Progression of vertebral fractures in long-term controlled acromegaly: a 9-year follow-up study

Pelsma, I.C.M.; Biermasz, N.R.; Pereira, A.M.; Furth, W.R. van; Appelman-Dijkstra, N.M.; Kloppenburg, M.; ... ; Claessen, K.M.J.A.

Progression of vertebral fractures in long-term controlled acromegaly: a 9-year follow-up study

I C M Pelsma[1], **N R Biermasz**[1], **A M Pereira**[1], **W R van Furth**[2], **N M Appelman-Dijkstra**[1], **M Kloppenburg**[3,4], **H M Kroon**[5] and **K M J A Claessen**[1]

[1]Department of Medicine, Division of Endocrinology, and Center for Endocrine Tumors Leiden, Leiden University Medical Center, Leiden, the Netherlands, [2]Department of Neurosurgery, and Center for Endocrine Tumors Leiden, Leiden University Medical Center, Leiden, the Netherlands, [3]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands, [4]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands, and [5]Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands

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

Abstract

Objective: Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) excess results in both reversible and irreversible musculoskeletal damage, including increased vertebral fracture (VF) risk. The prevalence of VFs is approximately 60% in controlled acromegaly patients, and these VFs can progress in time. We aimed to identify the course of VFs in a cohort of acromegaly patients in long-term remission and their associated risk factors during prolonged follow-up.

Methods: Thirty-one patients with acromegaly (49% female, median age 60 years (IQR 53–66)), who were in remission for ≥2 years, were included in this longitudinal, prospective, follow-up study. Spine radiographs of vertebrae Th4 to L4 were assessed for VFs using the Genant score, at baseline, after 2.6 years and 9.1 years. Progression was defined as either a new fracture or a ≥1-point increase in Genant score.

Results: The prevalence of VF at baseline was 87% (27/31 patients). Progression of VFs was observed in eleven patients (35.5%) during the 9.1-year follow-up period, with a total incidence rate of 65.5 per 1000 person years (males 59.8 per 1000 person years vs females 71.6 per 1000 person years). Patients treated with surgery or radiotherapy had a higher risk of VF progression in this cohort ($P = 0.030$).

Conclusions: In this cohort of long-term, well-controlled acromegalic patients, the prevalence and progression of VFs was high, showing that the deleterious effects of GH and IGF-1 excess on bone persist despite achievement of longstanding remission.

European Journal of Endocrinology
(2020) **183**, 427–437

Introduction

Acromegaly is a rare, chronic, and progressive endocrine disorder caused by a growth hormone (GH)-producing pituitary adenoma, resulting in elevated serum GH and insulin-like growth factor-1 (IGF-1) levels (1), which requires a multimodal, individualized treatment approach. Current treatment options are neurosurgery, radiotherapy, and medical therapy with somatostatin (SMS) analogues, cabergoline, or pegvisomant (PegV) (2, 3). Acromegaly patients suffer from many GH-induced systemic comorbidities, of which musculoskeletal complications are one of the most invalidating manifestations significantly impacting quality of life (QoL) (4, 5). While reversal of GH excess ameliorates most symptoms and mortality risk, the skeletal complications, for example, vertebral fractures (VF) and arthropathy, persist or even progress (6).

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-20-0415

Published by Bioscientifica Ltd.

Longstanding exposure to supraphysiologic GH and IGF-1 levels increase bone turnover in favor of bone formation, leading to normal or high-normal bone mineral density (BMD) in most patients (7). However, notwithstanding the 'reassuring' BMD data, vertebral resistance is significantly impaired in acromegaly patients. In acromegaly patients, the altered bone microarchitecture, resulting in cortical bone thickening and loss of trabecular volume, contributes to the increased fracture risk (8, 9, 10). These alterations persist after biochemical remission (8). The increased skeletal fragility is reflected by a high VF prevalence, up to 60%, both after long-term disease control and irrespective of BMD levels (7). Risk factors for VFs are male sex, active disease duration and untreated hypogonadism (11, 12, 13, 14).

Multiple small longitudinal studies have shown that, despite adequate biochemical control, VFs progress in 20–25% of treated acromegaly patients over a follow-up period of approximately 3 years, predominantly in males and patients with pre-existing VFs (15, 16). Furthermore, new VFs were described in 35% of medically treated patients during a follow-up period of 6.8 years (17).

In this long-term, follow-up study, we aimed to evaluate the course of VFs during a prolonged follow-up period of 9 years in a cohort of long-term, well-controlled acromegaly patients, focusing on the identification of risk factors for VF progression.

Subjects and methods

Study design

A graphic overview of the study design is shown in Fig. 1. This prospective cohort study was approved by the Medical Ethics Committee of LUMC and all participants gave written informed consent. This manuscript is written adhering to STROBE guidelines (18).

Patients

All acromegaly patients with ≥2 years of biochemical remission, visiting the outpatient clinic of the Leiden University Medical Center (LUMC), were invited to participate in a cross-sectional study in 2007, resulting in the inclusion of 89 patients for the baseline visit (11, 19, 20, 21, 22, 23, 24). Details on the regular follow-up and different treatment modalities of acromegaly in our center were described in more detail elsewhere (11, 15). All these patients were invited for a follow-up study visit in 2010 after a mean interval of 2.6 years (range 2.3–2.9 years), of whom 58 patients (65%) agreed to participate (15, 25, 26, 27, 28). All these 58 patients were invited for a second follow-up study visit in 2017 after a median total follow-up duration of 9.1 years (range 8.8–10.6 years), of whom 31 patients (53%) responded positively. Patients declined participation due to non–musculoskeletal-related health problems ($n=4$), lack of time ($n=2$), loss to follow-up ($n=9$), psychological reasons ($n=1$), being abroad ($n=1$), or for unknown reasons ($n=10$). Age, BMD and VF number at baseline did not differ between participants and non-participants, except for higher BMI among non-participants ($P=0.013$).

General parameters

At all three study visits, patients completed a standardized questionnaire providing data on demographics, medical history, and clinical risk factors for VFs, such as early menopause, previous fractures, and glucocorticoid use.

