# Acromegaly : irreversible clinical consequences

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Chapter 8.

# HIGH PREVALENCE OF VERTEBRAL FRACTURES DESPITE NORMAL BONE MINERAL DENSITY IN PATIENTS WITH LOING-TERM CONTROLLED ACROMEGALY.

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## ABSTRACT

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

**Design:** We conducted a case-control study

**Patients and measurements:** Eighty-nine patients (46% male, mean age: 58 years) were included. We studied vertebral and non-vertebral fractures, 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 vertebral fracture prevalence, data from a sample of the Dutch population (n=3469) was used.

**Results:** Vertebral fracture prevalence was 59% (men 64%, 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 vertebral fractures 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 vertebral fractures in acromegaly patients with long-term controlled disease, independently of BMD. In view of the significant morbidity and mortality associated with vertebral fractures in general and the inability of BMD to predict fracture risk in acromegalic patients, we propose to include vertebral fracture 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.

# INTRODUCTION

Growth hormone (GH) and insulin-like growth factor I (IGF-I) 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 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 bone mineral density (BMD) appear to be less consistent. In active acromegaly, high circulating concentrations of GH and IGF-I are associated with increased cortical BMD[6-10]. The reported effects of GH/IGF-I 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.* suggested that risk for non-vertebral fractures 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 [14]. In contrast, Bonadonna *et al*. found that in post-menopausal women with active acromegaly, the risk for vertebral fractures was high even in the presence of normal BMD, but that vertebral fractures were always associated with low BMD in controlled disease[15]. The same group also demonstrated an increase in vertebral fracture 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 vertebral and non-vertebral fractures 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.

## PATIENTS AND 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]. 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%) were included. 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/IGF-I, 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 transsphenoidal 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 in 2003 of Pegvisomant 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 IGF-I concentrations, by oral glucose tolerance tests (except in medically treated patients), and by evaluation of other pituitary functions. The Medical Ethics Committee approved the study protocol and informed consent was obtained from all patients.

### Study parameters

#### *Disease activity*

Activity of acromegaly was evaluated by measuring fasting serum GH and IGF-I concentrations, and by an oral glucose tolerance test. Control of acromegaly was defined by random fasting serum GH levels below 1.9 μg/L (~5 mU/L), normal IGF-I levels for age, and by normal glucose suppressed serum GH below 0.38 μg/L (~1 mU/L)[17]. Duration of disease control was based on time since normalization of IGF-I. 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 IGF-I concentration after treatment by transsphenoidal surgery, radiotherapy, and/or medical therapy.

### *Assessment of pituitary and gonadal function*

For evaluation of pituitary function thyroid stimulating hormone (TSH) deficiency was defined as a free thyroxine (fT4) level below the normal laboratory reference range (absolute value <10 pmol/L). Adrenocorticotropic hormone (ACTH) deficiency was defined as an inappropriate increase in cortisol levels (absolute value <0.55 umol/L) after stimulation by corticotrophin releasing hormone, or insulin tolerance test.

The history of each individual patient was carefully reviewed with respect to their gonadal function from the time of diagnosis to the present evaluation[18-19]. Patients with adequately treated hypogonadism throughout follow-up, which was defined as gonadal hormone replacement therapy (HRT) started within one year after the onset of hypogonadism, 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 suppleted within one year after onset of hypogonadism were considered eugonadal. Male patients with a total testosterone concentration below 8 nmol/L, present for > 1 yr 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 oestradiol concentration of less than 70 nmol/L (and low LH/ FSH in postmenopausal women) or natural menopause, were considered hypogonadal.

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

### *Biochemical assays*

Serum GH was measured with a sensitive immunofluorometric assay (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 0.03 mU/L; interassay coefficient of variation (CV) 2.0-9.0% of 0.25-40 mU/L) from 1992 onwards, and previously with the radioimmunoassay (RIA) assay (Biolab/Serono, Coinsins, Switzerland) calibrated

against WHO-IRP 66/21, with an interassay CV below 5% and a detection limit of 0.5 mU/L.

