CLINICAL STUDY

High prevalence of vertebral fractures despite normal bone mineral density in patients with long-term controlled acromegaly

M J E Wassenaar, N R Biermasz, N A T Hamdy, M C Zillikens¹, J B J van Meurs^{1,2}, F Rivadeneira^{1,2}, A Hofman², A G Uitterlinden^{1,2}, M P M Stokkel³, F Roelfsema, M Kloppenburg⁴, H M Kroon⁵, J A Romijn and A M Pereira

Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands, Departments of ¹Internal Medicine and ²Epidemiology, Erasmus Medical Center, PO Box 2060, 3000 CB Rotterdam, The Netherlands and Departments of ³Nuclear Medicine, ⁴Epidemiology and Rheumatology and ⁵Radiology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

(Correspondence should be addressed to N R Biermasz; Email: n.r.biermasz@lumc.nl)

Abstract

Objective: To establish the prevalence of osteoporosis, vertebral fractures (VFs), and non-VFs in acromegaly patients with long-term controlled disease and factors potentially influencing fracture risk. **Design:** Case-control study.

Patients and measurements: Eighty-nine patients (46% male, mean age: 58 years) were included. We studied VFs and non-VFs, bone mineral density (BMD), and markers of bone turnover. In 48 patients, BMD assessment was also obtained 7 years prior to the current study. To compare VF prevalence, data from a sample of the Dutch population ($n=3469$) were used.

Results: VF prevalence was 59% (men 64% and women 54%), significantly increased when compared with controls (odds ratio up to 6.5), and independent of the duration of disease control, BMD, markers of bone turnover, and acromegalic disease characteristics. Mean number of VFs per patient was 3.4 ± 0.3 (range 1–8). There was no relationship between the number and severity of fractures, parameters of bone turnover, and follow-up BMD measurements. BMD did not change during prolongation of follow-up by 7 years of controlled acromegaly.

Conclusion: There is a very high prevalence of VFs in acromegaly patients with long-term controlled disease, independently of BMD. In view of the significant morbidity and mortality associated with VFs in general and the inability of BMD to predict fracture risk in acromegalic patients, we propose to include VF assessment, for example by lateral conventional radiographs of the spine in the screening of patients with acromegaly, both at diagnosis and during follow-up after establishment of disease control.

European Journal of Endocrinology 164 475–483

Introduction

GH and insulin-like growth factor 1 (IGF1) act as anabolic hormones on bone by stimulating bone turnover, especially bone formation. It has also been suggested that the anabolic effects of GH on bone mineral density (BMD) may be sustained after cure of acromegaly (1–5), but duration of follow-up was relatively short in the majority of studies. The effects of GH excess on BMD appear to be less consistent. In active acromegaly, high circulating concentrations of GH and IGF1 are associated with increased cortical BMD (6–10). The reported effects of GH/IGF1 excess on trabecular BMD are more variable, with studies reporting either increased or decreased BMD at trabecular sites possibly due to the variable presence of hypogonadism (1, 3–5, 11–13).

It remains unclear whether the overall increase in BMD observed in patients with acromegaly is associated with a decrease in fracture risk. Data on fracture risk are conflicting in patients with active as well as controlled acromegaly. Vestergaard *et al.* (14) suggested that risk for non-vertebral fractures (non-VFs) is decreased in patients with active acromegaly compared with controls, that these patients sustain fractures at a later age, and that the fracture risk is independent of gonadal status. In contrast, Bonadonna *et al.* (15) found that in postmenopausal women with active acromegaly, the risk for VFs was high even in the presence of normal BMD, but that VFs were always associated with low BMD in controlled disease. The same group also demonstrated an increase in VF risk in men with acromegaly, especially in those with hypogonadism, irrespective of BMD (16). To date, the prevalence of

fractures in relation with BMD has not been assessed in acromegalic patients after long-term biochemical control.

The main objective of our study was to establish the prevalence of VFs and non-VFs in both men and women with controlled acromegaly for a mean of 14 years, and to study factors potentially modulating fracture risk in the controlled state of the disease.

Methods

Patient population

We invited 126 patients with sustained disease control of acromegaly for more than 2 years to participate in this study. All patients had an established diagnosis of acromegaly and were followed at the Department of Endocrinology of the Leiden University Medical Center after successful treatment and control of disease activity (17). Inclusion criteria were a previous history of acromegaly and disease control for 2 years or more. No exclusion criteria were applied. Thirty-seven patients were unwilling or unable to take part in the study. They declined for various reasons such as illness, travel distance to the outpatients' clinic, lack of time, or psychological reasons. A total of 89 of the 126 invited patients (71%) participated. The 37 non-participating patients did not differ from the participating patients in age, gender, body mass index (BMI), duration of active disease, pre-treatment GH/IGF1, type of primary treatment, duration of follow-up, and self-reported cervical, thoracic, and lumbar spine complaints based on an earlier study (18).

The first treatment option had always been trans-sphenoidal surgery performed by a single neurosurgeon and complemented when required by radiotherapy prior to 1985, or somatostatin (SMS) analogs from 1985 onwards. In a minority of patients, primary treatment was given in the form of depot formulations of SMS analogs from 1998 onwards. Since the availability of Pegvisomant in 2003 in The Netherlands, this drug was also used as treatment for therapy-resistant acromegaly. After establishment of cure, disease activity was assessed on a yearly basis by measurement of serum GH and IGF1 concentrations, by oral glucose tolerance tests (except in medically treated patients), and by evaluation of other pituitary functions. The study protocol was approved by the Medical Ethics Committee, and informed consent was obtained from all patients.

