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VI.

Progression of vertebral fractures despite long-term biochemical control of acromegaly: a prospective follow-up study

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ABSTRACT

BACKGROUND: In active acromegaly, pathologically elevated GH and IGF-1 levels are associated with increased bone turnover and a high bone mass, the latter being sustained after normalization of GH values. In a cross-sectional study design, we have previously reported a high prevalence of vertebral fractures (VFs) of about 60% in patients with controlled acromegaly, despite normal mean bone mineral density (BMD) values. Whether these fractures occur during the active acromegaly phase or after remission is achieved is not known.

OBJECTIVE: Our objective was to study the natural progression of VFs and contributing risk factors in patients with controlled acromegaly over a 2.5-year follow-up period.

METHODS: Forty-nine patients (mean age 61.3 ± 11.1 years, 37% female) with controlled acromegaly for ≥ 2 years following surgery, irradiation and/or medical therapy and not using bisphosphonates were included in the study. Conventional spine radiographs including vertebrae Th4-L4 were assessed for VFs according to the Genant method. VF progression was defined as development of new/incident fractures and/or a minimum 1-point increase in the Genant scoring of pre-existing VFs. BMD was assessed by dual-energy X-ray absorptiometry (Hologic 4500).

RESULTS : Prevalence of baseline VFs was 63%, being highest in men, and fractures were unrelated to baseline BMD. VF progression was documented in 20% of patients, especially in men and in case of ≥ 2 VFs at baseline. VF progression was not related to BMD values or BMD changes over time.

CONCLUSION: Findings from this longitudinal study show that VFs progress in the long term in 20% of patients with biochemically controlled acromegaly in the absence of osteoporosis or osteopenia. These data suggest that an abnormal bone quality persists in these patients after remission, possibly related to pre-treatment long-term exposure to high circulating levels of GH.

INTRODUCTION

Growth Hormone (GH) and Insulin-like Growth Factor-1 (IGF-1) are important regulators of bone growth modeling and remodeling during an individual's life span (1). IGF-1 mediates most of the effects of GH on skeletal metabolism via the IGF-1 receptor (2). GH and IGF-1 act as anabolic hormones on bone by stimulating proliferation, and to some extent, differentiation of osteoblasts. Osteoclastic bone resorption is also stimulated, resulting in an overall increase in bone remodeling (3;4).

In active acromegaly, pathologically high GH and IGF-1 levels increase bone turnover in favor of bone formation (2;5;6), resulting in an overall increase in bone mineral density (BMD). It has been suggested that high bone mass is sustained after long-term disease control (7-11). However, some studies have also reported a low BMD in patients with acromegaly, especially in the presence of concomitant hypogonadism (9;12). We have recently reported a remarkably high prevalence of vertebral fractures (VFs) (59%) in long-term cured acromegalic patients. The highest VF prevalence was observed in men, particularly in those with hypogonadism, and prevalence was significantly increased compared with that of the general population (13). Three other studies reported a comparably high VF prevalence in controlled acromegaly patients, independently of gonadal status (5;6;14), suggesting that VFs should be included in the panoply of complications of acromegaly. Since BMD has found to be normal in the majority of patients, the high VF risk is likely to be due to alterations in bone quality rather than a decrease in bone quantity. Another important factor in the acquisition of bone mass is the level of sex steroids, being illustrated by the development of osteopenia and an increased fracture risk in hypogonadal men and women and by the preservation of bone mass by restoration of normal endogenous sex steroid levels or by exogenous supplementation (15;16).

Because all studies reported to date have been cross-sectional studies, an important question remaining to be addressed is whether patients solely fracture during the active phase of acromegaly or whether they continue to sustain fractures after achievement of cure (17). Another question to be addressed is how to best identify acromegaly patients at risk for (vertebral) fractures, because BMD is a bad predictor of fracture risk in this form of secondary osteoporosis. In view of the increased morbidity and mortality associated with VFs, these questions are of clinical relevance in the long-term management of acromegaly. In a prospective study design, we evaluated the course of VFs and potential determinants for VF progression in the long-term follow-up of biochemically controlled acromegalic patients.