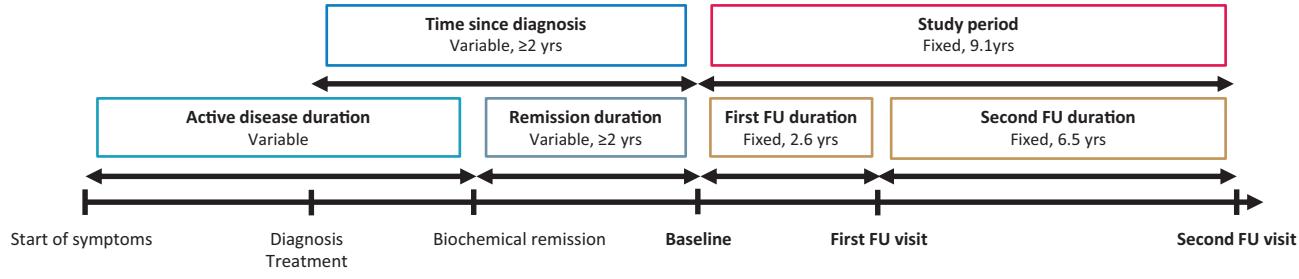

Figure 1

Overview of the study design. A schematic overview of study, including study parameters disease duration, remission duration and time since diagnosis, is depicted. FU, follow-up.

Acromegaly disease parameters

At least annual assessment of fasting serum GH and IGF-1 levels was performed in all patients to assess disease activity status. In non-medically treated patients, periodical oral glucose tolerance tests were performed to evaluate remission at the discretion of the treating physician. In PegV treated patients, GH was not evaluable. Disease remission was defined as normal IGF-1 levels for age (based on SD scores (SDS)) and normal glucose-suppressed GH levels. Biochemical disease control was defined as normal age-adjusted IGF-1 levels during medical treatment. Both patients cured by surgery or radiotherapy and those biochemically controlled using medication were considered to be in remission as previously described. Duration of active acromegaly was calculated using the estimated date of disease onset and the date of IGF-1 normalization following treatment (11, 15). Remission duration was calculated from the date of biochemical remission to the date of the second follow-up visit.

Assessment of pituitary and gonadal function

Hypopituitarism was defined as clinically significant hormone deficiencies of ≥1 pituitary axis requiring replacement therapy according to the following definitions (29, 30): TSH deficiency was defined as a free T4 level below <10 pmol/L. ACTH deficiency was defined as an insufficient increase in cortisol levels (<0.55 μmol/L) after stimulation by CRH or insulin tolerance test. GH deficiency (GHD) was assessed following clinical or biochemical suspicion. Male patients with a testosterone concentration <8.0 nmol/L for >1 year were considered hypogonadal. Female patients with prolonged untreated amenorrhea in the presence of a serum estradiol concentration <70 nmol/L or natural menopause were considered hypogonadal. Patients with adequately treated hypogonadism with replacement therapy <1 year after the onset of hypogonadism were considered eugonadal. Females with normal spontaneous menstrual cycles and patients using estrogen replacement therapy were also considered eugonadal.

Assays

For GH, a RIA assay (Biolab, Serona) was used before 1992, followed by a sensitive 22-kDa GH protein immunofluorometric assay (Wallac) from 1992–2005 (15). Starting in 2005, GH was measured using a nationally harmonized GH assay on the Immulite 2500/2000XPi immunoanalyser until November 3, 2017 (harmonization factor: 1.02) (31). Currently the IDS-iSYS analyser is used, including harmonization. Serum IGF-1 levels were determined by RIA (Incstar) (detection limit of 1.5 nmol/L and an inter-assay CV <11%) prior to 2005. Following 2005, serum IGF-1 concentrations were measured using immunometrics (Immulite 2500 system, Diagnostic Products Corporation). The intra-assay variations at mean plasma levels of 8 and 75 nmol/L were 5.0% and 7.5%, respectively. Since 2017, IGF-1 is measured on IDS-iSYS immunoanalyser. SD scores were used to evaluate IGF-1 levels, using λ-μ-σ smoothed reference curves for age- and sex-related normal levels based on measurements in 906 healthy individuals (32, 33).

Calcium and bone metabolism

Serum β-crosslaps (ng/mL, reference ranges depending on sex and age) and procollagen type 1 amino-terminal propeptide (P1NP) (ng/mL, reference ranges depending on sex and gonadal status) were determined using an electrochemoluminescent immunoassay (Modular Analytics E-170 system, Roche Diagnostics). Albumin-binding-adjusted serum calcium levels (reference range 2.15–2.55 nmol/L) were assessed using a semiautomated technique. 25-Hydroxyvitamin D was measured by RIA (Incstar/DiaSorin). Vitamin D deficiency was defined as serum levels <50 nmol/L (34). Dual energy X-ray absorptiometry (DXA) scans were not routinely performed during the study visits. Since guidelines for the treatment of bone health in acromegaly are lacking, for the management of osteoporosis in acromegaly patients, antiresorptive agents, either with or without vitamin D ± calcium supplementation, were given based on the expert opinion of the treating physician guided by the Dutch national guidelines (35).

Radiographic VF assessment

Plain lateral radiographs of the thoracic and lumbar spine, with the film centralized on Th7 and L3, respectively, were made by the same experienced radiology technician at all study visits following a standardized protocol. Vertebrae Th4 to L4 were assessed for the presence of VFs according to the validated Genant's semiquantitative method (36). The Genant Grades were defined as the following percentage reduction of the anterior, middle, and/or posterior height: grade 1 (mild fracture) 20–25%; grade 2

(moderate fracture) 25–40%; and grade 3 (severe fracture) >40%. Wedge, biconcave and concave fractures were distinguished. Spinal deformity index (SDI), a measure for VF severity, was calculated as the sum of the grades of all vertebrae and could vary from 0, that is, no VFs, to 39, that is, all VFs grade 3 (36, 37).

To facilitate the assessment of risk factors for VF progression, radiographs were evaluated in chronological order, blinded for patient characteristics (38). Radiographs were assessed simultaneously by a team of two experienced observers (H M K and K M J A C) in consensus, one of whom is a musculoskeletal radiologist (H M K). For five random patients, radiographs were scored twice to calculate intra-observer variability (intra-class coefficient (ICC) 0.919 (95%CI 0.895–0.938)). Two individual vertebrae were excluded because of pre-existing pathology. Progression of VFs was defined as the development of a new fracture or ≥1-point increase in the Genant Grade of a pre-existing VF.

Statistical analysis

Data analysis was performed using SPSS for Windows version 25.0 (SPSS Inc). The reliability analysis (ICC) was calculated using a two-way mixed model for single measurements. Data are presented as mean ± SD., median (interquartile range (IQR)) or *n* (%), unless otherwise specified. Changes over time were analyzed by parametric *t*-tests or repeated measures ANOVA or non-parametric Mann–Whitney *U*-test or Friedman tests when applicable. To assess risk factors, either χ^2 tests, Fishers exact tests, or binary logistic regression analyses, adjusting for age, sex, BMI, were performed in patients with and without VF progression. $P < 0.05$ was considered significant.