Study parameters

Disease activity Activity of acromegaly was evaluated by measuring fasting serum GH and IGF1 concentrations, and by an oral glucose tolerance test. Control of acromegaly was defined by random fasting serum GH levels below 1.9 $\mu\text{g/l}$ ($\sim 5 \text{ mU/l}$), normal IGF1 levels for age, and by normal glucose suppressed serum GH below

0.38 $\mu\text{g/l}$ ($\sim 1 \text{ mU/l}$) (19). Duration of disease control was based on time since normalization of IGF1. Disease duration was estimated using the reported date of onset of symptoms and signs, including facial changes on photographs, to the date of normalization of serum IGF1 concentration after treatment by transsphenoidal surgery, radiotherapy, and/or medical therapy.

Assessment of pituitary and gonadal function For evaluation of pituitary function, TSH deficiency was defined as a free thyroxine (fT_4) level below the normal laboratory reference range (absolute value $<10 \text{ pmol/l}$). ACTH deficiency was defined as an inappropriate increase in cortisol levels (absolute value $<0.55 \mu\text{mol/l}$) after stimulation by corticotrophin-releasing hormone or insulin tolerance test.

The history of each individual patient was carefully reviewed with respect to his/her gonadal function from the time of diagnosis to the present evaluation. Patients with adequately treated hypogonadism (defined as gonadal hormone replacement therapy started within 1 year after the onset of hypogonadism) throughout follow-up, were not considered hypogonadal. Thus, male patients with normal testosterone levels throughout follow-up (in relation to sex hormone-binding globulin concentration) or short-term hypogonadism, which had been adequately supplemented within 1 year after onset of hypogonadism, were considered eugonadal. Male patients with a total testosterone concentration below 8 nmol/l, present for >1 year in follow-up or prior to diagnosis, were considered hypogonadal. Female patients with normal spontaneous menstrual cycle, estrogen or contraceptive use, or with short-term amenorrhea subsequently treated with estrogen within 1 year were considered eugonadal. Female patients with prolonged untreated amenorrhea in the presence of low serum estradiol concentration of $<70 \text{ nmol/l}$ (and low LH/FSH in postmenopausal women) or natural menopause were considered hypogonadal.

All patients with hypopituitarism were appropriately treated with L-T_4 , hydrocortisone, testosterone, or estrogen substitution (in pre-menopausal women).

Biochemical assays Serum GH was measured with a sensitive immunofluorometric assay (Wallac, Turku, Finland), specific for the 22 kDa GH protein, calibrated against WHO International Reference Preparation (WHO IRP) 80/505 (detection limit 0.03 mU/l; inter-assay coefficient of variation (CV) 2.0–9.0% of 0.25–40 mU/l) from 1992 onwards, and previously with the RIA assay (Biolab/Serono, Coinsins, Switzerland) calibrated against WHO-IRP 66/21, with an inter-assay CV below 5% and a detection limit of 0.5 mU/l.

Until 2005, serum IGF1 concentrations were determined by an RIA (Incstar, Stillwater, MN, USA) with a detection limit of 1.5 nmol/l and an inter-assay CV below 11%. IGF1 is expressed as SDS for age- and

gender-related normal levels determined in the same laboratory (20). From 2005 onwards, serum IGF1 concentration (ng/ml) was measured using an immuno-metric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, CA, USA). The intra-assay CV was 5.0 and 7.5% at mean plasma levels of 8 and 75 nmol/l respectively. IGF1 levels were expressed as SDS, using lambda-mu-sigma smoothed reference curves based on measurements in 906 healthy individuals (21, 22).

The markers of bone turnover, β -crosslaps (bone resorption), and procollagen type 1 amino-terminal propeptide (P1NP) (bone formation) were measured by an electrochemoluminescent immunoassay with a Modular Analytics E-170 system (Roche Diagnostics). Vitamin 25(OH)D was measured by an RIA (Incstar/DiaSorin, Stillwater, MN, USA).

Bone mineral density measurements BMD was measured at the lumbar spine (L1 to L4) and total hip using dual energy X-ray absorptiometry (DXA, Hologic QDR 4500, Hologic Inc., Waltham, MA, USA) equipped with reference values based on the National Health and Nutrition Examination Survey (NHANES III). The same apparatus was used at baseline and follow-up in patients in whom a baseline DXA was available. In these patients, baseline *T*- and *Z*-scores were recalculated using the new NHANES III reference data.

WHO criteria was used to define osteopenia (*T*-score between -1.0 and -2.5) and osteoporosis (*T*-score of ≤ -2.5).

Forty-eight of the 89 patients included in the study had a baseline BMD measurement 7 years prior to the current study when their acromegaly had already been controlled for a mean of 10 years. These data have already been published (2). The current study assessed the effect of another 7 years (totally 17 years) of disease control on BMD.