PATIENTS AND METHODS

PATIENTS: All patients with acromegaly in long-term remission (≥ 2 years) after surgery (69%) or medical treatment (31%) and regularly followed up at the Department of Endocrinology and Metabolic Diseases of the Leiden University Medical Center were invited to take part in a cross-sectional study in 2007. Eighty-nine patients positively responded and were included in the study (18). All 89 patients were invited for a further evaluation of skeletal status after a mean interval of 31 ± 1.7 months (range 28-35 months), of whom 58 (65%) positively responded. Reasons for nonparticipation in the follow-up evaluation were non-musculoskeletal-related health problems (N=16), travel distance (N=6), lack of time (N=4), psychological reasons (N=3), or moving abroad (N=2). Demographic and disease characteristics did not differ between participants and nonparticipants in the follow-up study (*data not shown*), except for more women among non-participants ($p=0.025$). We excluded the 9 patients receiving bisphosphonate treatment at any time point during follow-up, so that 49 patients were included in the final analysis.

Clinical follow-up data were available yearly in all patients since initiation of treatment for acromegaly. From 1977 onward, first-line treatment was in the form of transsphenoidal surgery performed by a single experienced neurosurgeon. When required, adjuvant treatment was given in the form of radiotherapy (before 1985) or somatostatin (SMS) analogs (from 1985 onward). Since 1998, a small number of patients received treatment solely in the form of a depot formulation of long-acting SMS analogs. This treatment approach resulted in early postoperative control in 66% and late control in $>90\%$ of patients (19). From 2003 onward, Pegvisomant was used for treatment-resistant acromegaly.

Disease activity was assessed yearly by an oral glucose tolerance test (except in medically treated patients) and fasting serum GH and IGF-1 levels. Other pituitary functions were also evaluated yearly. Remission was defined as a normal glucose-suppressed serum GH $<1.25 \mu\text{g/L}$ (RIA assay until 1992) or $0.38 \mu\text{g/L}$ (immunofluorometric assay (IFMA) from 1992 onwards), serum GH levels $<1.9 \mu\text{g/L}$, and normal IGF-1 levels for age (from 1986 onwards). Treatment decisions were based on these remission criteria.

STUDY DESIGN: Fasting blood samples were obtained to assess GH and IGF-1 concentrations at baseline and at 2.5 years of follow-up. Conventional spine radiographs were obtained using a standardized protocol (*vide infra*) and BMD was assessed using dual energy X-ray absorptiometry (DXA) (Hologic QDR 4500) at the same time points. All patients had to complete a standardized questionnaire providing demographic data, data on medical history, and data on clinical risk factors for VFs, such as early menopause, previous fractures, glucocorticoid use and diagnosis of rheumatoid arthritis.

The Medical Ethics Committee approved the study protocol, and informed consent was obtained in all patients.

ACROMEGALY DISEASE PARAMETERS: Duration of active acromegaly was calculated from the estimated date of onset of the disease, defined as the date of onset of signs and symptoms or the date of changes in facial features using serial photographs, to the date of normalization of serum IGF-1 after surgery, irradiation and/or medical treatment. Duration of remission of acromegaly was calculated from the date of biochemical remission to the date of baseline evaluation at inclusion in the study. Cure was defined as normal glucose-suppressed age-related GH levels and IGF-1 levels after surgery and/or irradiation. Biochemical control was defined as normal serum IGF-1 levels for age during medical treatment. Both cured and biochemically controlled patients were referred to as being 'in remission'.

ASSESSMENT OF PITUITARY AND GONADAL FUNCTION:

Hypopituitarism was diagnosed on the basis of clinically significant hormone deficiencies in at least one axis, which required supplementation with L-T₄, hydrocortisone, testosterone or estrogens (in pre-menopausal women) according to the following definitions (20;21): TSH deficiency was defined as a free T₄ level below the normal laboratory reference range (absolute value <10pmol/l). ACTH deficiency was defined as an insufficient increase in cortisol levels (absolute value <0.55µmol/l) after stimulation by CRH or insulin tolerance test. GH deficiency (GHD) was not routinely assessed.