Results

Patient characteristics

Thirty-one patients were included (49% female; median age 60 years (IQR 53–66)), of whom baseline characteristics are depicted in Table 1. At baseline, 18 patients (58.1%) were in remission following surgery, of whom three patients received additional radiotherapy. The remaining 13 patients (41.9%) were treated with SMS analogues, either following surgery ($n=11$), radiotherapy ($n=1$) or a combination of both ($n=1$). During the study period, SMS analogues were discontinued in two patients, whereas SMS analogues were initiated in one patient following surgical treatment for recurrent disease. No patients received PegV.

Three male patients (18.8%) had substantial hypogonadal periods during follow-up (1, 3, and 6 years, respectively), followed by adequate testosterone replacement. During follow-up, one male patient developed hypogonadism, which lasted for 5 years prior to being adequately replaced. Eleven female patients (73.3%) were postmenopausal at baseline and four additional females (26.7%) went into menopause during follow-up, of whom one patient at the age of 42 years. All patients with diagnosed GHD prior to and during the study were adequately replaced.

Bone status

All patients had normal bone marker levels at baseline, except for one patient with slightly elevated β-crosslaps

Table 1 Clinical baseline characteristics of long-term remission acromegaly patients. Data are shown as median (IQR) or *n* (%).

Clinical characteristics	All patients (*n*=31)
Sex (female)	15 (48.4%)
Age (years)	60 (53–66)
BMI (kg/m^2)*	26.0 (23.5–31.2)
Baseline treatment status	
Without SMS analogue	19 (61.3%)
With SMS analogue	12 (38.7%)
Treatment	
Surgery	15 (48.4%)
SMS analogues	0 (0.0%)
Surgery + RT	3 (9.7%)
Surgery + SMS analogues	11 (35.5%)
RT + SMS analogues	1 (3.2%)
Surgery + RT + SMS	1 (3.2%)
Hypopituitarism	
Corticotrophs	5 (16.1%)
Thyreotrophs	5 (16.1%)
ADH deficiency	1 (3.2%)
GH deficiency	5 (16.1%)
Gonadotrophs	14 (45.2%)
Hypogonadism (male)	3 (18.8%)
Postmenopausal (female)	11 (73.3%)
Growth hormone (mU/L)	
Pre-treatment**	70 (26–133)
Baseline	1.38 (0.58–3.55)
IGF-1 (nmol/L)	
Pre-treatment***	53.0 (42.8–70.5)
SDS***	5.5 (4.1–6.7)
Baseline	18.4 (14.7–24.4)
SDS	1.1 (−0.2–1.9)
Disease duration (years)	5 (3–10)
Remission duration (years)	12 (7–17)

*Data available in 30 patients; **data available in 27 patients; ***data available in 24 patients.
IGF-1, insulin like growth factor-1; *n*, number of patients; RT, radiotherapy, SDS, standard deviation score; SMS, somatostatin analogues.

levels and one patient with increased P1NP levels (Table 2). Five patients (10.3%; three males/two females) had vitamin D deficiency at baseline, for which they received supplementation during follow-up. At the second follow-up visit, seven patients (22.6%; four males/three females) were receiving oral vitamin D supplementation. At baseline, two patients used anti-resorptive drugs, of whom one patient was treated prior to entering the study. During the study follow-up, four patients were treated with anti-resorptives. None of the patients were receiving anti-resorptive treatment at the second follow-up study visit.

Non-vertebral fractures

During the entire study period, only one male patient suffered from a traumatic clavicula fracture, as subjectively reported in the standardized questionnaire.

VFs at baseline

At baseline, 27 patients (87.1%) had ≥1 VF with a total of 79 recorded VFs. As shown in Fig. 2, a bimodal pattern of VF distribution, that is, two distinct peaks in VF number based on the vertebral location, was observed. Vertebrae Th8, Th9, Th11 and Th12 were fractured most frequently. At lumbar level, 14 grade-1 fractures and one grade-2 fracture were observed. At thoracic level, however, moderate and severe fractures were observed more frequently (namely, 53 grade-1 fractures, 6 grade-2 fractures and 2 grade-3 fractures).

Median number of VFs per patient was 2 (IQR 1–4) (males 2.5 (IQR 1–4) vs females 1 in (IQR 1–4), NS). Number of VFs at baseline was associated with active disease duration ($r=0.462$, $P=0.009$), but not with remission duration ($r=0.311$, $P=0.089$). Number of VFs at baseline was not associated with age, pre-treatment or baseline GH, or IGF-1 levels, and baseline markers of bone turnover.

VF progression

During 9.1 years of follow-up, VF progression occurred in 11 patients (35.5%; 7 females/4 males). In all patients, progression was defined as a new fracture. Two patients developed new grade-2 fractures, whereas the remaining nine patients developed new grade-1 fractures. Most progression was seen at vertebrae Th5 and Th8 (three new fractures). The number of VFs per patient increased significantly in time (median 2 (IQR 1–4) at baseline vs median 3 (IQR 1–5) at the second follow-up visit, $P=0.003$). Furthermore, SDI increased during follow-up (median 2 (IQR 1–4) at baseline vs median 3 (IQR 1–5), $P < 0.0001$). During a total follow-up of 290.1 years, 19 new VFs occurred, resulting in an overall incidence rate of 65.5 VFs per 1000 person years (males 59.8 per 1000 person years vs females 71.6 per 1000 person years, respectively).

VF progression during the first follow-up period was seen in three patients (two males/one female), all having one pre-existing VF at baseline. During the second follow-up duration, VF progression was observed in eight patients (two males/six females), with the number of baseline VFs ranging from 0 to 6. Therefore, VF progression appeared to occur more frequently between baseline and the first follow-up visit, with an incidence rate of 86.9 per 1000 person years (males 145.5 per 1000 person years vs females 25.4 per 1000 person years, respectively), compared to the period between the first and second follow-up visit having an incidence rate of 57.7 per 1000 person years (males 27.5 per 1000 person years vs females 89.7 per 1000 person years, respectively).

In Fig. 3A and C, respectively, the number of baseline VFs in relationship to the time since diagnosis,and age at baseline is depicted for progressive and non-progressive patients. Moreover, the course of VF progression in relationship to the time since diagnosis and age is shown for the progressive patients (Fig. 3B and D, respectively).

Table 2 Bone markers of long term remission acromegaly patients at baseline. Data are shown as median (IQR).