Vertebral and non-vertebral fractures Conventional lateral radiography of the thoracic and lumbar spine was performed in all patients. Radiographs were obtained at a standard fixed film focus distance by a single, experienced radiology technician. The radiographs were blindly evaluated by a specialized radiologist with considerable experience in skeletal radiology (H K), as well as by two of the other authors (M W/N B), using the semi-quantitative method proposed by Genant *et al.* (23) for assessment of vertebral deformities and fractures examining vertebrae T4–L5 (23, 24). The intra-observer variability was 1% for the lumbar spine and 3% for the thoracic spine. Inter-observer variability was 3% for the lumbar spine and 5% for the thoracic spine. The prevalence of non-VFs sustained after inappropriate trauma was evaluated by a structured self-reported questionnaire.

To enable comparison of the VF prevalence with controls, we used the radiological data from the

Rotterdam Study ($n=3469$), a prospective population-based cohort study of individuals aged 55 years and over. The study was designed to investigate the incidence and determinants of chronic disabling diseases. Rationale and design have been described previously (23, 25). The Medical Ethics Committee of Erasmus University Medical School has approved the Rotterdam Study, and written informed consent was obtained from each subject. At a follow-up visit, between 1997 and 1999, thoraco-lumbar radiographs of the spine were obtained. The follow-up radiographs were available for 3241 individuals, who survived an average of 7.4 years after baseline center visit and who were still able to come to our research center. All follow-up radiographs were scored for the presence of VF as described earlier (25).

Statistical analysis

SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Data are presented as mean (S.E.M.), unless otherwise stated. A *P* value <0.05 was considered significant. BMD, *T*- and *Z*-scores of the lumbar spine at baseline and follow-up in patients with and without VFs were analyzed by analysis of covariance with adjustments for age, gender, and BMI. Delta was calculated as follows: (follow-up value – baseline value)/baseline value. The prevalence of VFs in acromegaly was compared with a Dutch epidemiological control cohort by binary logistic regression analysis. Controls were the reference category. Factors potentially affecting VF risk were identified by binary logistic regression analysis with adjustments for age, gender, BMI, parameters of disease activity, and hypopituitarism, when appropriate.

Comparisons of the prevalence of VFs between male and female acromegalic patients, grouped according to gonadal status, were performed by binary logistic regression analysis with adjustments for age, gender, and BMI.

Results

Patient characteristics

Eighty-nine patients, 46 male and 43 female patients, with controlled acromegaly for at least 2 years, were included. Mean age was 58.3 ± 10.9 years, and male patients were significantly younger than their female counterparts (55.9 ± 10.7 vs 60.8 ± 11.9 years, $P=0.04$; Table 1). The mean estimated duration of active disease prior to remission was 8.9 ± 7.3 years (range 1–45 years). All patients had controlled disease for a mean of 14 years (range 2–28 years). In 50 patients, disease control was obtained after surgery only. In case of inadequate disease control, surgery was followed by additional radiotherapy in 16 patients,

Table 1 Demographic and clinical characteristics of acromegalic patients, grouped according to gender. Data are shown as mean (s.d.), unless mentioned otherwise.

	Males (n=46)	Females (n=43)	P value
Age (years)	55.9 (10.7)	60.8 (11.9)	0.04
BMI (kg/m ²)	28.7 (4.5)	28.3 (4.9)	0.77
Treatment (n (%))			
Surgery	31 (68%)	19 (44%)	0.12
Surgery + radiotherapy	7 (15%)	9 (21%)	0.86
Surgery + SMS	6 (13%)	8 (19%)	0.81
Surgery + radiotherapy + SMS	2 (4%)	1 (2%)	0.59
SMS	0 (—)	6 (14%)	—
Disease duration (years)	8.1 (5.1)	9.7 (9.1)	0.81
Duration of disease control (years)	14.5 (6.5)	13.7 (6.0)	0.40
GH (μg/l)			
Pre-treatment	40.27 (49.65)	32.65 (45.81)	0.75
Current	0.87 (1.77)	0.95 (0.96)	0.75
IGF1 SDS			
Pre-treatment	7.9 (4.7)	6.7 (4.7)	0.28
Current	0.6 (1.6)	0.5 (1.9)	0.75
Vitamin 25(OH)D (nmol/l)	79.6 (4.6)	79.9 (3.8)	0.82
β-crosslaps (ng/ml)	0.29 (0.1)	0.41 (0.1)	<0.01
P1NP (ng/ml)	30.2 (2.9)	45.5 (4.2)	<0.01
Hypopituitarism (n (%))	13 (28%)	16 (37%)	0.41
Hypogonadal/natural menopause (n (%))	8 (17%)	38 (88%)	<0.01

A P value <0.05 was considered significant. SMS, somatostatin analog; BMI, body mass index; IGF1, insulin-like growth factor 1; CI, confidence interval.

treatment with SMS analogs in 14 patients, and both postoperative radiotherapy and SMS analog treatment in 3 patients. Six other patients had SMS analogs as primary medical treatment. As per inclusion criteria, biochemical control was maintained since remission in the majority of patients for >14 years (n=71), and in 18 patients for 2–14 years. Twenty patients (23%) were still using SMS analogs at the time of the current evaluation.