With respect to gonadal function, patients with adequately treated hypogonadism (*i.e.* gonadal hormone replacement therapy started <1 year after the onset of hypogonadism) were considered eugonadal. Men with a total testosterone concentration of <8.0nmol/l for longer than 1 year during follow-up or documented prior to diagnosis, were considered hypogonadal. Female patients with normal spontaneous menstrual cycle,

those using estrogen replacement therapy or the pill, or patients with a history of only short-term amenorrhea who were treated with estrogen within 1 year of diagnosis were considered eugonadal. Females with prolonged untreated amenorrhea in the presence of a serum estradiol concentration of <70nmol/l or natural menopause were considered hypogonadal.

BIOCHEMICAL ASSAYS: Serum GH was measured with a sensitive IFMA (Wallac, Turku, Finland), specific for the 22 kDA GH protein, calibrated against World Health Organisation International Reference Preparation (WHO IRP) 80/505 (detection limit: 0.01µg/l, interassay coefficient of variation (CV): 1.6-8.4% of 0.01-15.38µg/l) from 1992 onwards. For the conversion of µg/l to mU/l, values were multiplied by 2.6. Before 1992, GH was measured by RIA (Biolab, Serona, Coissins, Switzerland), calibrated against WHO IRP 66/21 (detection limit: 0.5mU/l, with an interassay CV less than 5%; for the conversion of µg/l to mU/l, multiply by 2.6).

Until 2005, serum IGF-1 concentrations were determined by a RIA (Incstar; Stillwater, MN, USA) with a detection limit of 1.5nmol/l and an inter-assay CV below 11%. IGF-1 is expressed as standard deviation score (SDS) for age- and sex-related normal levels determined in the same laboratory (32). From 2005 onwards, serum IGF-1 concentrations (nmol/l) were measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, CA, USA). The intra-assay variations at mean plasma levels of 8 and 75nmol/l were 5.0 and 7.5%, respectively. IGF-1 levels were expressed as SDS, using lambda-mu-sigma smoothed reference curves based on measurements in 906 healthy individuals (22;23).

Markers of bone-turnover, beta-crosslaps (bone resorption) and procollagen type 1 amino-terminal propeptide (P1NP) (bone formation), were measured by an electrochemolumiscent immunoassay with a Modular Analytics E-170 system (Roche Diagnostics, Almere, The Netherlands). Serum calcium (adjusted for albumin binding) was measured by a semiautomated technique. 25-hydroxyvitamin D was measured by RIA (Incstar/DiaSorin, Stillwater, MN, USA). Serum concentrations of intact PTH (reference range 1.5-8 pmol/l) were measured using Immulite 2500 (Siemens Diagnostics, Breda, The Netherlands).

BMD MEASUREMENTS: BMD was measured at the lumbar spine (L1-L4) and total hip using DXA (Hologic QDR 4500, Hologic Inc., Waltham, MA, USA) equipped with reference values based on the National Health and Nutrition Examination Survey (NHANES III). World Health Organization (WHO) criteria were used to define osteopenia (T-score between -1.0 and -2.5) and osteoporosis (T-score \leq -2.5). Baseline BMD data have already been published for the original cohort (13). Follow-up BMD data were available in a subset of 15 patients (31%) in the context of standard patient care.

RADIOGRAPHIC PROTOCOL AND VF ASSESSMENT: Conventional lateral radiographs of the thoracic and lumbar spine were performed by an experienced radiology technician following a standardized protocol, with the film centralized on Th7 and L3, respectively, at baseline and after 2.5 years of follow-up. Radiographs obtained in individual patients at both time points were assessed unpaired for presence of VFs in Th4 to L4 according to the validated Genant's semiquantitative method (24). Grade 1 (mild fracture) was defined as approximately 20% to 25% reduction in anterior, middle and/or posterior height; Grade 2 (moderate fracture) was defined as approximately 25% to 40% reduction in anterior, middle and/or posterior height; Grade 3 (severe fracture) was defined as approximately >40% reduction in anterior, middle and/or posterior height. Radiographs were blinded for any patient characteristics and were individually assessed by two independent observers (H.M.K. and K.M.J.A.C.), one of whom is an experienced musculoskeletal radiologist (H.M.K.). In case of discrepancy in assessment, a consensus opinion was obtained. The intra-observer and interobserver variability were good, as depicted by intra-correlation coefficients (ICCs) of, respectively, 0.950 and 0.901. Individual vertebrae with confounding pathology were excluded (5 vertebrae).

