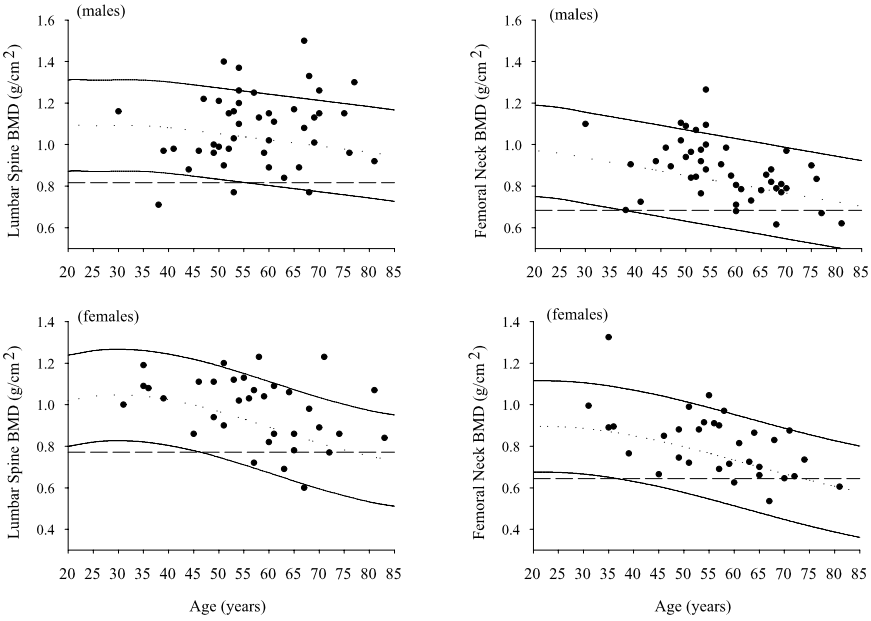

Figure 2. Scatter plots of lumbar spine BMD (left panels) and femoral neck BMD (right panels) and age in male (upper panels) and female (lower panels) patients cured after treatment for acromegaly. Closed circles: individual patients; interrupted line: mean BMD for age; solid lines: −2 S.D. and + 2 S.D.; dashed line: T score − 2.5 S.D.

Table 2. Bone mineral density at the lumbar spine and hip sites in cured acromegalic patients

	BMD (g/cm^2)	Z-score	T-score
Lumbar spine	1.02 ± 0.02	0.36 ± 0.17	-0.50 ± 0.17
Femoral neck	0.85 ± 0.02	0.51 ± 0.13	-0.87 ± 0.15
Trochanter Area	0.76 ± 0.02	0.58 ± 0.14	-0.13 ± 0.15
Intertrochanter Area	1.06 ± 0.02	-0.19 ± 0.14	-0.97 ± 0.14
Ward's Triangle	0.56 ± 0.02	-0.17 ± 0.12	-2.16 ± 0.15
Total Hip	0.94 ± 0.02	0.13 ± 0.13	-0.70 ± 0.14

Data are shown as mean ± SEM.

Predictive factors for BMD

GH/IGF-I status and BMD. No significant correlations were present between serum GH and IGF-I concentrations at the time of diagnosis or at the time of BMD assessment and BMD at the lumbar spine or femoral neck. There was no relationship between estimated duration of active acromegaly and BMD measurements after remission of acromegaly.