Thirty-eight male patients were eugonadal (30 with preserved gonadal function and 8 with hypogonadism and adequate replacement treatment with androgens), whereas eight males were hypogonadal (no or inadequate replacement treatment during follow-up). The mean testosterone level at the study visit was 14.2 ± 3.2 nmol/l. Five female patients were eugonadal (four were pre-menopausal with normal gonadal function and one had adequate gonadal steroid replacement therapy for hypogonadism), whereas 38 women were postmenopausal. The mean duration of hypogonadism was comparable in males and females. Twenty-two patients (25%) used hydrocortisone replacement therapy (standard dose 20 mg/day). All, but two patients were vitamin D replete as evidenced by 25(OH)₂D levels >75 nmol/l. Eight patients received calcium and vitamin D supplements, and three patients had been treated with bisphosphonates for up to 4.5 years, but these drugs had been discontinued at least 2.5 years prior to the present study. Three patients are

currently being treated with bisphosphonates and had received these agents for a mean of 6.5 years (range: 3.5–9.5 years).

There were no differences in duration of active disease, duration of remission, serum GH levels, IGF1 SDS at diagnosis or at study evaluation, and the prevalence of pituitary hormone deficiencies, including LH/FSH deficiency between both genders.

Markers of bone turnover were within the normal laboratory reference ranges in all patients. Estrogen-depleted women had higher rates of bone turnover than estrogen-replete women, hypogonadal males, or eugonadal males as evidenced by significantly greater P1NP and β-crosslaps concentrations (data not shown).

Bone mineral density measurements

Mean BMD at the lumbar spine was 1.01 ± 0.02 g/cm², mean T-score was -0.51 ± 0.18 , and mean Z-score was $+0.45 \pm 0.20$. Mean BMD at the total hip was 0.88 ± 0.02 g/cm², mean T-score was -0.47 ± 0.12 , and mean Z-score was $+0.46 \pm 0.10$. BMD, T- and Z-scores of the lumbar spine did not differ between patients with or without VFs, nor after adjustment for age, gender, BMI, and gonadal status (Table 2).

Five patients had osteoporosis, and 14 patients had osteopenia at one or more sites.

Vertebral and non-vertebral fractures

Prevalence of vertebral fractures The prevalence of VFs was 59%, and was not different between patients with controlled disease for 2–14 years (57%) and those with controlled disease for longer than 14 years (59%). There was a gender difference in the prevalence of VFs with more men than women with one or more documented VF (56 vs 44%; $P=0.02$). Hypogonadal men had a significantly higher prevalence of VFs (86%) than eugonadal (19%) or hypogonadal (49%) women ($P<0.05$; Fig. 1).

Fifty-five percent of patients had one or more fractures at the level of the thoracic spine, and 18% had one or more fracture at the levels of the lumbar spine. Mean number of VFs was 3.4 ± 0.3 (range 1–8 fractures) per patient. The most common fractures were anterior wedge fractures (73%), followed by biconcave fractures (18%), and crush fractures (15%; $P<0.01$). The grade of the VFs varied from mild (69%) to intermediate (20%) to severe (11%).

Patients demonstrated significantly more VFs than controls in all age groups. Odds ratios varied from 6.5 (95% CI 3.4–12.4) in patients 61–65 years to 2.3 (95% CI 1.3–3.6) in patients >76 years when compared with controls (Table 3).

Prevalence of non-vertebral fractures Thirty-one patients (35%) sustained one or more non-VFs during

Table 2 BMD (g/cm²), T- and Z-scores of the lumbar spine at baseline and follow-up in patients with and without VF. Data are shown as mean (S.E.M.) unless mentioned otherwise.

	Vertebral fractures (VF)		Difference (95% CI)	P value
	No VF (n = 15 (34%))	VF (n = 27 (66%))		
BMD lumbar spine				
Baseline	1.06 (0.04)	1.00 (0.03)	−0.06 (−0.18–0.06)	0.29
Follow-up	1.01 (0.04)	1.00 (0.03)	0.01 (−0.10–0.11)	0.90
Delta	−0.01 (0.02)	0.00 (0.01)	0.02 (−0.02–0.06)	0.26
T-score lumbar spine				
Baseline	−0.19 (0.35)	−0.53 (0.27)	−0.23 (−1.23–0.82)	0.66
Follow-up	−0.50 (0.35)	−0.69 (0.26)	0.32 (−0.94–1.00)	0.95
Delta	−0.06 (0.25)	−0.10 (0.17)	−0.37 (−1.02–0.27)	0.25
Z-score lumbar spine				
Baseline	0.74 (0.42)	0.12 (0.27)	−0.49 (−1.50–0.53)	0.34
Follow-up	0.56 (0.41)	0.40 (0.26)	−0.01 (−0.95–0.93)	0.96
Delta	0.04 (0.16)	0.24 (0.96)	−0.46 (−3.39–2.47)	0.75

Data were analyzed by analysis of covariance with adjustments for age, gender, and BMI. Delta was calculated as follows: (follow-up value − baseline value)/baseline value. CI, confidence interval; n, number; BMD, bone mineral density; BMI, body mass index.

follow-up since establishment of biochemical control of acromegaly. The prevalence was 37% in men and 33% in women. Fractures of the feet, tibia, humerus, radius, wrist, and hand were variably reported. The most common fracture sites were wrist (29%) and tibia (26%).

Changes in BMD in patients in sustained remission

The subgroup of 48 patients who had a baseline DXA 7 years prior to the present study were in sustained

remission for 17.4 ± 6.3 years. Seventeen of these patients (41%) had hypopituitarism with hormone substitution. Six patients had been treated with oral bisphosphonates, of whom three patients for up to 4.5 years but they had discontinued these drugs for at least 2 years before evaluation, and three patients were still receiving these agents for a mean of 7 years. These six patients were excluded from analysis of sequential changes in BMD.