Progression of VFs was defined as the development of new/incident VFs (in patients with no VFs or in patients with previous VFs in other vertebrae) and/or the documented minimum 1-point increase in the Genant scoring in pre-existing VFs during the period of follow-up.

Statistical analysis

SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA), was used for data analysis. Data are presented as mean (SD), unless otherwise stated. $P < 0.05$ was considered to be significant. Patient characteristics were grouped according to sex. BMD changes over time were analyzed by a Paired Samples *T* test. Mean baseline BMD, mean current BMD and mean BMD changes were studied compared patients with and without VF progression, using a binary logistic regression analysis, adjusted for age, sex and body mass index (BMI). An χ^2 test was used to assess VF progression rate according to the number of prevalent VFs at baseline.

Potential risk factors for VF progression were identified by binary logistic regression analysis, adjusted for age, sex, BMI, parameters of disease activity, and the presence of hypopituitarism.

RESULTS

Patient characteristics

Forty-nine patients with well-controlled acromegaly (mean age 61.3±11.1 years, 37% female) were included in the study (*Table 1*). Patients had been in remission for a mean of 17.0±7.1 years and mean actual IGF-1 SDS was 0.63±1.39. In 36 patients (73%), remission was achieved by surgery with additional radiotherapy, when required. The remaining 13 patients (27%) received long-acting SMS analogs, either as sole treatment or as postoperative treatment after transsphenoidal surgery (mean duration of treatment 105 (range 21-91) months). One patient received additional treatment with Pegvisomant. Thirty male patients were considered eugonadal (24 with preserved gonadal function, 6 with adequate androgen replacement), and only one was hypogonadal. Mean testosterone level at follow-up was 13.4±4.8 nmol/L. Two females were considered eugonadal (pre-menopausal with normal gonadal function), and 16 were post-menopausal. One patient had diabetes mellitus type 1 and two patients had diabetes mellitus type 2.

All patients were Vitamin D replete at baseline and were still so at the end of study evaluation, except for 2 patients (25-hydroxyvitamin D concentrations <25nmol/L). Ten and 8 patients received respectively calcium and Vitamin D supplements during follow-up.

Bone markers

Mean baseline P1NP and β -crosslaps concentrations were, respectively, 39.4±20.9ng/mL and 0.39±0.20ng/mL. All values were within the normal laboratory reference range, except for slightly elevated P1NP levels in 4 postmenopausal women at baseline and 2 postmenopausal women at follow-up.

Values are means (SD) unless stated otherwise. Patient characteristics were grouped according to sex and were analyzed by Independent Samples T test or X2 test, when appropriate. Disease cure is defined as normal glucose-suppressed GH levels and IGF-1 levels for age after surgery and/or irradiation.

Yr, years; GH, Growth Hormone; IGF-1, Insulin-like Growth Factor-1; BMI, body mass index; SMS, somatostatin (analogs); GHD, Growth Hormone Deficiency; PTH, parathyroid hormone; RA, rheumatoid arthritis.

**, one patient is co-treated with Pegvisomant.*

Table 1. Clinical characteristics of 49 patients with acromegaly, grouped according to sex