Gonadal status and BMD. There were no significant differences in BMD measurements at the lumbar spine or femoral neck between male patients with normal gonadal status and those with hypogonadism. In females, hypogonadism predominantly due to a natural menopause, and not to hypopituitarism, was associated with lower BMD at the lumbar spine (P = 0.01)

Table 3. Biochemical and patients characteristics of patients with and without osteoporosis

	Osteoporosis n=12	No osteoporosis n=67	P value [1]
Sex (F/M)	6/6	39/28	ns
Hypogonadal/eugonadal	male: 3/3	male: 8/31	ns
	female: 5/1	female: 14/14	ns
Age (yr)	64.58 ± 3.57	55.78 ± 1.41	0.018
Duration of remission (yr)	15.42 ± 2.40	9.31 ± 0.76	0.004
Duration of active disease (yr)	15.33 ± 3.00	13.21 ± 1.24	ns
Radiotherapy (Y/N) [2]	5/7	23/44	ns
IGF-SD	0.41 ± 0.30	-0.16 ± 0.14	ns
GH (mU/L)	1.45 ± 0.46	1.82 ± 0.21	ns
Alk. Phosphatase (U/L)	76.75 ± 4.90	76.77 ± 3.46	ns
Osteocalcin (µg/L)	1.63 ± 0.46	2.04 ± 0.27	ns
Calcium/creatinin ratio (mmol/mmol)	0.56± 0.09	0.39 ± 0.03	ns
Hydroxyprolin/creatinin ratio (µmol/mmol)	15.43 ± 2.65	15.77 ± 1.02	ns
BMD femoral neck	0.66 ± 0.02	0.89 ± 0.02	<0.001
Z score femoral neck	-0.77 ± 0.19	0.77 ± 0.13	<0.001
BMD lumbar spine	0.87 ± 0.06	1.06 ± 0.02	<0.001
Z score lumbar spine	-0.56 ± 0.61	0.62 ± 0.15	0.01

Osteoporosis was defined as a T-score of < -2.5 at the femoral neck or lumbar spine site. [1] ns = not significant. [2] Y = yes, N=no.

and femoral neck (P = 0.03) than was eugonadism. However, Z scores at these sites were similar in hypogonadal and eugonadal women, suggesting that the difference in BMD may be explained by the difference in age.

Other factors influencing BMD. According to univariate stepwise regression analysis, BMD and Z scores of both lumbar spine and femoral neck were not affected by current GH and IGF-I concentrations (IGF-I S.D. score), by duration of active acromegaly, by need for glucocorticoid replacement therapy or by the presence of hypogonadism. Pituitary irradiation had a highly significant negative effect on BMD (P = 0.0008) and Z scores at the femoral neck (P = 0.0028), and this effect was independent of the covariates age (P = 0.000 003) and hypogonadism (P = 0.13). In contrast, lumbar spine BMD or Z scores did not appear to be influenced by pituitary irradiation.

Analysis of patients with long-term remission of acromegaly. In a separate analysis, we studied BMD data in 59 patients (32 male and 27 female patients) who had been in remission for at least 5 years. In these patients, mean BMD of the lumbar spine was 1.01±0.02 g/cm^2 and that of the femoral neck was 0.82±0.02 g/cm^2 with corresponding T scores of –0.52±0.2 and –1.05±0.2. Z scores were high at both the lumbar spine 0.41±0.20 g/cm^2 (P = 0.045) and femoral neck 0.38±0.15 g/cm^2 (P = 0.017). The effect of the duration of remission on bone mass was

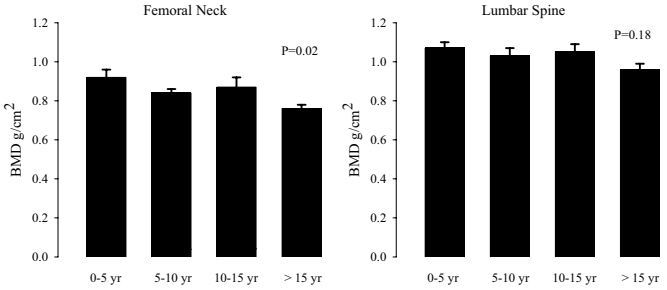

Figure 3. BMD of the femoral neck and lumbar spine (g/cm^2) in cured acromegalics, grouped according to duration of remission, which is expressed as number of years since normalisation of IGF-I and divided into 5-year bins. Whereas lumbar spine BMD remained stable, femoral neck BMD significantly decreased with time after remission.