At baseline, mean BMD was 1.02 ± 0.03 g/cm² at the lumbar spine and 0.96 ± 0.03 g/cm² at the total hip. Four patients had osteoporosis, and 11 patients had osteopenia at one or more sites. After a mean follow-up period of 7 years, mean BMD was 1.01 ± 0.03 g/cm² at the lumbar spine and 0.83 ± 0.02 g/cm² at the total hip ($P = \text{NS}$). Five patients had osteoporosis, and 18 patients had osteopenia at one or more sites. Overall, there was no significant change in BMD over time at either the lumbar spine or total hip sites. There was no significant difference in BMD changes between men and women (Fig. 2).

There was also no significant difference in baseline, delta BMD, or current BMD at the lumbar spine or at the total hip between patients with and without documented VFs (Table 2). Changes in BMD from baseline were not affected by gender, current GH and IGF1 concentrations, duration of active acromegaly, duration of follow-up, gonadal status, or the presence of hypopituitarism. Pituitary irradiation was associated with a significant negative effect on BMD ($P = 0.05$) and Z-scores ($P = 0.03$) of the total hip, which persisted after adjusting for age and gonadal status ($P = 0.01$).

Figure 1 Prevalence of vertebral fractures in male- and female-cured acromegalic patients, grouped according to gonadal status. * $P < 0.05$. Data were analyzed by binary logistic regression analysis with adjustments for age, gender, and BMI.

Analysis of potential risk factors for increased vertebral fracture risk

Gender represented a significant risk factor for VF, with men being significantly more at risk. There was no significant relationship between the prevalence of VFs

Table 3 Prevalence of vertebral fractures by age category in acromegaly patients compared with a Dutch epidemiological control cohort. Data were analyzed by binary logistic regression analysis. Controls were the reference category.

Age category	Subjects		Vertebral fracture cases		Odds ratio	95% CI	P value
	Acromegaly (n=89)	Controls (n=3469)	Acromegaly (n (%))	Controls (n (%))			
<55	19	—	11 (59%)	—	—	—	—
56–60	25	826	13 (53%)	25 (3%)	3.7	1.3–10.9	0.01
61–65	18	955	8 (44%)	48 (5%)	6.5	3.4–12.4	<0.001
66–70	15	796	10 (67%)	72 (9%)	4.4	2.4–8.2	<0.001
71–75	8	560	7 (88%)	73 (13%)	2.4	1.3–4.3	<0.01
>76	4	332	3 (75%)	37 (11%)	2.3	1.3–3.6	<0.01

and age, BMI, age at diagnosis, duration of active disease, pre-treatment or controlled levels of GH/IGF1, type of treatment, duration of controlled disease, the presence of hypopituitarism, markers of bone turnover, treatment with bisphosphonates, current or delta in BMD in patients with or without VFs (Table 4). Use of glucocorticoids and a longer duration of remission tended to be associated with VFs ($P=0.07$).

Discussion

This study indicates a high prevalence of VFs in acromegalic patients with sustained controlled disease for a mean of 14 years. Approximately, 60% of these patients had suffered at least one VF. The prevalence of these VFs was considerably increased when compared with a large Dutch cohort of the general population (25). These fractures in acromegaly patients occurred independent of age, severity or duration of disease activity, type of treatment, presence of hypopituitarism, or BMD, and despite normal vitamin 25(OH)D concentrations. There was a significantly increased prevalence of fractures in men, particularly in the presence of hypogonadism. Apparently, fractures are another

feature of the irreversible changes in the skeleton present in acromegalic patients with long-term biochemical control (26).

There was no significant decrease in BMD at any site measured in the subgroup of patients in which BMD was measured with an interval of 7 years, despite increasing age of the population studied. We have previously demonstrated a sustained maintenance of BMD particularly at trabecular sites after > 10 years of correction of GH excess (2). In the present study, we extend these observations to > 17 years of follow-up, suggesting that the beneficial effect of GH excess on BMD is long-lasting, although apparently this does not protect from risk of fractures, as an increase in BMD may not necessarily translate to improved bone quality (27).

Control data on VFs were derived from a large Dutch epidemiological study, which did not include subjects younger than 55, since the occurrence of VFs is very unlikely in that age group (25). The prevalence of VFs in acromegalic patients largely exceeded the prevalence in the control population, in all age groups (25). In addition, large European population-based cohort studies also report a much lower prevalence of VFs in both men and women (28–32), comparable to the findings in the Dutch reference cohort. Our findings, based on the scoring of two independent scorers and confirmed by an experienced radiologist, demonstrate that the prevalence of VFs in acromegalic women, but even more so in acromegalic men, exceeds the reported prevalence of VFs in the general population, including the Dutch population.

The results of this study are in keeping with data from another group that studied the prevalence of VFs in 36 postmenopausal females and 40 male patients with controlled (~60%) or active acromegaly (15, 16). That study reported a comparable high prevalence of VFs of 53% in females and 57% in male patients (15, 16). However, some differences between our study and the previous studies have to be highlighted. First, the duration of disease control was much longer in our patients, and there are no data available on VFs in acromegaly with controlled disease for more than 14 years. Second, all our patients were vitamin D replete and received hormonal substitution, where applicable. Logistic regression analysis demonstrated that, after

Figure 2 BMD and Z-scores in male- and female-cured acromegalic patients at baseline and follow-up. ($n=42$). In order to eliminate the effect of age and gender, we used Z-scores in addition to BMD.