Clinical characteristics	Males (N = 31)	Females (N = 18)	P value
Age (yr)	60.1 (11.1)	63.5 (10.9)	0.30
BMI (kg/m ²)	29.6 (4.5)	28.0 (4.9)	0.28
Treatment (n (%))			
Surgery only	21 (68%)	8 (44%)	0.11
Surgery + RT	2 (7%)	5 (28%)	0.04
SMS analogues			
Primary	0 (0%)	2 (11%)	0.06
Following surgery *	7 (23%)	2 (11%)	0.32
Following RT	1 (3%)	0 (0%)	0.45
Following surgery + RT	0 (0%)	1 (6%)	0.19
Hypopituitarism (n (%))	10 (32%)	6 (35%)	0.83
Corticotrope failure	8 (26%)	4 (22%)	0.78
GHD	4 (13%)	5 (29%)	0.17
Thyrotrope failure	3 (10%)	4 (22%)	0.23
Gonadotrope failure	6 (19%)	0 (0%)	0.05
Hypogonadal/natural menopause (n (%))	1 (3%)	16 (89%)	<0.01
Disease duration (yr)	8.0 (5.3)	9.4 (11.2)	0.60
Duration of remission (yr)	17.3 (6.5)	16.5 (8.2)	0.71
GH (μ g/L)			
Pre-treatment	41.2 (55.4)	24.3 (23.5)	0.28
Actual	0.5 (0.5)	1.3 (2.2)	0.21
IGF-1 SDS			
Pre-treatment	7.43 (3.92)	5.22 (1.99)	0.03
Baseline	0.63 (2.09)	0.95 (1.55)	0.59
Actual	0.72 (1.32)	0.45 (1.54)	0.58
Calcium (mmol/l)	2.34 (0.10)	2.36 (0.09)	0.61
PTH (pmol/l)	6.0 (3.0)	5.3 (2.1)	0.43
Vitamin D 25(OH) (nmol/L)			
Baseline	73.3 (32.0)	71.9 (24.3)	0.88
Actual	55.7 (21.9)	54.5 (22.4)	0.89
β -crosslaps (ng/mL)	0.24 (0.11)	0.36 (0.16)	0.01
P1NP (ng/mL)	27.2 (8.8)	37.1 (19.2)	0.08
Current smoking (n (%))	7 (23%)	3 (17%)	0.69
Glucocorticoid use (n (%))	8 (26%)	6 (35%)	0.49
RA (n (%))	0 (0%)	0 (0%)	1.00
Diabetes mellitus (n (%))	2 (6%)	1 (6%)	0.35

BMD measurements

BASELINE BMD MEASUREMENTS: At baseline, mean BMD at the lumbar spine was 1.05 ± 0.15 g/cm², mean T-score was -0.12 ± 1.32 , and mean Z-score was 0.99 ± 1.53 . Mean BMD at the total hip was 0.96 ± 0.16 g/cm², mean T-score was

-0.53 ± 2.29 , and mean Z-score was 1.06 ± 2.51 . Three patients (6%) had osteoporosis at baseline, and 13 patients had osteopenia (27%) at one or more measured sites.

LONGITUDINAL BMD MEASUREMENTS AFTER 31 MONTHS OF FOLLOW-UP IN PATIENTS WITH SUSTAINED REMISSION OF ACROMEGALY (N=15): Follow-up DXA (2010) was available in 15 patients (5 M, 10 F), who were in sustained remission for 18.1 (range 11-28) years after treatment. Ten patients (67%) had hypopituitarism with adequate hormone substitution; all females were postmenopausal. Nine and 7 patients received calcium and Vitamin D supplements, respectively.

In this subset, mean BMD did not change at the lumbar spine (1.00 ± 0.20 g/cm² at baseline and 1.00 ± 0.19 g/cm² at follow-up) or at the total hip (0.89 ± 0.19 g/cm² at baseline and 0.88 ± 0.17 g/cm² at follow-up) (Figure 1). Changes in BMD did not differ between men and women.

Evaluation of vertebral fractures at baseline and at follow-up

BASELINE EVALUATION OF VERTEBRAL FRACTURES (PREVALENT FRACTURES): As previously reported, VF prevalence was high at baseline (63%) (13). Mean number of VFs per patient was 2.3 ± 1.4 (range 1-6). VF prevalence was higher in men than in women (74% vs 44%, $p=0.039$). Most fractures were documented in the thoracic vertebrae Th12 (N=13), Th9 (N=10) and Th8 (N=9). The VF grade varied from mild (Grade 1: 93%) to moderate (Grade 2: 7%); no severe fractures (Grade 3) were observed. Figure 2a depicts the VF number at different vertebral levels, showing a typical bimodal pattern with peaks at Th9 and Th11-L1 in males. In females, fractures of vertebrae Th7 and Th8 were the most frequently observed. Figure 2b shows the VF severity distribution at different vertebral levels.