Until 2005, serum IGF-I concentrations were determined by a RIA (Incstar; Stillwater, MN, USA) with a detection limit of 1.5 nmol/L and an inter-assay CV below 11%. IGF-I is expressed as standard deviation scores (SD) for age- and gender-related normal levels determined in the same laboratory[20]. From 2005 onwards serum IGF-I concentration (ng/ml) was measured using an immunometric 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. IGF-I levels were expressed as SD score, using lambda-mu-sigma (LMS) smoothed reference curves based on measurements in 906 healthy individuals[21-22].

The markers of bone-turnover, beta-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, Almere, The Netherlands). Vitamin D25OH was measured by RIA (Incstar/DiaSorin, Stillwater, MN, USA).





*Bone mineral density (BMD) measurements*

Bone mineral density 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.

World Health Organization (WHO) criteria were used to define osteopenia (T-score between -1.0 and -2.5) and osteoporosis (T-score of $\leq$-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 (HK), as well as by two of the other authors (MW/NB), using the semi quantitative method proposed by Genant *et al.* for assessment of vertebral deformities and fractures examining vertebrae T4-L5[23]. 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-vertebral fractures sustained after inappropriate trauma was evaluated by a structured self-reported questionnaire.

To enable comparison of the vertebral fracture 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 1997-1999, 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 centre visit and who were still able to come to our research centre. All follow-up radiographs were scored for the presence of vertebral fracture as described earlier[25].

## Statistics

SPSS for windows version 16.0 (SPSS inc., Chicago, IL, USA) was used for data analysis. Data are presented as mean (SEM), unless otherwise stated. BMD, T- and Z-scores of the lumbar spine at baseline and follow-up in patients with and without vertebral fractures, were analyzed by analysis of covariance with adjustments for age, gender, and BMI. Delta was calculated by: (follow-up value-baseline value) / baseline value. The prevalence of vertebral fractures in acromegaly was compared with a Dutch epidemiological control cohort by binary logistic regression analysis. Controls were the reference category. Factors potentially affecting vertebral fracture 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 vertebral fractures 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 *(Table 1)*

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). The mean estimated duration of active disease prior to remission was 8.9 ± 7.3 years (range 1 to 45 yrs). All patients had controlled disease for a mean of 14 years (range 2 to 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, 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 8 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 (4 were pre-menopausal with normal gonadal function and 1 had adequate gonadal steroid replacement therapy for hypogonadism), whereas 38 women were post-menopausal. The mean duration of hypogonadism was comparable in males and females. All, but two patients were vitamin D replete as evidenced by $25(OH)_2$ D levels >75 nmol/L. Eight patients received calcium and vitamin D supplements and 3 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 were currently 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 and IGF-I SD-scores at diagnosis or at study evaluation, and the prevalence of pituitary hormone deficiencies, including luteinizing hormone (LH)/ follicle stimulating hormone (FSH) deficiency between both genders.

**Table 1.** Demographic and Clinical characteristics of acromegalic patients, grouped according to gender.

| | Males N=46 | Females N=43 | P-value |
|---|---|---|---|
| **Age (yrs)** | 55.9 (10.7) | 60.8 (11.9) | 0.04 |
| **BMI (kg/m²)** | 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 (yrs)** | 8.1 (5.1) | 9.7 (9.1) | 0.81 |
| **Duration of disease control (yrs)** | 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 |
| **IGF-I SD scores** | | | |
| Pre-treatment | 7.9 (4.7) | 6.7 (4.7) | 0.28 |
| Current | 0.6 (1.6) | 0.5 (1.9) | 0.75 |
| **Vitamine D 25 (OH) (nmol/L)** | 79.6 (4.6) | 79.9 (3.8) | 0.82 |
| **Beta-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 |

Data are shown as mean (SD), unless mentioned otherwise. A p-value <0.05 was considered significant. Yr: years, kg/m²: kilograms per square meter, µg/L: micrograms per liter, SD: standard deviation, SMS: somatostatin analog, BMI: body mass index, IGF-I:insulin like growth factor, CI: confidence interval.

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 beta-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 ± 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 ± 0.10. BMD. T- and Z-scores of the lumbar spine did not differ between patients with and without vertebral fractures, 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.