Table 4 Factors potentially affecting vertebral fracture (VF) risk in acromegaly patients with long-term disease control. Data are depicted as mean (S.E.M.), unless mentioned otherwise. Data were analyzed by binary logistic regression analysis, with adjustments for age, gender, BMI, parameters of disease activity, and hypopituitarism, when appropriate.

	Vertebral fractures (VF)		P value
	No VF (n=37)	VF (n=52)	
Gender (n (%))			0.02
Males	17 (46%)	29 (56%)	
Females	20 (54%)	23 (44%)	
Age (years)	56.5 (1.9)	59.5 (1.6)	0.23
BMI (kg/m ²)	27.9 (0.8)	28.9 (0.7)	0.89
Length (cm)	175.9 (1.8)	175.6 (1.4)	0.45
Weight (kg)	86.6 (2.9)	86.9 (2.6)	0.31
Age at diagnosis (years)	41.2 (2.2)	40.3 (2.1)	0.96
Disease duration (years)	8.7 (1.0)	8.9 (1.3)	0.52
Duration since diagnosis (years)	16.9 (1.5)	20.1 (1.4)	0.85
Duration of remission (years)	12.5 (1.0)	15.2 (1.0)	0.07
Pre-treatment fasting GH (µg/l)	36.4 (7.6)	37.0 (7.3)	0.77
Pre-treatment IGF1 SDS	7.8 (0.9)	6.7 (0.8)	0.11
Hypogonadism (n (%))	18 (47%)	27 (52%)	0.85
Hydrocortisone replacement (n (%))	5 (14%)	17 (33%)	0.07
P1NP (ng/ml)	38.3 (4.0)	37.2 (3.2)	0.66
β-crosslaps (ng/ml)	0.37 (0.04)	0.35 (0.03)	0.73
BMD lumbar spine (follow-up) (g/cm ²)	1.02 (0.04)	1.01 (0.02)	0.52
T-score lumbar spine	−0.40 (0.34)	−0.53 (0.21)	0.62
Z-score lumbar spine	0.63 (0.32)	0.57 (0.25)	0.58
BMD total hip (follow-up) (g/cm ²)	0.89 (0.03)	0.87 (0.02)	0.36
T-score total hip	−0.43 (0.24)	−0.50 (0.14)	0.38
Z-score total hip	0.55 (0.18)	0.41 (0.13)	0.51

n, number; IGF1, insulin-like growth factor 1; P1NP, procollagen type 1 amino-terminal propeptide; BMD, bone mineral density.

correction for all potentially influencing factors, hypogonadism, particularly in men, was associated with VF risk. Unfortunately, it was not possible to determine when the VFs had occurred, as most of these fractures were asymptomatic. As a consequence, we were unable to discriminate fractures that had occurred at the time of active acromegaly from those that occurred during the long period of disease control. Irrespective of this issue, these fractures may have significant clinical implications regarding morbidity and mortality since VFs are associated with decreased quality of life, increased morbidity and mortality, and increased risk of new (non) VFs (33–38). Longitudinal studies are required to address these topics and to assess the contribution of other risk factors for these fractures, including vitamin D, (replacement for) hypopituitarism, and of glucocorticoid replacement at a low dose.

GH and IGF1 are important anabolic hormones for the bone. In fact, most of the effects of GH are mediated by systemic and/or local IGF1, which enhances the differentiated function of osteoblasts and bone formation, although GH may also act directly on bone cells (39). On the other hand, chronic GH and IGF1 excess, which are present in active acromegaly, may impair bone quality, independently of any change in BMD, and apparently increase the risk of fractures, the most important consequence of a decrease in bone quality.

The high prevalence of VFs in the presence of normal BMD may be due to an overestimation of lumbar spine

BMD due to irreversible, structural modifications of the spine, such as degenerative changes and vertebral deformities as a consequence of a prolonged exposure of the skeleton to GH excess in the active stage of acromegaly. BMD of the hip is less affected by structural changes in bone. However, there was no association between low BMD of the hip and VFs, in accordance with the results recently published by Mazziotti *et al.* (16). Six patients were (in the past) treated with bisphosphonates, and these patients were excluded from analysis of sequential changes in BMD. The exclusion of these patients did not affect our conclusions.

In conclusion, our findings indicate a high prevalence of VFs in acromegalic patients during very long follow-up of controlled disease, independently of BMD. Our data also suggest that BMD is maintained during prolongation of follow-up of patients with biochemical control of acromegaly. In view of the significant morbidity associated with VFs, we advocate the inclusion of lateral conventional radiographs of the thoracic and lumbar spine in the screening of all patients with acromegaly both at diagnosis and during follow-up after establishment of disease control.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture, and Science, the Ministry for Health, Welfare, and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. This study is funded by the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), The Netherlands Genomics Initiative (NGI)/Netherlands Organization for Scientific Research (NWO) (project no. 050-060-810), and funding from the European Commission framework 7 program GEFOS (grant 201865).