Bone markers	Total population $n=31$	Male $n=16$	Female $n=15$	*P*-value
Calcium (nmol/L)	2.34 (2.28–2.45)	2.41 (2.29–2.48)	2.32 (2.27–2.45)	0.232
Vitamin D (nmol/L)	73 (59–91)	71 (57–86)	74 (59–94)	0.74
β-crosslaps (ng/mL)*	0.35 (0.23–0.57)	0.32 (0.23–0.39)	0.43 (0.22–0.66)	0.377
P1NP (ng/mL)**	34 (27–43)	33 (23–42)	34 (30–43)	0.305

Bone markers at baseline were depicted for the total population ($n=31$) and for male ($n=16$) and female patients ($n=15$) separately.
*Data available for 29 patients, data missing for one male and one female patient; **data available for 30 patients, data missing for one male patient.
n, number of patients.

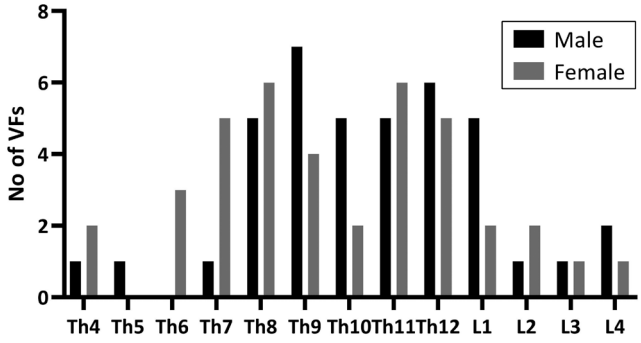

Figure 2

Bimodal pattern of distribution of VFs at baseline in male and female patients. At baseline, the number of VFs were assessed at thoracic vertebrae Th4 to Th12 and at lumbar vertebrae L1 to L4. VF counts are depicted for male (black bars) and female patients (grey bars) separately. L, lumbar vertebrae; Th, thoracic vertebrae; VF, vertebral fracture.

Risk factors for VF progression

As shown in Table 3, patients cured after surgery with or without adjuvant radiotherapy had a higher risk of VF progression than patients on current medical treatment ($P=0.030$). VF progression was not related to pre-treatment IGF-1 levels, active disease or remission duration, hypogonadism, and SDI at baseline.

Discussion

This prospective longitudinal cohort study is the first to study the spontaneous course of VFs in patients with acromegaly after long-term disease control, and it demonstrates VF progression in 35% of patients during a 9-year follow-up period. Strikingly, this progression occurred more frequently in the subset of patients without (current) medical therapy.

Baseline VF prevalence was 87.1% with a clear association between VF number and active disease duration, although the exact timing of VF occurrence prior to the start of the study, including an active and remission phases, remains unknown. VF rates in patients with active disease are speculated to be even higher. Previous studies have shown VF progression in 20–25% of treated acromegaly patients during a 3-year follow-up period (15, 16). Our VF incidence rate of 35% during 9.1 years of prolonged follow-up in remission seems to be significantly higher than the general population, particularly in males. In the Rotterdam Study, a representative sample of the Dutch population, VF incidence was 10.9 per 1000 person years (males 5.9 per 1000 person years and females 14.7 per 1000 person years, respectively) during 6.3 years of follow-up (39). In the subgroup of individuals between 55–65 years with

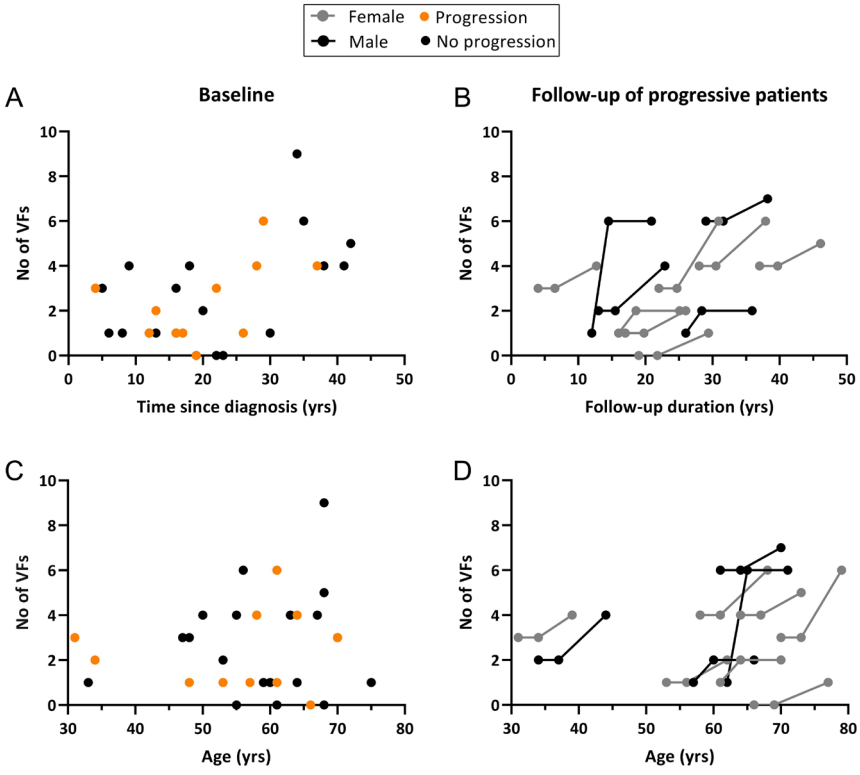

Figure 3

Course of VF progression in long-term remission acromegaly patients. (A and C) Number of VFs are depicted for all patients compared to their respective time since diagnosis (A) or age (C) at baseline. Patients with progression during the study period are depicted in orange, whereas patients without VF progression during the study period are depicted in black. (B and D) For progressive patients, number of VFs are depicted compared to their respective time since diagnosis (B) and age (D) at baseline (first dot), first follow-up (second dot) and second follow-up study visit (third dot). Male patients are depicted in black, and female patients are depicted in grey. Because of the small sample size of the study population, no statistical analyses were performed. VF, vertebral fracture.

Table 3 Risk factors for VF progression in patients with acromegaly in long-term remission. Data are shown as median (IQR) or as *n* (%). Potential risk factors for progression are depicted for patients with VF progression ($n = 11$) and patients without progression ($n = 20$). Binary logistic regression analyses in patients with and without progression were performed. All analyses were corrected for age, sex, and BMI.