**Table 2.** BMD, T- and Z-scores of the lumbar spine at baseline and follow-up in patients with and without vertebral fractures (VF).

| | Vertebral fractures (VF) | | Difference (95% -CI) | P-value |
|---|---|---|---|---|
| | No VF | VF | | |
| | n=15 (34%) | 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 shown as mean (SEM) unless mentioned otherwise. BMD was measured in (g/cm²). Data were analyzed by analysis of covariance with adjustments for age, gender, and BMI. Delta was calculated by: (follow-up value-baseline value) / baseline value. CI: confidence interval, n: number, BMD: bone mineral density, BMI: body mass index.

## Vertebral and non-vertebral fractures

### *Prevalence of vertebral fractures*

The prevalence of vertebral fractures 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 vertebral fractures with more men than women with one or more documented vertebral fracture (56 *vs.* 44%; p=0.02). Hypogonadal men had a significantly higher prevalence of vertebral fractures (86%) than eugonadal (19%) or hypogonadal (49%) women (p<0.05) (*Figure 1*).

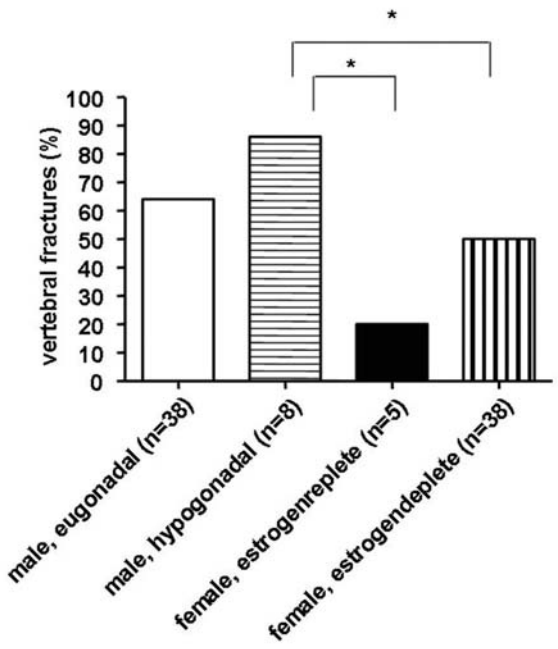


**Figure 1.** Prevalence of vertebral fractures in male and female cured acromegalic patients, grouped according to gonadal status. *p <0.05. Data were analyzed by binary logistic regression analysis with adjustments for age, gender, and BMI.

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 vertebral fractures 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 vertebral fractures varied from mild (69%) to intermediate (20%) to severe (11%).

Patients demonstrated significantly more vertebral fractures than controls in all age groups. Odds ratio's varied from 6.5 (95% CI 3.4-12.4) in patients 61-65 year 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-vertebral fractures during 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%).

**Table 3.** prevalence of vertebral fractures by age category in acromegaly patients compared with a Dutch epidemiological control cohort

| Age | Subjects | | Vertebral fracture cases | | | | |
|---|---|---|---|---|---|---|---|
| | Acromegaly | Controls | Acromegaly | Controls | Odds | 95% CI | P-value |
| | n=89 | n=3469 | N (%) | N (%) | ratio | | |
| <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 | <0.01 |
| 66-70 | 15 | 796 | 10 (67 %) | 72 (9 %) | 4.4 | 2.4-8.2 | <0.01 |
| 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 |

Data were analyzed by binary logistic regression analysis. Controls were the reference category. Age in years.

## Changes in BMD in patients with sustained disease 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 3 patients for up to 4.5 years but they had discontinued these drugs for at least 2 years before evaluation, and 3 patients were still receiving these agents for a mean of 7 years. These 6 patients were excluded from analysis of sequential changes in BMD.





