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Treatment of Acromegalic Osteopathy in Real-life Clinical Practice: The BAAC (Bone Active Drugs in Acromegaly) Study

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Abstract

Background

Vertebral fractures (VFs) are a frequent complication of acromegaly, but no studies have been so far published on effectiveness of antiosteoporotic drugs in this clinical setting.
Objective
To evaluate whether in real-life clinical practice bone active drugs may reduce the risk of VFs in patients with active or controlled acromegaly.

Study design

Retrospective, longitudinal study including 9 tertiary care endocrine units.

Patients and Methods

Two hundred and forty-eight patients with acromegaly (104 males; mean age 56.00 ± 13.60 years) were evaluated for prevalent and incident VFs by quantitative morphometric approach. Bone active agents were used in 52 patients (20.97%) and the median period of follow-up was 48 months (range 12-132).

Results

During the follow-up, 65 patients (26.21%) developed incident VFs in relationship with pre-existing VFs (odds ratio [OR] 3.75; $P < .001$), duration of active acromegaly (OR 1.01; $P = .04$), active acromegaly at the study entry (OR 2.48; $P = .007$), and treated hypoadrenalism (OR 2.50; $P = .005$). In the entire population, treatment with bone active drugs did not have a significant effect on incident VFs ($P = .82$). However, in a sensitive analysis restricted to patients with active acromegaly at study entry (111 cases), treatment with bone active drugs was associated with a lower risk of incident VFs (OR 0.11; $P = .004$), independently of prevalent VFs (OR 7.65; $P < .001$) and treated hypoadrenalism (OR 3.86; $P = .007$).

Conclusions

Bone active drugs may prevent VFs in patients with active acromegaly.

Skeletal fragility is an emerging complication of acromegaly, characterized by increased bone turnover, profound abnormalities in bone microstructure, and high risk of vertebral fractures (VFs) (1). VFs were reported in 30% to 40% of patients with acromegaly in close relationship with duration of exposure to growth hormone (GH) hypersecretion, hypogonadism, and pre-existing VFs (2). VFs may be a clinically relevant complication of acromegaly due to their potential impact on morbidity and quality of life (3). Acromegalic subjects with VFs may be predisposed to kyphosis, sagittal spine imbalance, and back pain (4, 5). However, the management of skeletal fragility in acromegaly is a clinical challenge since VFs may occur even in the presence of normal bone mineral density (BMD) (4, 6); the biochemical control of acromegaly does not always normalize the risk of fractures (7, 8), and some drugs used for treatment of acromegaly may produce effects on skeletal health independently of GH hypersecretion (9). Furthermore, different from the other forms of secondary osteoporosis in which bone active drugs can improve BMD and decrease the risk of fractures (1, 10), the effectiveness of antiosteoporotic therapies in acromegalic osteopathy has not yet been investigated (11).

In this retrospective, multicenter study reflecting real-life clinical practice, we aimed to evaluate for the first time whether treatment with bone active drugs may reduce the risk of VFs in patients with active and controlled acromegaly.

Materials and Methods

Subjects and protocol

The study included 248 patients with acromegaly (144 females, 104 males) attending 9 tertiary care endocrine units in the period between 2003 and 2019. The inclusion criteria were (1) diagnosis of acromegaly; (2) age older than 18 years; (3) availability of at least 2 spine X-rays; (3) full availability of data on diagnosis, treatment, and clinical outcome of acromegaly; (4) follow-up of at least 12 months. Exclusion criteria were (1) use of bone active drugs (except calcium and vitamin D) in the 12 months prior to study entry; (2) untreated primary hyperparathyroidism; (3) untreated hyperthyroidism; (4) neoplastic disease in progression; (5) surgical intervention of the spine; (6) clinical history of spine trauma. The primary endpoint of the study was the incidence of VFs during treatment with bone active drugs versus no treatment in patients with active or controlled acromegaly. As secondary endpoints, we explored the impact of prevalent VFs, hypopituitarism, and diabetes mellitus on risk of incident VFs.