Eight patients (14%) sustained a non-vertebral fracture after establishment of biochemical control (prevalence in women vs men: 15% vs 13%), giving an incidence rate of 7.8 / 1000 person-years for non-vertebral fractures sustained after achieving remission. Most common fracture site was the hip (N=2).

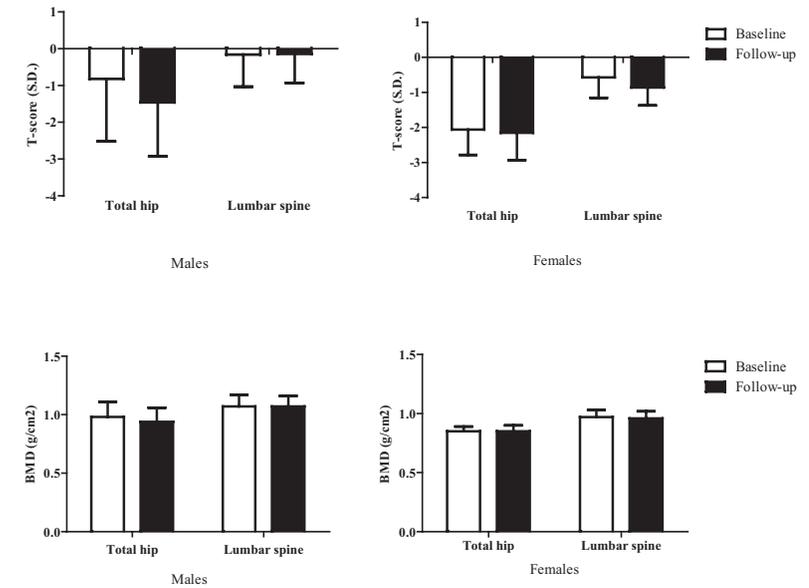


Figure 1. BMD and T-scores in 15 patients with long-term controlled acromegaly, stratified for sex, at baseline and after 31 months of follow-up (N=15)

Data are presented as mean \pm SD. Mean BMD and T-scores were presented for 15 acromegaly patients with available follow-up DXA. T-scores reflect the number of standard deviations (SD) above or below the mean for a healthy 30-year old adult of the same sex and ethnicity as the patient. No changes in mean BMD were observed at either the lumbar spine or total hip after a 2.5-year follow-up period.

BMD, bone mineral density; SD, standard deviation.

VERTEBRAL FRACTURE PROGRESSION AND/OR INCIDENT FRACTURES OVER 31 MONTHS OF FOLLOW-UP: VF progression was observed in 10 patients (20%) (29% in men and 5.6% in women), especially at vertebra Th7 (wedge fractures). Eight patients (16%), of whom 3 (6%) had no previous VFs, developed new fractures; one patient showed progression of already existing VFs, and one patient had new fractures in addition to demonstrating progression of preexisting VFs. After excluding the only hypogonadal man, VF progression was seen in 30% of eugonadal men. Excluding the two premenopausal women resulted in VF progression in 6.3% of postmenopausal women.

ANALYSIS OF POTENTIAL RISK FACTORS FOR PROGRESSION OF VERTEBRAL FRACTURES: Patients with ≥ 2 VFs at baseline had a 9.0-fold increase in risk of VF progression than patients with only one or no VFs at baseline ($p=0.005$) (Figure 3). Risk of progression tended to be higher in males than in females (OR=7.0 (0.8-60.4), $p=0.067$). Age, BMI, menopausal state, duration of active disease, or pre-treatment/current IGF-1 SDS were not related to VF progression. VF progression rate did not differ between different types of treatment for acromegaly and no effect of Vitamin D status was found.

As assessed in the subset of 15 patients with available follow-up DXA, baseline BMD, current BMD or BMD changes at either the lumbar spine or total hip did not differ between patients with and without VF progression, adjusted for age, sex and BMI.