evaluated by dividing patients into four time periods depending on the duration of remission: (less than 5 years (n = 20), 5–10 years (n = 18), 10–15 years (n = 18) and more than 15 years (n = 23)). BMD measurements were considered dependent variables and time periods independent variables. Age, the use of pituitary irradiation, IGF-I concentrations, hypopituitarism and GH concentrations at the time of BMD measurement were used as covariates. After correction for covariates, the duration of remission remained a significant, independent negative predictor of femoral neck BMD (P = 0.01), also expressed as a Z score (P = 0.019) (Fig. 3). There was no significant relationship between duration of remission and lumbar spine BMD.

DISCUSSION

In this cross-sectional study of 79 acromegalic patients who achieved remission, surgically, medically or after irradiation, as evidenced by normal IGF-I concentrations for age that were maintained for a mean duration of follow-up of 10 years, we observed BMD measurements within or above the normal reference range. Mean BMD remained normal at both lumbar spine and femoral neck sites in patients with sustained remission for at least 5 years.

To our knowledge, this is the first study reporting long-term data on BMD measurements in acromegalics after normalisation of GH excess. In active acromegaly, most studies report an increase in BMD at the femoral neck, which consists predominantly of cortical bone (3, 14–16), although a number of other studies report also normal BMD measurements at this site (17, 18). Increased BMD has also been reported at the radius (19, 20). Only a few studies report increased BMD at the lumbar spine (15, 16, 18), most studies describing normal BMD measurements at this site (3, 4, 14, 16–18, 21). A decrease in BMD has not been reported at any site measured in active acromegaly. In active acromegaly, histomorphometric studies report increased bone turnover at cortical, but not trabecular, sites (22, 23). Cortical bone mass (24, 25) and trabecular bone volume are increased (24) or normal, albeit with increased mean trabecular thickness (25). Recently, decreased trabecular biomechanical competence, apparent

volumetric density and increased trabecular bone content of calcium were reported in active acromegaly, suggesting increased trabecular mineralisation (26). However, the latter report contrasts with the normal or increased trabecular bone turnover in active acromegaly and the increased bone turnover observed in iliac crest biopsies during GH replacement in GHD patients (22, 24, 27). GH administration to aged rats leads to increased cortical bone mass and increased cortical bone strength, but cancellous bone is not significantly affected (28, 29). A rat model resembling acromegaly, with gonadal dysfunction, also displays increased cortical bone mass, without changes in vertebral body cancellous bone mass (30). Collectively, these studies suggest that chronic overexposure to GH leads to increased cortical bone mass by subperiosteal apposition without a major effect on trabecular bone mass.

Limited data are available on changes in cortical or trabecular bone mass after disease cure and normalisation of GH levels. In only one study, including a small number of patients and unclear follow-up duration, are lumbar spine and femoral neck BMD reported to be similar in patients with active or cured acromegaly (15). No significant change in BMD was observed in the short-term after treatment with octreotide (17). A further study reported a decrease in (peripheral) fracture risk in active acromegalic patients years before the diagnosis of acromegaly, and a non-significant reduction in fracture risk in patients years after diagnosis of acromegaly compared with controls (31).