Bone active drugs were prescribed in each endocrine unit according to the guidelines for treatment of primary osteoporosis and the Italian reimbursement criteria in force during the study period. Acromegaly was diagnosed by failure of suppression of serum GH concentrations below 1 ng/mL after a 75-g oral glucose load together with fasting plasma insulin-like growth factor (IGF)-I

concentrations above the normal ranges for age (12). Patients under somatostatin receptor ligands (SRLs) treatment were evaluated by measurement of serum random GH and IGF-I, those under pegvisomant were evaluated by serum IGF-I alone, whereas patients treated with neurosurgery alone were evaluated by GH after a 75-g oral glucose load and serum random GH and IGF-I (13). Acromegaly was defined as controlled if the IGF-I values were in the reference ranges for age and, in patients under SRLs and after neurosurgery, random GH was below 1.0 ng/mL. When the 75-g oral glucose load was performed, the GH values at or below 0.4 ng/mL were considered expression of cured disease (13). Patients with discordant GH and IGF-I values were considered controlled by therapy if IGF-I values were in the normal range for age (14). The biochemical evaluation of acromegaly was performed in each endocrine unit measuring GH and IGF-I by assays in use during the study period. Specifically, GH and IGF-I were measured by a chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics Products, UK) in 240 patients, whereas the remaining 8 patients were evaluated using radioimmunoassay (SM-C-RIA-CT, DIAsource ImmunoAssays, Belgium) and immunoradiometric assay (IRMA GH, Beckman Coulter, Czech Republic) for IGF-I and GH measurements, respectively. In all patients, the duration of active disease was estimated on the basis of clinical history, that is, when the patient recalled appearance of signs and symptoms of the disease, and duration of uncontrolled disease during medical treatment. During the study period, all patients were evaluated and managed for coexistent hypopituitarism (15). Glucocorticoid deficiency was defined by basal serum cortisol values lower than 3 µg/dL or by 1 µg corticotrophin-stimulated cortisol below 18 µg/dL. Hypothyroidism was defined by serum free thyroxine below the reference ranges. In men, hypogonadism was diagnosed by measuring morning total testosterone levels; in those patients in whom total testosterone concentrations were near the lower limit of the normal range, sex hormone-binding protein was measured for calculating the bioavailable testosterone (16). In women, hypogonadism was defined by irregular or absent menstrual cycles. Patients with diagnosis of hypogonadism under chronic replacement treatment with sex steroids were considered eugonadal. For the study purposes, untreated hypogonadism and postmenopausal status were considered together in the evaluation of determinants of VFs. The presence of diabetes mellitus was defined by fasting plasma glucose values ≥126 mg/dL or 2-hour plasma glucose values ≥200 mg/dL during 75-g oral glucose load (17). This latter test was performed in patients with fasting plasma glucose values below 126 mg/dL and before starting SRL treatment. For patients without history of diabetes undergoing treatment with SRLs, the diagnosis of diabetes was made only by the measurement of fasting glucose.

Assessment of VFs

VFs were detected on lateral spine X-rays using a qualitative evaluation of vertebral shape and quantitative morphometric assessment. Using a cursor, 6 points were marked on each vertebral body

to describe vertebral shape. Anterior (Ha), middle (Hm), and posterior (Hp) vertebral heights were measured and height ratios (Ha/Hp, Ha/Hm, Hm/Hp) were calculated for each vertebra from T4 to L4. Prevalent and incident VFs were assessed on the spine X-rays at baseline and follow-up, respectively. According to the quantitative morphometric method (18), the fractures were defined as mild, moderate, and severe on the basis of height ratio decreases of 20% to 25%, 25% to 40%, and more than 40% respectively. Spine deformity index (SDI) was calculated by summing the score of each vertebral fracture assigned on the basis of the grade of fracture (score 1, 2, or 3 for mild, moderate, and severe fractures, respectively) (19). Incident VFs were defined as new fractures (from no VF to any grade of VF) between baseline and the follow-up. Prevalent and incident VFs were assessed by one observer for each Endocrine Unit.

This multicenter retrospective observational study was approved by the local Ethics Committees (Mantova, Cremona and Lodi; Brescia; Casa Sollievo della Sofferenza, IRCCS, San Giovanni Rotondo; Humanitas Clinical and Research Center, IRCCS, Rozzano; Fondazione Policlinico Universitario "Agostino Gemelli," Rome; City of Health and Sciences University Hospital of Turin; Milano Area 2; Regionale, Regione Liguria); patients gave their consent to use clinical data for research purposes.

Statistical analysis

Data were described as number and percentage, or mean and standard deviation, as appropriate. Associations of variables with antiosteoporotic therapies were explored. Association with possible risk factors for VFs was explored with logistic regression analysis. All risk factors with $P < .25$ were then submitted to backward multivariable logistic regression analysis. $P < .05$ was considered to be significant. A sensitivity analysis of patients with or without active acromegaly at the study entry was also performed. All analyses were made using Stata15.