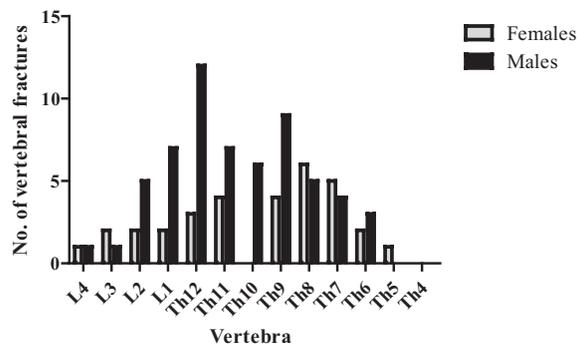


Figure 2A. Distribution of prevalent VFs at different vertebral levels at baseline, for male and female patients with long-term controlled acromegaly

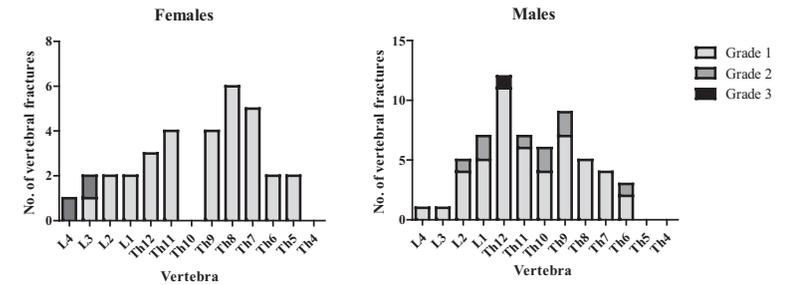


Figure 2B. Severity distribution of VFs at baseline, for male and female patients with long-term controlled acromegaly

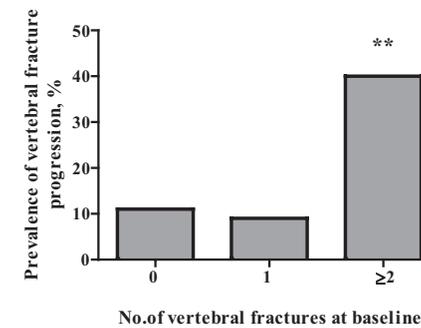


Figure 3. VF progression over 31 months of follow-up according to number of baseline VFs in 49 long-term controlled acromegaly patients

Risk for VF progression in relation to number of baseline VFs is presented. Patients with at least 2 VFs at baseline had a 9.0-fold increased risk of VF progression compared to patients with no or one VF at baseline ($p=0.005$).

VF, vertebral fracture.

DISCUSSION

Data from this longitudinal study of VFs in patients with acromegaly demonstrate that VFs progress in 20% of patients with long-term biochemically controlled acromegaly during a mean follow-up period of 31 months. These findings suggest that VFs do not solely develop during the active phase of acromegaly, but continue to represent a problem after biochemical control or cure. We have previously shown that normal BMD is maintained during long-term follow-up of up to 17 years after cure. This, however, does not appear to protect against VF progression. Men and patients demonstrating two or more prevalent VFs appear to be more at risk for VF progression.

GH and IGF-1 are important anabolic hormones. Most of the effects of GH is mediated by systemic and/or local IGF-1, enhancing the differentiated function of osteoblasts and bone formation, although GH may also act directly on bone cells (1). On the other hand, IGF-1 also induces receptor activator of nuclear factor κ B ligand (RANK-L) synthesis and, as a consequence, osteoclastogenesis. In contrast to IGF-1, GH stimulates the production of osteoprotegerin, which competes with the RANK-L receptor, thereby impairing osteoclastogenesis (2). IGF-1 increases the number of remodeling sites, thereby increasing bone activity and diminishing bone strength.

In acromegaly, in which patients are exposed to pathologically high GH and IGF-1 levels for long periods, appropriate treatment by surgery, radiotherapy, medical therapy, or a combination of these treatment modalities considerably improves many of the comorbidities associated with this disorder (25). It is clear, however, that despite long-term biochemical control, a number of skeletal manifestations of acromegaly persist, possibly as a consequence of the severe albeit transient GH excess the skeleton has been originally exposed to. These skeletal complications are associated with increased morbidity and decreased quality of life (26;27). In this respect, a VF is one of the most invalidating (irreversible) complications of acromegaly, occurring in approximately 60% of treated patients (5;6;13;14). Highest VF prevalence has been reported in men, especially in the presence of hypogonadism (13).