After clinical remission, a number of factors may play a role in eliminating any potential beneficial effect of long-term exposure to the anabolic effects of GH on the skeleton. Age is a clear contender, representing an independent risk factor for bone loss, which becomes more relevant as duration of cure lengthens. In the present study, however, the impact of duration of remission on femoral neck BMD remained significant also after correction for age. Pituitary hormone deficiencies, mainly as a result of pituitary irradiation, may also play a significant role in subsequent bone loss. Deficiency of oestrogens and androgens leads to an increased rate of bone remodelling and shifts the balance between bone formation and resorption in favour of the latter (32). In our study, 27% of male patients were (temporarily) hypogonadal pre- and/or postoperatively. In contrast, most female patients, except for postmenopausal women, received adequate sex steroid supplementation when hypogonadism was diagnosed, so that, at the time of the study, only five female patients had untreated hypogonadism. In acromegaly, the relationship between gonadal status and BMD has not been clearly established, probably due to small group sizes and the heterogeneity of patients with regard to the severity and duration of hypogonadism and time of onset of the GH excess, duration and severity of hypogonadism, and the presence or absence of other anterior pituitary deficiencies in the studies reported. Some studies thus report significantly lower BMD at the lumbar spine in hypogonadal patients with active acromegaly than in eugonadal patients or controls (3, 15–19, 33). Other studies report no difference in BMD at the lumbar spine between eugonadal and hypogonadal patients with active acromegaly (16, 17, 21). The lack of correlation between gonadal status and BMD in our cohort could be explained by the

overall limited duration of untreated hypogonadism. An increased bone volume in acromegaly could affect BMD findings. We did not perform quantitative computed tomography (QCT) on the patients to evaluate directly volumetric trabecular bone density. However, Scillitani et al. (3) reported a high correlation between volumetric trabecular bone density, as measured by QCT, and areal BMD, as measured by DXA, in active acromegaly; this was comparable to correlations found in normal controls.

In the present study, we focused our analysis on cured acromegalic patients, using strict biochemical parameters to define remission whether achieved medically or surgically. Our data suggest that the anabolic effect of GH excess is maintained in the long term after effective treatment of GH excess. In active acromegaly, there is a well-established positive relationship between serum GH concentrations and markers of bone formation, such as osteocalcin and carboxyterminal propeptide of type I collagen (PICP) (34–36), and bone resorption, such as cross-links of type I collagen (N-telopeptide) (35, 37). Biochemical markers of bone turnover are reported to normalise, when the GH excess is controlled with somatostatin analogues or GH receptor blockade therapy (34, 38). As expected, bone turnover was normal in most of our patients, with a tendency to correlate positively with IGF-I concentrations. Despite these findings, it is of note that our patients still demonstrated BMD measurements within or above the normal range more than 5 years after sustained remission. There was, however, no relationship between the BMD measurements and duration of exposure to high GH concentrations as expressed by duration of disease activity.

An intriguing finding in our study is that pituitary irradiation was an independent negative predictor of BMD at cortical sites. In this respect, it is of note that patients who had undergone pituitary irradiation demonstrated more pituitary deficiencies ($P = 0.001$) and had a marginally lower IGF-I S.D. score ($P = 0.055$) than non-irradiated patients. In the irradiated group, the mean Z score at the femoral neck was 0.02 ± 0.24, a value significantly lower than the mean Z score in non-irradiated patients (0.83 ± 0.14), but similar to that reported in GHD acromegalics (39). This finding has led us to hypothesise that the lower BMD measurements specifically observed at the femoral neck in patients who underwent pituitary irradiation may be due to some degree of diminished GH secretion.

In conclusion, our data demonstrate that patients successfully treated for acromegaly by surgery and/or multimodality therapy, and in whom remission was sustained for a mean of 10 years, maintain a BMD within or above the normal range, consistent with sustained anabolic action on the skeleton. Bone loss does occur in the longer term (>15 years), but only at the cortical sites. Pituitary irradiation is an independent negative predictor of BMD likely to be due to associated pituitary deficiencies, probably including some degree of diminished GH secretion. Whether long-term maintenance of BMD is associated with improvement in bone quality and thus with a decrease in the risk of fractures remains to be established.