References

- Battista C, Chiodini I, Muscarella S, Guglielmi G, Mascia ML, Carnevale V & Scillitani A. Spinal volumetric trabecular bone mass in acromegalic patients: a longitudinal study. *Clinical Endocrinology* 2008 **70** 378–382. (doi:10.1111/j.1365-2265.2008.03322.x)
- Biermasz NR, Hamdy NA, Pereira AM, Romijn JA & Roelfsema F. Long-term maintenance of the anabolic effects of GH on the skeleton in successfully treated patients with acromegaly. *European Journal of Endocrinology* 2005 **152** 53–60. (doi:10.1530/eje.1.01820)
- Bolanowski M, Daroszewski J, Medras M & Zadrozna-Sliwka B. Bone mineral density and turnover in patients with acromegaly in relation to sex, disease activity, and gonadal function. *Journal of Bone and Mineral Metabolism* 2006 **24** 72–78. (doi:10.1007/s00774-005-0649-9)
- Lesse GP, Fraser WD, Farquharson R, Hipkin L & Vora JP. Gonadal status is an important determinant of bone density in acromegaly. *Clinical Endocrinology* 1998 **48** 59–65. (doi:10.1046/j.1365-2265.1998.00349.x)
- Scillitani A, Battista C, Chiodini I, Carnevale V, Fusilli S, Ciccarelli E, Terzolo M, Oppizzi G, Arosio M, Gasperi M, Arnaldi G, Colao A, Baldelli R, Ghiggi MR, Gaia D, Di Somma C, Trischitta V & Liuzzi A. Bone mineral density in acromegaly: the effect of gender, disease activity and gonadal status. *Clinical Endocrinology* 2003 **58** 725–731. (doi:10.1046/j.1365-2265.2003.01777.x)
- Aloia JE, Petrak Z, Ellis K & Cohn SH. Body composition and skeletal metabolism following pituitary irradiation in acromegaly. *American Journal of Medicine* 1976 **61** 59–63. (doi:10.1016/0002-9343(76)90041-3)
- Halse J, Melsen F & Mosekilde L. Iliac crest bone mass and remodelling in acromegaly. *Acta Endocrinologica* 1981 **97** 18–22. (doi:10.1530/acta.0.0970018)
- Ezzat S, Melmed S, Endres D, Eyre DR & Singer FR. Biochemical assessment of bone formation and resorption in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 1993 **76** 1452–1457. (doi:10.1210/jc.76.6.1452)
- Ho PJ, Fig LM, Barkan AL & Shapiro B. Bone mineral density of the axial skeleton in acromegaly. *Journal of Nuclear Medicine* 1992 **33** 1608–1612.
- Kaji H, Sugimoto T, Nakaoka D, Okimura Y, Kaji H, Abe H & Chihara K. Bone metabolism and body composition in Japanese patients with active acromegaly. *Clinical Endocrinology* 2001 **55** 175–181. (doi:10.1046/j.1365-2265.2001.01280.x)
- Diamond T, Nery L & Posen S. Spinal and peripheral bone mineral densities in acromegaly: the effects of excess growth hormone and hypogonadism. *Annals of Internal Medicine* 1989 **111** 567–573.
- Kayath MJ & Vieira JG. Osteopenia occurs in a minority of patients with acromegaly and is predominant in the spine. *Osteoporosis International* 1997 **7** 226–230. (doi:10.1007/BF01622293)
- Zgliczynski W, Kochman M, Misiorowski W & Zdunowski P. In acromegaly, increased bone mineral density (BMD) is determined by GH-excess, gonadal function and gender. *Neuro Endocrinology Letters* 2007 **28** 621–628.
- Vestergaard P & Mosekilde L. Fracture risk is decreased in acromegaly – a potential beneficial effect of growth hormone. *Osteoporosis International* 2004 **15** 155–159. (doi:10.1007/s00198-003-1531-z)
- Bonadonna S, Mazziotti G, Nuzzo M, Bianchi A, Fusco A, De Marinis L & Giustina A. Increased prevalence of radiological spinal deformities in active acromegaly: a cross-sectional study in postmenopausal women. *Journal of Bone and Mineral Research* 2005 **20** 1837–1844. (doi:10.1359/JBMR.050603)
- Mazziotti G, Bianchi A, Bonadonna S, Cimino V, Patelli I, Fusco A, Pontecorvi A, De Marinis L & Giustina A. Prevalence of vertebral fractures in men with acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 4649–4655. (doi:10.1210/jc.2008-0791)
- Biermasz NR, Dekker FW, Pereira AM, van Thiel SW, Schutte PJ, van Dulken H, Romijn JA & Roelfsema F. Determinants of survival in treated acromegaly in a single center: predictive value of serial insulin-like growth factor I measurements. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 2789–2796. (doi:10.1210/jc.2003-032041)
- Biermasz NR, Pereira AM, Smit JW, Romijn JA & Roelfsema F. Morbidity after long-term remission for acromegaly: persisting joint-related complaints cause reduced quality of life. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 2731–2739. (doi:10.1210/jc.2004-2297)
- Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JW, Romijn JA & Roelfsema F. Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 5369–5376. (doi:10.1210/jc.2004-0669)
- Janssen YJ, Frolich M & Roelfsema F. A low starting dose of genotropin in growth hormone-deficient adults. *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 129–135. (doi:10.1210/jc.82.1.129)
- Cole TJ. The LMS method for constructing normalized growth standards. *European Journal of Clinical Nutrition* 1990 **44** 45–60.
- Rikken B, van Doorn J, Ringeling A, Van den Brande JL, Massa G & Wit JM. Plasma levels of insulin-like growth factor (IGF)-I, IGF-II and IGF-binding protein-3 in the evaluation of childhood growth hormone deficiency. *Hormone Research* 1998 **50** 166–176. (doi:10.1159/000023268)
- Genant HK, Wu CY, van Kuijk C & Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *Journal of Bone and Mineral Research* 1993 **8** 1137–1148. (doi:10.1002/jbmr.5650080915)
- McCloskey EV, Spector TD, Eyres KS, Fern ED, O'Rourke N, Vasikaran S & Kanis JA. The assessment of vertebral deformity: a method for use in population studies and clinical trials. *Osteoporosis International* 1993 **3** 138–147. (doi:10.1007/BF01623275)
- Van der Klift M, De Laet CE, McCloskey EV, Hofman A & Pols HA. The incidence of vertebral fractures in men and women: the Rotterdam Study. *Journal of Bone and Mineral Research* 2002 **17** 1051–1056. (doi:10.1359/jbmr.2002.17.6.1051)
- Wassenaar MJ, Biermasz NR, van Duinen N, van der Klaauw AA, Pereira AM, Roelfsema F, Smit JW, Kroon HM, Kloppenburg M & Romijn JA. High prevalence of arthropathy, according to the definitions of radiological and clinical osteoarthritis, in patients with long-term cure of acromegaly: a case-control study. *European Journal of Endocrinology* 2009 **160** 357–365. (doi:10.1530/EJE-08-0845)
- Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Black DM, Hillier TA, Hochberg MC, Vogt MT & Orwoll ES. Hip fracture in women without osteoporosis. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 2787–2793. (doi:10.1210/jc.2004-1568)
- Ismail AA, O'Neill TW, Cockerill W, Finn JD, Cannata JB, Hoszowski K, Johnell O, Matthis C, Raspe H, Raspe A, Reeve J & Silman AJ. Validity of self-report of fractures: results from a prospective study in men and women across Europe. EPOS