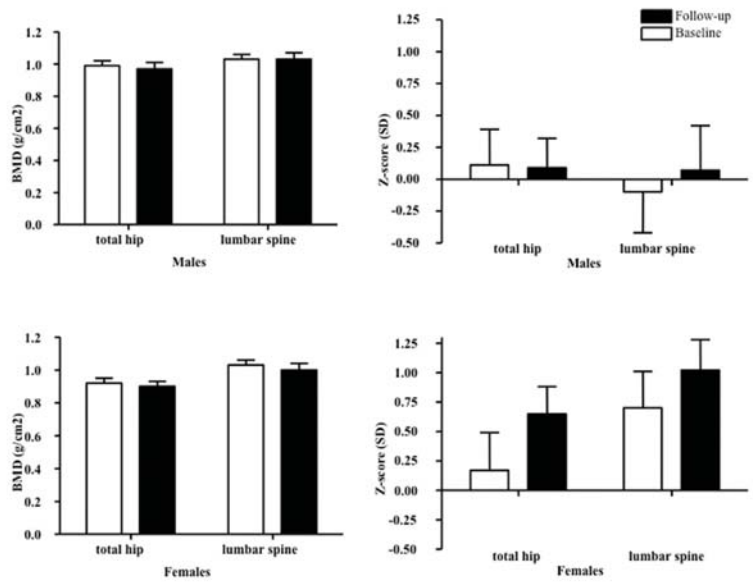


**Figure 2.** BMD and Z-scores in male and female cured acromegalic patients at baseline and follow-up. (n=42). In order to eliminate the effect of age and gender we used Z-scores in addition to BMD.

At baseline, mean BMD was 1.02 ± 0.03 g/cm$^2$ at the lumbar spine and 0.96 ± 0.03 g/cm$^2$ 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/cm$^2$ at the lumbar spine and 0.83 ± 0.02 g/cm$^2$ at the total hip. 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 (*Figure 2*).

**Table 4.** Factors potentially affecting vertebral fracture (VF) risk in acromegaly patients with long-term disease control.

| | Vertebral fractures (VF) | | |
|---|---|---|---|
| | **No VF n=37** | **VF n=52** | **P-value** |
| **Gender (n(%))** | | | 0.02 |
| Males | 17 (46 %) | 29 (56 %) | |
| Females | 20 (54 %) | 23 (44 %) | |
| **Age (yrs)** | 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 (yrs)** | 41.2 (2.2) | 40.3 (2.1) | 0.96 |
| **Disease duration (yrs)** | 8.7 (1.0) | 8.9 (1.3) | 0.52 |
| **Duration since diagnosis (yrs)** | 16.9 (1.5) | 20.1 (1.4) | 0.85 |
| **Duration of remission (yrs)** | 12.5 (1.0) | 15.2 (1.0) | 0.07 |
| **Pre-treatment fasting GH (ug/l)** | 36.4 (7.6) | 37.0 (7.3) | 0.77 |
| **Pre-treatment IGF-I SD scores** | 7.8 (0.9) | 6.7 (0.8) | 0.11 |
| **Hypogonadism (n(%))** | 18 (47 %) | 27 (52 %) | 0.85 |
| **P1NP (ng/ml)** | 38.3 (4.0) | 37.2 (3.2) | 0.66 |
| **Beta-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 |

Data are depicted as mean (SEM), unless mentioned otherwise. Data were analyzed by binairy logistic regression analysis, with adjustments for age, gender, BMI, parameters of disease activity, and hypopituitarism, when appropriate. SEM: standard error of the mean, n: number, yrs: years, kg: kilogram, m: meter, cm: centimeter, GH: growth hormone, IGF-I: insulin-like growth factor type I, SD: standard deviation, P1NP: procollagen type 1 amino-terminal propeptide, BMD: bone mineral density.

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 vertebral fractures (*Table 2*). Changes in BMD from baseline were not affected by gender, current GH and IGF-I 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).

### Analysis of potential risk factors for increased vertebral fracture risk

Gender represented a significant risk factor for vertebral fractures, with men being significantly more at risk. There was no significant relationship between the prevalence of vertebral fractures and age, BMI, age at diagnosis, duration of active disease, pre-treatment or controlled levels of GH / IGF-I, type of treatment, duration of controlled disease, the presence of hypopituitarism, markers of bone turnover, treatment with bisphosphonates, and for current or delta BMD in patients with and without vertebral fractures (*Table 4*).