REFERENCES

1. Albright F, Reifenstein ECJ 1948 The Parathyroid Glands and Metabolic Bone Disease. Selected Studies, pp 188–196. Baltimore: Williams & Wilkins
2. Ohlsson C, Bengtsson BA, Isaksson OG, Andreassen TT, Slootweg MC 1998 Growth hormone and bone. Endocr Rev 19:55–79
3. Scillitani A, Battista C, Chiodini I, et al. 2003 Bone mineral density in acromegaly: the effect of gender, disease activity and gonadal status. Clin Endocrinol (Oxf) 58:725–731
4. Chiodini I, Trischitta V, Carnevale V, Liuzzi A, Scillitani A 2001 Bone mineral density in acromegaly: does growth hormone excess protect against osteoporosis? J Endocrinol Invest 24:288–291
5. Janssen YJ, Frolich M, Roelfsema F 1997 A low starting dose of genotropin in growth hormone-deficient adults. J Clin Endocrinol Metab 82:129–135
6. Biermasz NR, van Dulken H, Roelfsema F 2000 Long-term follow-up results of postoperative radiotherapy in 36 patients with acromegaly. J Clin Endocrinol Metab 85:2476–2482
7. Biermasz NR, Dekker FW, Pereira AM, et al. 2004 Determinants of survival in treated acromegaly in a single center: predictive value of serial insulin-like growth factor I measurements. J Clin Endocrinol Metab 89; 2789–2796
8. Biermasz NR, van Dulken H, Roelfsema F 2000 Ten-year follow-up results of transsphenoidal microsurgery in acromegaly. J Clin Endocrinol Metab 85:4596–4602
9. Biermasz NR, Thiel van SW, Pereira AM, et al. 2004 Decreased quality of life in patients with acromegaly despite long-term cure of GH excess. J Clin Endocrinol Metab 89:5369–5376
10. Prockop DJ, Udenfriend S 1960 A specific method for the analysis of hydroxyproline in tissues and urine. Anal Biochem 1:228–239
11. Wahner HW, Looker A, Dunn WL, Walters LC, Hauser MF, Novak C 1994 Quality control of bone densitometry in a national health survey (NHANES III) using three mobile examination centers. J Bone Min Res 9:951–960
12. Genant HK, Grampp S, Gluer CC, et al. 1994 Universal standardization for dual x-ray absorptiometry: patient and phantom cross-calibration results. J Bone Min Res 9:1503–1514
13. Staal KP, Roos JC, Manoliu RA, Kostense PJ, Lips P 2004 Variations in diagnostic performances of dual-energy X-ray absorptiometry in the northwest of The Netherlands. Osteopor Int 15:335–344
14. Kotzmann H, Bernecker P, Hubsch P, et al. 1993 Bone mineral density and parameters of bone metabolism in patients with acromegaly. J Bone Min Res 8:459–465
15. Lesse GP, Fraser WD, Farquharson R, Hipkin L, Vora JP 1998 Gonadal status is an important determinant of bone density in acromegaly. Clin Endocrinol (Oxf) 48:59–65
16. Kaji H, Sugimoto T, Nakaoka D, et al. 2001 Bone metabolism and body composition in Japanese patients with active acromegaly. Clin Endocrinol (Oxf) 55:175–181
17. Ho PJ, Fig LM, Barkan AL, Shapiro B 1992 Bone mineral density of the axial skeleton in acromegaly. J Nucl Med 33:1608–1612
18. Kayath MJ, Vieira JG 1997 Osteopenia occurs in a minority of patients with acromegaly and is predominant in the spine. Osteopor Int 7:226–230
19. Diamond T, Nery L, Posen S 1989 Spinal and peripheral bone mineral densities in acromegaly: the effects of excess growth hormone and hypogonadism. Ann Intern Med 111:567–573
20. Jockenhovel F, Rohrbach S, Deggerich S, Reinwein D, Reiners C 1996 Differential presentation of cortical and trabecular peripheral bone mineral density in acromegaly. Eur J Med Res 1:377–382
21. Bolanowski M, Wielgus W, Milewicz A, Marciniak R 2000 Axial bone mineral density in patients with acromegaly. Acad Rad 7:592–594
22. Roelfsema F 1976 Quantitation of bone turnover in biopsy specimens from the iliac crest in acromegaly and Cushing's syndrome. In Proceedings of the first workshop on bone morphology. Ed. ZFG Jaworsky. Ottowa: University of Ottowa Press
23. Broulik P, Kragstrup J, Mosekilde L, Melsen F 1982 Osteon cross-sectional size in the iliac crest: variation in normals and patients with osteoporosis, hyperparathyroidism, acromegaly, hypothyroidism and treated epilepsia. Acta Path Microbiol Imm Scand 90:339–344