- Study Group. European Prospective Osteoporosis Study Group. *Osteoporosis International* 2000 **11** 248–254. (doi:10.1007/s001980050288)
- 29 Ismail AA, O'Neill TW, Cooper C & Silman AJ. Risk factors for vertebral deformities in men: relationship to number of vertebral deformities. European Vertebral Osteoporosis Study Group. *Journal of Bone and Mineral Research* 2000 **15** 278–283. (doi:10.1359/jbmr.2000.15.2.278)
 - 30 Silman AJ, O'Neill TW, Cooper C, Kanis J & Felsenberg D. Influence of physical activity on vertebral deformity in men and women: results from the European Vertebral Osteoporosis Study. *Journal of Bone and Mineral Research* 1997 **12** 813–819. (doi:10.1359/jbmr.1997.12.5.813)
 - 31 Lunt M, Felsenberg D, Reeve J, Benevolenskaya L, Cannata J, Dequeker J, Dodenhof C, Falch JA, Masaryk P, Pols HA, Poor G, Reid DM, Scheidt-Nave C, Weber K, Varlow J, Kanis JA, O'Neill TW & Silman AJ. Bone density variation and its effects on risk of vertebral deformity in men and women studied in thirteen European centers: the EVOS Study. *Journal of Bone and Mineral Research* 1997 **12** 1883–1894. (doi:10.1359/jbmr.1997.12.11.1883)
 - 32 Ferrar L, Jiang G, Cawthon PM, San VR, Fullman R, Lambert L, Cummings SR, Black DM, Orwoll E, Barrett-Connor E, Ensrud K, Fink HA & Eastell R. Identification of vertebral fracture and non-osteoporotic short vertebral height in men: the MrOS Study. *Journal of Bone and Mineral Research* 2007 **22** 1434–1441. (doi:10.1359/jbmr.070608)
 - 33 Johnell O & Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporosis International* 2006 **17** 1726–1733. (doi:10.1007/s00198-006-0172-4)
 - 34 Ross PD, Davis JW, Epstein RS & Wasnich RD. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. *Annals of Internal Medicine* 1991 **114** 919–923.
 - 35 Ross PD, Genant HK, Davis JW, Miller PD & Wasnich RD. Predicting vertebral fracture incidence from prevalent fractures and bone density among non-black, osteoporotic women. *Osteoporosis International* 1993 **3** 120–126. (doi:10.1007/BF01623272)
 - 36 Nevitt MC, Ross PD, Palermo L, Musliner T, Genant HK & Thompson DE. Association of prevalent vertebral fractures, bone density, and alendronate treatment with incident vertebral fractures: effect of number and spinal location of fractures. The Fracture Intervention Trial Research Group. *Bone* 1999 **25** 613–619. (doi:10.1016/S8756-3282(99)00202-1)
 - 37 Black DM, Arden NK, Palermo L, Pearson J & Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *Journal of Bone and Mineral Research* 1999 **14** 821–828. (doi:10.1359/jbmr.1999.14.5.821)
 - 38 Burger H, van Daele PL, Algra D, Hofman A, Grobbee DE, Schutte HE, Birkenhager JC & Pols HA. Vertebral deformities as predictors of non-vertebral fractures. *BMJ* 1994 **309** 991–992.
 - 39 Giustina A, Mazziotti G & Canalis E. Growth hormone, insulin-like growth factors, and the skeleton. *Endocrine Reviews* 2008 **29** 535–559. (doi:10.1210/er.2007-0036)

Received 7 January 2011

Accepted 21 January 2011