Parameters	Progression $n = 11$	No progression $n = 20$	OR (95% CI)	*P*-value
Age, years	58 (48–68)	60 (54–68)	NA	NA
Sex (female)	7 (63.6%)	8 (40.0%)	NA	NA
BMI	24.8 (23.5–28.9)	28.1 (23.5–31.2)	NA	NA
Treatment with surgery or RT	10 (90.9%)	9 (45.0%)	20.66 (1.34–318.98)	0.030
Active disease duration at baseline (years)	5 (3–10)	6 (3–13)	0.97 (0.83–1.1)	0.633
Remission duration at baseline (years)	13 (11–17)	11 (5–17)	1.08 (0.93–1.26)	0.299
Pre-treatment IGF-1 (nmol/L)	48.5 (40.3–60.5)	56.5 (44.3–76.5)	0.96 (0.91–1.02)	0.146
Hypogonadism at baseline	7 (63.6%)	7 (35.0%)	4.20 (0.26–67.27)	0.311
SDI at baseline	2 (1–4)	3 (1–5)	0.95 (0.67–1.34)	0.753

IGF-1, insulin-like growth-factor 1; OR, odds ratio; RT, radiotherapy; SDI, Spinal Deformity Index; NA, not applicable.

pre-existing VFs, VF incidence was much lower than in acromegalics (males 7.2 per 1000 person years males vs females 6.9 per 1000 person years). In individuals between 65–75 years of age, the VF incidence numbers in the general population rise dramatically, although solely in males, VF incidence in the general population remains lower than in acromegalic patients (males 6.9 per 1000 person years vs females 83.7 per 1000 person years, respectively). Therefore, male acromegaly patients appear to have the highest VF risk, especially when compared to the general population.

Remarkably, medically treated patients were less likely to manifest VF progression than patients without SMS analogues. Therefore, medically treated patients show an interesting difference between an increased risk of arthropathy progression and a decreased risk of VF progression (26, 28). Disease status in acromegaly patients is usually divided into active disease and biochemical remission. We propose adding a third category: patients with controlled smoldering disease. After non-curative treatment, many patients maintain slightly elevated GH levels and (near-)normal IGF-1 levels, which might be supraphysiologic for individuals. Since GH is secreted in a pulsatile manner, and GH and IGF-1 are secreted following an ultradian and circadian rhythm, and act locally, these patients with smoldering disease might not classify as uncontrolled based on current definitions of remission (40). This potential slight elevation of GH and IGF-1 might have protective effects on bone. Furthermore, SMS analogues and PegV have been shown to have pleiotropic and, therefore, potential protective effects on bone, which might explain the observed lower fracture rates in the medically treated patients of our cohort (41, 42). Additionally, acromegalic patients under treatment with pasireotide showed lower risk of incident VFs compared to patients treated with PegV (17). Moreover, overtreatment by surgery or irradiation resulting in consequential mild GHD might contribute to the higher fracture risk in non-medically treated patients, because of the diminished bone quality in these patients (5, 43, 44).

Duration of disease, pre-treatment IGF-1 levels and SDI, reflective of the severity of VFs (45), could not be detected as risk factors for VF progression, probably due to insufficient power in a relatively small patient population and the variability of IGF-1 exposure during follow-up (15, 16, 17). Sex differences, however, appear to play an important role in VF incidence, although the mechanisms remain unclear (5, 46, 47). Androgens and estrogens might mediate the effects of both IGF-1 and adiposity on bone quality (48). Moreover, sex-dependent effects of IGF binding proteins (IGFBPs) might play a role in fracture susceptibility. IGFBP2 and IGFBP4, specifically, have been proposed as mediators for the effects of IGF-1 on bone (47). Rodent studies have shown that both IGFBP2 and IGFBP4 knock-out mice have an sex-dependent altered bone microenvironment, with male mice being affected by knocking out either IGFBP2 or IGFBP4, whereas female mice were unaffected by knocking out IGFBP2 and demonstrated opposite effects of knocking out IGFBP4 (49, 50, 51, 52, 53). These sex-dependent effects are in line with the observation that male patients were more severely affected.

BMD in acromegalic patients has been notoriously unreliable, since DXA does not take the structural changes due to GH excess into account (5, 47, 54). Exposure to increased GH/IGF-1 levels decreases the quality of trabecular microarchitecture, whereas cortical proliferation increases (8, 9, 10). Since DXA cannot

differentiate between trabecular and cortical bone, BMD measures are normal or even high in acromegaly patients (7). Additionally, bone enlargement and degenerative joint disease might lead to an overestimation of BMD (55, 56, 57). Therefore, structural, regular VF assessment using plain radiographs is performed in our center, based on patient risk profiles.

New imaging modalities have been proposed for the assessment of the skeletal status of acromegalic patients based on other forms of secondary osteoporosis (58, 59, 60, 61). In patients with acromegaly, CT studies confirmed the presence of an impaired microarchitecture, during both active and controlled disease (9, 62, 63), and its relationship to VFs (62). Valuable, non-invasive alternatives for bone quality assessment could be 3D-SHAPER and the trabecular bone score, with lower radiation exposure rates (64, 65, 66). Micro-indentation is a promising method to investigate bone material strength (67), previously showing lower bone material strength in treated acromegaly patients (68). Micro-indentation has been incorporated in clinical practice in our center.

To date, treatment of fragility fractures in acromegaly patients is unknown. One effective measure for decreasing fracture risk is restoration of eugonadism and amelioration of GH or IGF-1 excess (46). Trials assessing the efficacy of antiresorptive treatment in acromegaly are lacking, but in other forms of high-bone-turnover-osteoporosis, antiresorptive treatment increased BMD scores significantly (46). Antiresorptive therapy has been postulated to be most effective during active acromegaly, when bone turnover is high. Future studies should focus on the effects of antiresorptive treatment, combined with the assessment of a clinically applicable measure of skeletal fragility, which should be incorporated into clinical practice.

The main limitation of this study is the limited number of patients resulting in insufficient power to detect risk factors for the occurrence and progression of VFs. Another limitation is the high baseline VF prevalence, probably as a result of selection bias, since patients with more complaints are possibly more likely to participate in follow-up studies, although subjective joint complaint scores were similar in participants and non-participants (data not shown). Furthermore, we included radiological grade-1 fractures in our analyses, of which the predictive role for future fractures in primary osteoporosis remains debatable, since the prognostic impact of these fractures in acromegaly remains unknown. Although the assessment of BMD has limitations in acromegaly (*vide supra*), one of the study's limitations is refraining from measuring BMD, since worsening of bone mass and persisting osteoporosis are established risk factors for VFs.