Results

The study included 248 patients with acromegaly, mean age 56.0 ± 13.6, 104 (41.94%) males. Table 1 shows the clinical data at study entry. Active acromegaly, hypoadrenalism, hypothyroidism, hypogonadism, and diabetes mellitus were found in 111 (44.80%), 79 (31.90%), 88 (35.50%), 92 (37.10%), and 80 (32.30%), respectively. At the study entry, 78 patients (31.50%) had VFs, which were either moderate/severe or multiple in 42 cases. In patients with prevalent VFs, the median SDI was 2 (range 1-16).

Outcome of acromegaly during the follow-up

Patients were followed up for a median period of 48 months (range 12-132). Among 137 patients with baseline cured/controlled acromegaly, 132 patients remained so for the entire study period (36 patients cured by neurosurgery alone, 65 treated with SRLs, 8 with pegvisomant, 2 with cabergoline, and 21 with combination therapies), whereas 5 patients (1 patient after neurosurgery, 1 under pegvisomant, and 3 under SRL therapy) showed active disease at the end of follow-up. Among 111 patients with active acromegaly at study entry, 77 patients had controlled disease at the end of follow-up (19 with neurosurgery alone, 39 with SRLs, 3 with pegvisomant, and 16 with combination therapies), whereas 34 patients remained with active disease notwithstanding the treatments. During the follow-up, all patients with hypothyroidism and hypoadrenalism were treated with l-thyroxine and cortisone acetate or hydrocortisone, respectively. Among patients with hypogonadism at study entry, 33 patients were treated with sex steroids during the follow-up, whereas 59 patients remained with untreated hypogonadism. Patients with diabetes mellitus were treated with several antidiabetic drugs (metformin, sulfonylurea, repaglinide, incretins, and insulin).

Skeletal outcome during the follow-up

Fifty-two patients (20.97%) started treatment with bone active agents (30 with oral alendronate 70 mg/week, 9 with oral risedronate 35 mg/week, 1 with intravenous zoledronate 5 mg /yearly, 3 with subcutaneous denosumab 60 mg every 6 months, 3 with subcutaneous teriparatide 20 µg/day, 2 with oral raloxifene 60 g/day, 1 with oral strontium ranelate 2 g/day, and 3 with sequential therapies). One hundred and ninety-two patients (77.40%) received vitamin D3 (in combination with calcium in 67 cases, alone in 125 cases). One patient (0.40%) was treated with calcium supplements without vitamin D. Doses of vitamin D3 ranged from 800 to 4000 units per day, and the daily doses of calcium were between 500 and 1200 mg.

Patients undergoing treatment with bone active drugs were significantly older (65.00 ± 10.50 years vs 53.60 ± 13.40 years; $P < .001$), more frequently received calcium supplements (50.00% vs 21.43%; $P < .001$), more frequently had VFs at the study entry (61.54% vs 23.47%; $P < .001$), had diabetes mellitus (46.15% vs 28.57%; $P = .016$), more frequently had with untreated hypogonadism or in the postmenopausal period (82.69% vs 57.65%; $P = .001$), and had lower prevalence of treated hypoadrenalism (19.23% vs 35.20%; $P = .026$) compared patients who were not treated with bone active agents; there were no significant differences in sex ($P = .229$), rate of active acromegaly at the study entry ($P = .476$), duration of active acromegaly ($P = .070$), duration of follow-up ($P = .104$), treated hypothyroidism ($P = .424$), and treatment with vitamin D3 ($P = .163$).

During the follow-up, 65 out of 248 patients (26.21%) developed new VFs. In these patients, the median SDI was 3 (range 1-18). Patients experiencing incident VFs more frequently had prevalent VFs, treated hypoadrenalism, active acromegaly, and longer duration of active disease than patients who did not fracture (Table 2). In the multivariate logistic regression analysis, incident VFs

maintained significant associations with prevalent VFs, duration of active acromegaly, active acromegaly at study entry, and treated hypoadrenalism (Table 3).