## DISCUSSION

This study indicates a high prevalence of vertebral fractures in acromegalic patients with sustained controlled disease for a mean of 14 years. Approximately 60% of these patients had suffered at least one vertebral fracture. The prevalence of these vertebral fractures was considerably increased when compared with a large Dutch cohort of the general population[25]. These fractures in acromegaly patients occurred independently of age, severity or duration of disease activity, type of treatment, presence of hypopituitarism, or BMD, and despite normal vitamin 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] (see *Figure 3* for an image of the fractures)

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 par-

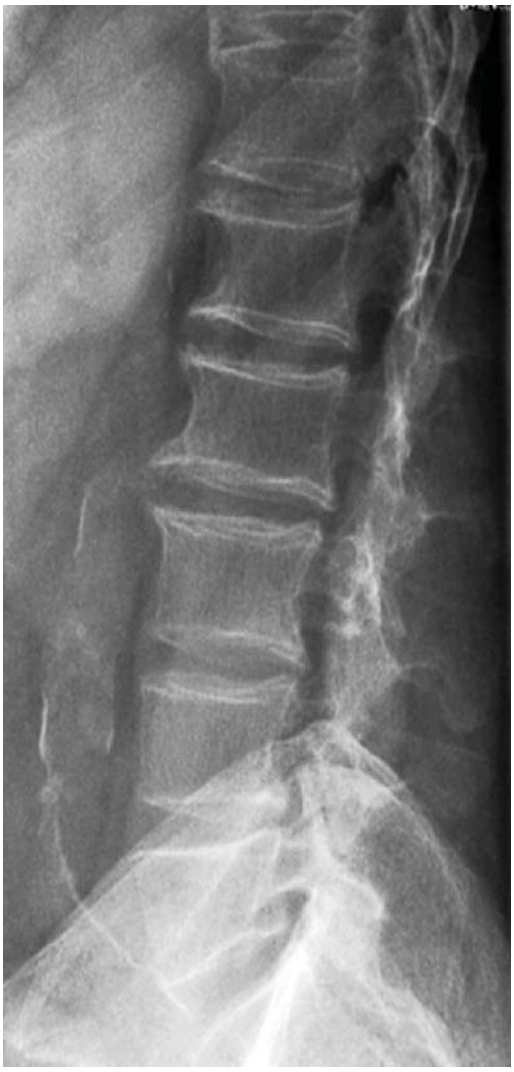

**Figure 3.** This radiograph of the lumbar spine shows grade 1 and 2 morphometric vertebral deformities, some endsplate sclerosis, and osteophytosis. Apparent in this radiograph is the calcification of the aorta. These changes in a patient 18.5 years after control of disease activity illustrate how the irreversible, structural modifications of the spine caused by GH excess during the active period of acromegaly, may lead to an overestimation of lumbar spine BMD. Note the relatively wide intervertebral discs and mild posterior scalloping of the vertebral bodies, compatible with the underlying disorder.

ticularly 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 in improved bone quality[27].

Control data on vertebral fractures were derived from a large Dutch epidemiological study, that did not include subjects younger than 55, since the occurrence of vertebral fractures is very unlikely in that age group[25]. The prevalence of vertebral fractures 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 vertebral

fractures 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 vertebral fractures in acromegalic women, but even more so in acromegalic men, exceeds the reported prevalence of vertebral fractures 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 vertebral fractures in 36 post-menopausal females and 40 male patients with controlled (~60%) or active acromegaly[15-16]. Those studies reported a comparable high prevalence of vertebral fractures of 53% in females, and 57% in male patients. 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 vertebral fractures in acromegaly with controlled disease for more than 14 years. Second, all our patients were vitamin D replete and received hormonal substitution, when applicable. Logistic regression analysis demonstrated that, after correction for all potentially influencing factors, hypogonadism, particularly in men, was associated with vertebral fracture risk. Unfortunately, it was not possible to determine when the vertebral fractures 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 vertebral fractures are associated with decreased quality of life, increased morbidity and mortality, and increased risk of new (non)vertebral fractures[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 age.

GH and IGF-I are important anabolic hormones for bone. In fact, most of the effects of GH are mediated by systemic and/or local IGF-I, 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 IGF-I excess, such as 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 vertebral fractures 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 vertebral fractures, 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 vertebral fractures 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 vertebral fractures, 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.

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