To our knowledge, this is the first prospective study on VF progression in well-controlled acromegaly patients with a follow-up duration of almost 10 years, showing a very high VF prevalence with even further progression in time, especially in patients not receiving medical therapy. The exact mechanisms by which GH and IGF-1 affect bone quality remain to be elucidated. Ideally, prospective studies with multiyear follow-up duration should be performed in larger cohorts to replicate our results. Moreover, future studies should assess whether timely intervention with antiresorptive drugs is beneficial in the prevention of fractures in this specific form of secondary osteoporosis.

Declaration of interest

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

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

1 Caron P, Brue T, Raverot G, Tabarin A, Cailleux A, Delemer B, Renoult PP, Houchard A, Elaraki F & Chanson P. Signs and symptoms of acromegaly at diagnosis: the physician's and the patient's perspectives in the ACRO-POLIS study. *Endocrine* 2019 **63** 120–129. (https://doi.org/10.1007/s12020-018-1764-4)

2 Biermasz NR, Romijn JA, Pereira AM & Roelfsema F. Current pharmacotherapy for acromegaly: a review. *Expert Opinion on Pharmacotherapy* 2005 **6** 2393–2405. (https://doi.org/10.1517/14656566.6.14.2393)

3 Giustina A, Chanson P, Kleinberg D, Bronstein MD, Clemmons DR, Klibanski A, van der Lely AJ, Strasburger CJ, Lamberts SW, Ho KK *et al*. Expert consensus document: a consensus on the medical treatment of acromegaly. *Nature Reviews: Endocrinology* 2014 **10** 243–248. (https://doi.org/10.1038/nrendo.2014.21)

4 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. (https://doi.org/10.1210/jc.2004-2297)

5 Claessen KM, Mazziotti G, Biermasz NR & Giustina A. Bone and joint disorders in acromegaly. *Neuroendocrinology* 2016 **103** 86–95. (https://doi.org/10.1159/000375450)

6 Colao A, Ferone D, Marzullo P & Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocrine Reviews* 2004 **25** 102–152. (https://doi.org/10.1210/er.2002-0022)

7 Mazziotti G, Biagioli E, Maffezzoni F, Spinello M, Serra V, Maroldi R, Floriani I & Giustina A. Bone turnover, bone mineral density, and fracture risk in acromegaly: a meta-analysis. *Journal of Clinical*

Endocrinology and Metabolism 2015 **100** 384–394. (https://doi.org/10.1210/jc.2014-2937)
8 Dalle Carbonare L, Micheletti V, Cosaro E, Valenti MT, Mottes M, Francia G & Davi MV. Bone histomorphometry in acromegaly patients with fragility vertebral fractures. *Pituitary* 2018 **21** 56–64. (https://doi.org/10.1007/s11102-017-0847-1)
9 Madeira M, Neto LV, de Paula Paranhos Neto F, Barbosa Lima IC, Carvalho de Mendonca LM, Gadelha MR & Fleiuss de Farias ML. Acromegaly has a negative influence on trabecular bone, but not on cortical bone, as assessed by high-resolution peripheral quantitative computed tomography. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 1734–1741. (https://doi.org/10.1210/jc.2012-4073)
10 Ueland T, Ebbesen EN, Thomsen JS, Mosekilde L, Brixen K, Flyvbjerg A & Bollerslev J. Decreased trabecular bone biomechanical competence, apparent density, IGF-II and IGFBP-5 content in acromegaly. *European Journal of Clinical Investigation* 2002 **32** 122–128. (https://doi.org/10.1046/j.1365-2362.2002.00944.x)
11 Wassenaar MJ, Biermasz NR, Hamdy NA, Zillikens MC, van Meurs JB, Rivadeneira F, Hofman A, Uitterlinden AG, Stokkel MP, Roelfsema F *et al*. High prevalence of vertebral fractures despite normal bone mineral density in patients with long-term controlled acromegaly. *European Journal of Endocrinology* 2011 **164** 475–483. (https://doi.org/10.1530/EJE-10-1005)
12 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. (https://doi.org/10.1210/jc.2008-0791)
13 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. (https://doi.org/10.1359/JBMR.050603)
14 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* 2009 **70** 378–382. (https://doi.org/10.1111/j.1365-2265.2008.03322.x)
15 Claessen KM, Kroon HM, Pereira AM, Appelman-Dijkstra NM, Verstegen MJ, Kloppenburg M, Hamdy NA & Biermasz NR. Progression of vertebral fractures despite long-term biochemical control of acromegaly: a prospective follow-up study. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 4808–4815. (https://doi.org/10.1210/jc.2013-2695)
16 Mazziotti G, Bianchi A, Porcelli T, Mormando M, Maffezzoni F, Cristiano A, Giampietro A, De Marinis L & Giustina A. Vertebral fractures in patients with acromegaly: a 3-year prospective study. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 3402–3410. (https://doi.org/10.1210/jc.2013-1460)
17 Chiloiro S, Mazziotti G, Giampietro A, Bianchi A, Frara S, Mormando M, Pontecorvi A, Giustina A & De Marinis L. Effects of pegvisomant and somatostatin receptor ligands on incidence of vertebral fractures in patients with acromegaly. *Pituitary* 2018 **21** 302–308. (https://doi.org/10.1007/s11102-018-0873-7)
18 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC & Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Annals of Internal Medicine* 2007 **147** 573–577. (https://doi.org/10.7326/0003-4819-147-8-200710160-00010)
19 Wassenaar MJ, Biermasz NR, Bijsterbosch J, Pereira AM, Meulenbelt I, Smit JW, Roelfsema F, Kroon HM, Romijn JA & Kloppenburg M. Arthropathy in long-term cured acromegaly is characterised by osteophytes without joint space narrowing: a comparison with generalised osteoarthritis. *Annals of the Rheumatic Diseases* 2011 **70** 320–325. (https://doi.org/10.1136/ard.2010.131698)
20 Wassenaar MJ, Biermasz NR, Kloppenburg M, van der Klaauw AA, Tiemensma J, Smit JW, Pereira AM, Roelfsema F, Kroon HM & Romijn JA. Clinical osteoarthritis predicts physical and psychological QoL in acromegaly patients. *Growth Hormone and IGF Research* 2010 **20** 226–233. (https://doi.org/10.1016/j.ghir.2010.02.003)
21 Wassenaar MJ, Biermasz NR, Pereira AM, van der Klaauw AA, Smit JW, Roelfsema F, van der Straaten T, Cazemier M, Hommes DW, Kroon HM *et al*. The exon-3 deleted growth hormone receptor polymorphism predisposes to long-term complications of acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 4671–4678. (https://doi.org/10.1210/jc.2009-1172)
22 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. (https://doi.org/10.1530/EJE-08-0845)
23 Wassenaar MJ, Cazemier M, Biermasz NR, Pereira AM, Roelfsema F, Smit JW, Hommes DW, Felt-Bersma RJ & Romijn JA. Acromegaly is associated with an increased prevalence of colonic diverticula: a case-control study. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 2073–2079. (https://doi.org/10.1210/jc.2009-1714)
24 Biermasz NR, van 't Klooster R, Wassenaar MJ, Malm SH, Claessen KM, Nelissen RG, Roelfsema F, Pereira AM, Kroon HM, Stoel BC *et al*. Automated image analysis of hand radiographs reveals widened joint spaces in patients with long-term control of acromegaly: relation to disease activity and symptoms. *European Journal of Endocrinology* 2012 **166** 407–413. (https://doi.org/10.1530/EJE-11-0795)
25 Claessen KMJA, Canete AN, de Bruin PW, Pereira AM, Kloppenburg M, Kroon HM & Biermasz NR. Acromegalic arthropathy in various stages of the disease: an MRI study. *European Journal of Endocrinology* 2017 **176** 779–790. (https://doi.org/10.1530/EJE-16-1073)
26 Claessen KM, Kloppenburg M, Kroon HM, Romijn JA, Pereira AM & Biermasz NR. Two phenotypes of arthropathy in long-term controlled acromegaly? A comparison between patients with and without joint space narrowing (JSN). *Growth Hormone and IGF Research* 2013 **23** 159–164. (https://doi.org/10.1016/j.ghir.2013.05.003)
27 Claessen KM, Ramautar SR, Pereira AM, Romijn JA, Kroon HM, Kloppenburg M & Biermasz NR. Increased clinical symptoms of acromegalic arthropathy in patients with long-term disease control: a prospective follow-up study. *Pituitary* 2014 **17** 44–52. (https://doi.org/10.1007/s11102-013-0464-6)
28 Claessen KM, Ramautar SR, Pereira AM, Smit JW, Roelfsema F, Romijn JA, Kroon HM, Kloppenburg M & Biermasz NR. Progression of acromegalic arthropathy despite long-term biochemical control: a prospective, radiological study. *European Journal of Endocrinology* 2012 **167** 235–244. (https://doi.org/10.1530/EJE-12-0147)
29 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. (https://doi.org/10.1210/jc.2003-032041)
30 Biermasz NR, van Dulken H & Roelfsema F. Ten-year follow-up results of transsphenoidal microsurgery in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 4596–4602. (https://doi.org/10.1210/jcem.85.12.7042)
31 Ross HA, Lentjes EW, Menheere PM, Sweep CG & Endocrinology Section and project group 'Calibration 2000' of the SKML (Dutch Foundation for Quality Assessment in Clinical Laboratories). Harmonization of growth hormone measurement results: the empirical approach. *Clinica Chimica Acta: International Journal of*