In the entire population, treatment with bone active drugs did not induce any significant effect on incident VFs (Table 3). However, when the analysis was restricted to patients with active acromegaly at study entry, treatment with bone active drugs was associated with lower incidence of VFs compared with untreated patients (14.29% vs 41.11%; P = .021) (Fig. 1). In this subgroup of patients, treatment with bone active drugs maintained a significant association with incident VFs (OR 0.11; 95% CI 0.02-0.50; P = .004) independently of prevalent VFs (odds ratio [OR] 7.65; 95% confidence interval [CI] 2.55-22.95; P < .001) and treated hypoadrenalism (OR 3.86; 95% CI 1.46-10.22; P = .007). When acromegaly was controlled at study entry, incident VFs occurred more frequently in treated versus untreated patients with bone active drugs (32.26% vs 14.15%; P = .022) (Fig. 1). The result did not change when the patient with controlled acromegaly treated with strontium ranelate was excluded from the analysis (data not shown). However, patients with controlled acromegaly receiving bone active drugs were significantly older (65.30 ± 13.30 years vs 56.50 ± 12.70 years; P < .001), more frequently had untreated hypogonadism or were in the postmenopausal period (83.87% vs 57.55%; P = .02), and more frequently showed prevalent VFs (58.06% vs 21.70%; P < .001) than patients who were not treated with bone active drugs. In the multivariate analysis performed in patients with controlled acromegaly, incident VFs were significantly associated with prevalent VFs (OR 3.14, 95% CI 1.23-8.04; P = .017), untreated hypogonadism or postmenopausal status (OR 4.00, 95% CI 1.19-13.45, P = .025), but not with antiosteoporotic drugs (OR 2.22; 95%CI 0.76-6.45; P = .145).

Discussion

In this retrospective study, antiosteoporotic therapies were found to be effective in decreasing the risk of VFs when acromegaly was active, independently of pre-existing VFs and duration of active disease. This effect was not observed in patients with controlled acromegaly, in whom incident VFs were correlated with pre-existing VFs and untreated hypogonadism.
Several studies have consistently demonstrated that patients with acromegaly develop skeletal fragility with a high risk of VFs (11). In this multicenter study, including for the first time a large population of acromegaly patients evaluated for skeletal health, incident VFs were reported in about one-quarter of patients after a median period of 4 years and, in agreement with previous observations provided by smaller longitudinal studies (7, 8, 20), the fractures developed mainly in patients with pre-existing fractures who had been exposed to a longer duration of active acromegaly. This latter finding is consistent with the concept that VFs are a direct consequence of GH hypersecretion which causes an increase in bone turnover, bone loss, and profound alterations in bone structure (1). The

close relationship between prevalent and incident VFs in our patients with active and controlled acromegaly is further proof that morphometric VFs are markers of skeletal fragility, similarly to patients with primary osteoporosis in whom a single VF increases more than 3 times the risk to develop further fractures (21). From this point of view, morphometric assessment of VFs even in the absence of specific symptoms and signs may be the cornerstone in the management of skeletal fragility in patients with acromegaly (22).

Consistently with previous reports of skeletal fragility in hypogonadal patients with acromegaly (23-25), our study showed that even in real-life clinical practice untreated hypogonadism may be a risk factor of VFs, specifically in patients with controlled/cured acromegaly. This finding suggests that a normal sex hormone milieu is likely required to guarantee the recovery of a normal skeletal strength after control of GH hypersecretion. The interplay among different neuroendocrine axes is crucial for maintaining skeletal health in physiology and pathophysiology.

An interesting finding of this study was the relationship between incident VFs and central hypoadrenalism. The association was statistically significant in patients with active acromegaly and was independent of pre-existing VFs. The reasons for this association were not clarified by our retrospective study, but it is reasonable to hypothesize that glucocorticoid replacement therapy may have played a role. There is evidence that in real-life clinical practice several patients with hypoadrenalism may be overtreated with possible alterations in several clinical endpoints (26). Higher doses of either cortisone acetate or hydrocortisone were shown to be associated with bone loss and higher risk of fractures (27-29). Besides the pathophysiological aspects, the results of this study provide a rationale for proactively and comprehensively evaluating skeletal health in patients with coexistent active acromegaly and hypoadrenalism.

A single clinical study reported an association between VFs and diabetes mellitus in male patients with controlled acromegaly (30). Such an association was not confirmed in this study, likely because of potential biases in the retrospective enrolment of the patients.

This study evaluated for the first time the effectiveness of antiosteoporotic drugs in patients with acromegaly. Notwithstanding the low awareness of acromegalic osteopathy in real-life clinical practice (31), bone active agents were used in 20% of patients with acromegaly evaluated for skeletal fragility. Most treated patients received drugs targeting osteoclastogenesis and bone resorption (ie, mainly bisphosphonates) that are expected to be beneficial for the skeleton by decreasing activation frequency, refilling remodeling space, and increasing mineralization. Using these drugs, the fracture risk significantly decreased only in patients with active acromegaly, whereas antiosteoporotic therapies were not shown to be effective when acromegaly was controlled. These results are consistent with the concept that increased bone resorption is the main mechanism of bone loss and skeletal fragility in patients exposed to GH hypersecretion (32, 33). However, the absent effectiveness of antiresorptive drugs in controlled acromegaly may reflect the hypothesis that in this setting impairment of osteoblastogenesis may be the predominant mechanism of altered bone

microarchitecture and high risk of fractures (24, 34-38). One could argue that antiresorptive drugs in patients with controlled acromegaly may prevent recovery of osteoblast function, based on the concept that osteoclasts are a source of bone formation-stimulating factors by which these cells may promote osteoblastogenesis and bone formation (39).