Because most previous studies on VFs in acromegaly were of a cross-sectional design, it is difficult to retrospectively discriminate which VFs occurred during the active acromegaly state and which VFs were sustained after disease remission (17). To date, it is still not known whether GH/IGF-1 control reduces this fracture risk. The 20% VF progression rate in adequately controlled acromegaly

patients demonstrated in the present study suggests that risk factors for VFs still prevail after achievement of biochemical control. In keeping with earlier studies, progression was greatest in men and in patients with two or more prevalent VFs at baseline (28;29). Our data were consistent with a recent study of Mazziotti *et al.* longitudinally investigating VF progression in a cohort of both active and controlled acromegalics (30). In that particular study, in which control was achieved by medical therapy in the majority, a VF progression rate of 25% over 3 years was observed in their subset of patients with controlled acromegaly.

The high VF prevalence observed in acromegalic patients was interestingly associated with a normal BMD (13), suggesting that BMD is a poor predictor of fracture risk in acromegaly, as is also the case in other forms of secondary osteoporosis (3;4;31). These data also suggest that bone quality may be altered in these patients, potentially irreversibly (32). A note of caution, however, is that BMD at the lumbar spine may be overestimated due to the high prevalence of degenerative changes in acromegaly, induced by prolonged exposure to GH excess (18). Imaging modalities to assess bone quality such as microindentation may allow a better evaluation of fracture risk than DXA in these patients (32;33).

Several comorbidities of acromegaly have been independently associated with fracture risk itself. For example, diabetes mellitus, both type 1 and type 2, is associated with an increased fracture risk, which was reported to be due to increased bone resorption resulting in bone loss and low bone turnover (34). (35). However, in the present study of controlled acromegaly, the number of patients with diabetes was very small. Also hypogonadism is an important factor. However, in the present study, we were not able to analyze the VF progression rate in hypogonadal men nor to explore whether hypogonadism is a risk factor for progression, being limited by the fact that only one man was hypogonadal. However, as described in our previous study, hypogonadal men had the highest VF prevalence of 86% when compared to eugonadal women (19%) and hypogonadal women (49%) (13). These former data strongly suggest that in acromegalic patients in long-term biochemical remission, hypogonadism is also associated with an increased VF risk.

Studies investigating VF progression in general population over 2 to 3 years are scarce; most studies had longer follow-up. Several studies, especially randomized controlled trials of bisphosphonates studying fracture risk in postmenopausal women, reported a VF progression rate of 5-7% over 4 to 5 years of follow-up in the control arm without bisphosphonate use (36-38). Although study designs are not fully comparable, the VF progression rate in acromegaly patients in remission is suggested to be much higher than in the general population. This study has a number of strengths and limitations. Of the study's strengths are the relatively large number of acromegaly patients studies with well-documented follow-up, data including follow-up radiographs, VF scoring by two independent experienced observers with low intra- and interobserver variability, and the adequate supplementation of pituitary hormone deficiencies, which may have otherwise potentially increased fracture risk. We also excluded patients using bisphosphonate treatment to avoid confounding effects of this antiresorptive medication on fracture risk, although by doing so, we also excluded the patients with the worst risk for further fractures. The main limitation of this study may be the inclusion of Grade 1 fractures in our analysis. Although the predictive value of Genant grade 1 fractures for future fractures remains debatable, the prognostic impact of these fractures for future fractures in acromegaly patients is not known. Patients with these mild-grade fractures were therefore included in the final analysis of data from this study.

In conclusion, we demonstrated that VFs progress in 20% of patients with long-term biochemically controlled acromegaly in the absence of osteoporosis or osteopenia. These data suggest persisting poor bone quality possibly related to long-term exposure to high circulating GH levels, although this also remains to be established. Based on our findings and the morbidity and mortality attached to VFs, we recommend the inclusion of VF assessment in the follow-up evaluation of acromegaly patients, also after establishment of biochemical remission, to allow timely therapeutic intervention to prevent further fractures. Future studies are needed to address the pathophysiological basis of the changes in bone quality leading to the high VF risk in long-term controlled acromegaly.

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