Clinical Chemistry 2014 **432** 72–76. (https://doi.org/10.1016/j.cca.2014.01.008)
32 Cole TJ. The LMS method for constructing normalized growth standards. *European Journal of Clinical Nutrition* 1990 **44** 45–60.
33 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. (https://doi.org/10.1159/000023268)
34 Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate? *Journal of Steroid Biochemistry and Molecular Biology* 2004 **89–90** 611–614. (https://doi.org/10.1016/j.jsbmb.2004.03.040)
35 CBO. Richtlijn Osteoporose en Fractuurpreventie, 2011. (available at: https://wwwvolksgezondheidenzorginfo/bestanden/documenten/cborichtlijn-osteoporose-en-fractuurpreventie-2011). Accessed on 12 June 2020.
36 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. (https://doi.org/10.1002/jbmr.5650080915)
37 Minne HW, Leidig G, Wuster C, Siromachkostov L, Baldauf G, Bickel R, Sauer P, Lojen M & Ziegler R. A newly developed spine deformity index (SDI) to quantitate vertebral crush fractures in patients with osteoporosis. *Bone and Mineral*. 1988 **3** 335–349.
38 van Der Heijde D, Boonen A, Boers M, Kostense P & van Der Linden S. Reading radiographs in chronological order, in pairs or as single films has important implications for the discriminative power of rheumatoid arthritis clinical trials. *Rheumatology* 1999 **38** 1213–1220. (https://doi.org/10.1093/rheumatology/38.12.1213)
39 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. (https://doi.org/10.1359/jbmr.2002.17.6.1051)
40 Steyn FJ & Ngo ST. Endocrine rhythms of growth hormone release: insights from animal studies. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2017 **31** 521–533. (https://doi.org/10.1016/j.beem.2017.10.009)
41 Giustina A, Mazziotti G, Torri V, Spinello M, Floriani I & Melmed S. Meta-analysis on the effects of octreotide on tumor mass in acromegaly. *PLoS ONE* 2012 **7** e36411. (https://doi.org/10.1371/journal.pone.0036411)
42 Maison P, Tropeano AI, Macquin-Mavier I, Giustina A & Chanson P. Impact of somatostatin analogs on the heart in acromegaly: a metaanalysis. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 1743–1747. (https://doi.org/10.1210/jc.2006-2547)
43 He X & Barkan AL. Growth hormone therapy in adults with growth hormone deficiency: a critical assessment of the literature. *Pituitary* 2020 **23** 294–306. (https://doi.org/10.1007/s11102-020-01031-5)
44 Jorgensen JOL & Juul A. THERAPY OF ENDOCRINE DISEASE: Growth hormone replacement therapy in adults: 30 years of personal clinical experience. *European Journal of Endocrinology* 2018 **179** R47–R56. (https://doi.org/10.1530/EJE-18-0306)
45 Kerkeni S, Kolta S, Fechtenbaum J & Roux C. Spinal deformity index (SDI) is a good predictor of incident vertebral fractures. *Osteoporosis International* 2009 **20** 1547–1552. (https://doi.org/10.1007/s00198-008-0832-7)
46 Mazziotti G, Frara S & Giustina A. Pituitary diseases and bone. *Endocrine Reviews* 2018 **39** 440–488. (https://doi.org/10.1210/er.2018-00005)
47 Mazziotti G, Lania AGA & Canalis E. MANAGEMENT OF ENDOCRINE DISEASE: Bone disorders associated with acromegaly: mechanisms and treatment. *European Journal of Endocrinology* 2019 **181** R45–R56. (https://doi.org/10.1530/EJE-19-0184)
48 Cauley JA. Estrogen and bone health in men and women. *Steroids* 2015 **99** 11–15. (https://doi.org/10.1016/j.steroids.2014.12.010)
49 Xi G, Rosen CJ & Clemmons DR. IGF-I and IGFBP-2 stimulate AMPK activation and autophagy, which are required for osteoblast differentiation. *Endocrinology* 2016 **157** 268–281. (https://doi.org/10.1210/en.2015-1690)
50 Zhang M, Faugere MC, Malluche H, Rosen CJ, Chernausek SD & Clemens TL. Paracrine overexpression of IGFBP-4 in osteoblasts of transgenic mice decreases bone turnover and causes global growth retardation. *Journal of Bone and Mineral Research* 2003 **18** 836–843. (https://doi.org/10.1359/jbmr.2003.18.5.836)
51 Maridas DE, DeMambro VE, Le PT, Nagano K, Baron R, Mohan S & Rosen CJ. IGFBP-4 regulates adult skeletal growth in a sex-specific manner. *Journal of Endocrinology* 2017 **233** 131–144. (https://doi.org/10.1530/JOE-16-0673)
52 Xi G, Wai C, DeMambro V, Rosen CJ & Clemmons DR. IGFBP-2 directly stimulates osteoblast differentiation. *Journal of Bone and Mineral Research* 2014 **29** 2427–2438. (https://doi.org/10.1002/jbmr.2282)
53 DeMambro VE, Le PT, Guntur AR, Maridas DE, Canalis E, Nagano K, Baron R, Clemmons DR & Rosen CJ. Igfbp2 deletion in ovariectomized mice enhances energy expenditure but accelerates bone loss. *Endocrinology* 2015 **156** 4129–4140. (https://doi.org/10.1210/en.2014-1452)
54 Mazziotti G, Maffezzoni F, Frara S & Giustina A. Acromegalic osteopathy. *Pituitary* 2017 **20** 63–69. (https://doi.org/10.1007/s11102-016-0758-6)
55 Melmed S, Casanueva FF, Klibanski A, Bronstein MD, Chanson P, Lamberts SW, Strasburger CJ, Wass JA & Giustina A. A consensus on the diagnosis and treatment of acromegaly complications. *Pituitary* 2013 **16** 294–302. (https://doi.org/10.1007/s11102-012-0420-x)
56 Romijn JA. Acromegalic arthropathy: current perspectives. *Endocrine* 2013 **43** 245–246. (https://doi.org/10.1007/s12020-012-9781-1)
57 Ueland T, Fougner SL, Godang K, Schreiner T & Bollerslev J. Serum GH and IGF-I are significant determinants of bone turnover but not bone mineral density in active acromegaly: a prospective study of more than 70 consecutive patients. *European Journal of Endocrinology* 2006 **155** 709–715. (https://doi.org/10.1530/eje.1.02285)
58 dos Santos CV, Vieira Neto L, Madeira M, Alves Coelho MC, de Mendonca LM, Fde P-N, Lima IC, Gadelha MR & Farias ML. Bone density and microarchitecture in endogenous hypercortisolism. *Clinical Endocrinology* 2015 **83** 468–474. (https://doi.org/10.1111/cen.12812)
59 de Waard EAC, de Jong JJA, Koster A, Savelberg HHCM, van Geel TA, Houben AJHM, Schram MT, Dagnelie PC, van der Kallen CJ, Sep SJS *et al.* The association between diabetes status, HbA1c, diabetes duration, microvascular disease, and bone quality of the distal radius and tibia as measured with high-resolution peripheral quantitative computed tomography-the Maastricht Study. *Osteoporosis International* 2018 **29** 2725–2738. (https://doi.org/10.1007/s00198-018-4678-3)
60 Cusano NE, Rubin MR, Silva BC, Tay YD, Williams JM, Agarwal S, Omeragic B, Guo XE & Bilezikian JP. Skeletal microstructure and estimated bone strength improve following parathyroidectomy in primary hyperparathyroidism. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 196–205. (https://doi.org/10.1210/jc.2017-01932)
61 Hansen S, Hauge EM, Rasmussen L, Jensen JE & Brixen K. Parathyroidectomy improves bone geometry and microarchitecture in female patients with primary hyperparathyroidism: a one-year prospective controlled study using high-resolution peripheral quantitative computed tomography. *Journal of Bone and Mineral Research* 2012 **27** 1150–1158. (https://doi.org/10.1002/jbmr.1540)
62 Maffezzoni F, Maddalo M, Frara S, Mezzone M, Zorza I, Baruffaldi F, Doglietto F, Mazziotti G, Maroldi R & Giustina A. High-resolution-cone beam tomography analysis of bone microarchitecture in patients with acromegaly and radiological vertebral fractures. *Endocrine* 2016 **54** 532–542. (https://doi.org/10.1007/s12020-016-1078-3)