24. Halse J, Melsen F, Mosekilde L 1981 Iliac crest bone mass and remodelling in acromegaly. Acta Endocrinol (Copenh) 97:18–22
25. Roelfsema F, Van der Sluys Veer J, Smeenk D 1970 Quantitation of bone and bone turnover in biospsy specimens from the iliac crest in acromegaly. Ir J Med Sci 7:498
26. Ueland T, Ebbesen EN, Thomsen JS, et al. 2002 Decreased trabecular bone biomechanical competence, apparent density, IGF-II and IGFBP-5 content in acromegaly. Eur J Clin Invest 32:122–128
27. Bravenboer N, Holzmann P, de Boer H, Roos JC, van der Veen EA, Lips P 1997 The effect of growth hormone (GH) on histomorphometric indices of bone structure and bone turnover in GH-deficient men. J Clin Endocrinol Metab 82:1818–1822
28. Andreassen TT, Jorgensen PH, Flyvbjerg A, Orskov H, Oxlund H 1995 Growth hormone stimulates bone formation and strength of cortical bone in aged rats. J Bone Min Res 10:1057–1067
29. Andreassen TT, Melsen F, Oxlund H 1996 The influence of growth hormone on cancellous and cortical bone of the vertebral body in aged rats. J Bone Min Res 11:1094–1102
30. Morimoto I, Kai K, Okada Y, et al. 2000 Skeletal changes in rats bearing mammosomatotrophic pituitary tumors: a model of acromegaly with gonadal dysfunction. Bone 26:255–261
31. Vestergaard P, Mosekilde L 2004 Fracture risk is decreased in acromegaly – a potential beneficial effect of growth hormone. Osteopor Int 15:155–159
32. Manolagas SC, Kousteni S, Jilka RL 2002 Sex steroids and bone. Rec Progr Horm Res 57:385–409
33. Scillitani A, Chiodini I, Carnevale V, et al. 1997 Skeletal involvement in female acromegalic subjects: the effects of growth hormone excess in amenorrheal and menstruating patients. J Bone Min Res 12:1729–1736
34. Terzolo M, Piovesan A, Osella G, et al. 1993 Serum levels of bone Gla protein (osteocalcin, BGP) and carboxyterminal propeptide of type I procollagen (PICP) in acromegaly: effects of long-term octreotide treatment. Calc Tiss Int 52:188–191
35. Legovini P, Menis de E, Breda F, et al. 1997 Long-term effects of octreotide on markers of bone metabolism in acromegaly: evidence of increased serum parathormone concentrations. J Endocrinol Invest 20:434–438
36. de la Piedra C, Carbo E, Larranaga J, et al. 1988 Correlation among plasma octeocalcin, growth hormone, and somatomedin C in acromegaly. Calc Tiss Int 43:44–45
37. Ezzat S, Melmed S, Endres D, Eyre DR, Singer FR 1993 Biochemical assessment of bone formation and resorption in acromegaly. J Clin Endocrinol Metab 76:1452–1457
38. Fairfield WP, Sesmilo G, Katznelson L, et al. 2002 Effects of a growth hormone receptor antagonist on bone markers in acromegaly. Clin Endocrinol (Oxf) 57:385–390
39. Feldt-Rasmussen U, Abs R, Bengtsson BA, et al. 2002 Growth hormone deficiency and replacement in hypopituitary patients previously treated for acromegaly or Cushing's disease. Eur JEndocrinol 146:67–74