63 Silva PPB, Amlashi FG, Yu EW, Pulaski-Liebert KJ, Gerweck AV, Fazeli PK, Lawson E, Nachtigall LB, Biller BMK, Miller KK *et al*. Bone microarchitecture and estimated bone strength in men with active acromegaly. *European Journal of Endocrinology* 2017 **177** 409–420. (https://doi.org/10.1530/EJE-17-0468)

64 Godang K, Olarescu NC, Bollerslev J & Heck A. Treatment of acromegaly increases BMD but reduces trabecular bone score: a longitudinal study. *European Journal of Endocrinology* 2016 **175** 155–164. (https://doi.org/10.1530/EJE-16-0340)

65 Hong AR, Kim JH, Kim SW, Kim SY & Shin CS. Trabecular bone score as a skeletal fragility index in acromegaly patients. *Osteoporosis International* 2016 **27** 1123–1129. (https://doi.org/10.1007/s00198-015-3344-2)

66 Kuzma M, Vanuga P, Sagova I, Pavai D, Jackuliak P, Killinger Z, Binkley NC, Winzenrieth R, Genant HK & Payer J. Non-invasive DXA-derived bone structure assessment of acromegaly patients: a cross-sectional study. *European Journal of Endocrinology* 2019 **180** 201–211. (https://doi.org/10.1530/EJE-18-0881)

67 Herrera S & Diez-Perez A. Clinical experience with microindentation in vivo in humans. *Bone* 2017 **95** 175–182. (https://doi.org/10.1016/j.bone.2016.11.003)

68 Malgo F, Hamdy NAT, Rabelink TJ, Kroon HM, Claessen KMJA, Pereira AM, Biermasz NR & Appelman-Dijkstra NM. Bone material strength index as measured by impact microindentation is altered in patients with acromegaly. *European Journal of Endocrinology* 2017 **176** 339–347. (https://doi.org/10.1530/EJE-16-0808)

Received 23 April 2020
Revised version received 6 July 2020
Accepted 20 July 2020