This study has limitations. Weaknesses of the study include the retrospective design and the variety of antiosteoporotic drugs used, mainly due to the multicenter nature of the study. The retrospective design and the variable duration of follow-up did not allow one to calculate the exact timing of VF development and to build survival curves. However, the duration of follow-up between fractured and nonfractured patients was comparable, suggesting that the risk of VFs might not be time dependent provided that acromegaly was controlled. This study reflected the management of acromegalic osteopathy in real-life clinical practice; the assignment of antiosteoporotic drugs was not randomized. Therefore, the distribution of antiresorptive and anabolic drugs in the treated patients did not allow testing the possible differences between these drugs in preventing VFs. Moreover, the lack of randomization may have contributed to the unexpected high incidence of VFs in patients with controlled acromegaly treated with bone active drugs. Antiosteoporotic drugs were given to patients with more severe osteoporosis (ie, those with pre-existing VFs) and in those with independent risk factors of fractures (eg, untreated hypogonadism or post menopause). Another limitation was related to the noncentralized assessment of VFs, which may have caused heterogeneous results among the different centers involved in the study. To minimize this potential bias, a single operator in each center performed the morphometric assessment of VFs and only new fractures (ie, from no VF to any grade of VF) were considered as incident fractures, excluding the progression of pre-existing VFs from the analyses (ie, from grade mild/moderate to moderate/severe fractures), which require more precision in vertebral height measurements. The lack of centralization in hormonal assays might cause pitfalls in defining active and controlled acromegaly across centers, although the use of a chemiluminescent immunometric assay in more than 96% of patients may have limited the heterogeneity of biochemical data.

In conclusion, this large study provided the first convincing evidence that drugs targeting osteoclastogenesis and bone resorption may be effective in preventing VFs in patients with active acromegaly.

Abbreviations

- **BMD** -bone mineral density
- **CI -** confidence interval
- **GH -** growth hormone
- **IGF -** insulin-like growth factor

- **SDI -** spine deformity index
- **SRL -** somatostatin receptor ligand
- **VF -** vertebral fracture
- **OR -** odds ratio

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Additional Information

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Table 1.

Demographical and clinical data of 248 patients with acromegaly at study entry

Variables	
Age (years)	56.0 ± 13.6
Sex (M/F)	104/144
Therapies for acromegaly	
Neurosurgery alone	58 (23.39)
SRLs	124 (50.00)
Pegvisomant	14 (5.65)
Cabergoline	2 (0.81)
Combination therapies	50 (20.16)
Active acromegaly	111 (44.80)
Duration of active disease (months)	48 (12-186)
Hypothyroidism	88 (35.50)
Hypoadrenalism	79 (31.90)
Hypogonadism	92 (37.10)
Postmenopausal status	97 (39.11)
Diabetes mellitus	80 (32.30)
Prevalent total VFs	78 (31.45)

Variables	
Prevalent multiple/moderate-severe VFs	42 (16.93)
Baseline SDI in fractured patients	2 (1-16)

Categorical data are presented as n/n or n (%), whereas continuous data are presented as either mean ± SD or median and ranges, according to the data distribution.

Abbreviations: F, female; M, male; SDI, spine deformity index; SRLs, somatostatin receptor ligands; VFs, vertebral fractures.

Table 2.

Clinical data of patients experiencing incident vertebral fractures (VFs) during the follow-up compared with those who did not fracture

	Incident VFs		
	Yes	**No**	*P*
N	65	183	
Age (years)	56.9 ± 13.9	55.7 ± 13.6	0.484
Sex (M/F)	33/32	71/112	0.093
Active acromegaly at the study entry	40 (61.54)	71 (38.80)	0.002

	Incident VFs		
	Yes	**No**	*P*
Active acromegaly at the follow-up	15 (23.08)	24 (13.11)	0.058
Duration of active acromegaly (months)	62 (12-186)	36 (12-180)	0.001
Treated hypoadrenalism	31 (47.69)	48 (26.23)	0.002
Treated hypothyroidism	21 (32.31)	67 (36.61)	0.533
Untreated hypogonadism + postmenopausal status	45 (69.23)	111 (60.66)	0.219
Diabetes mellitus	25 (38.46)	55 (30.05)	0.213
Prevalent VFs	34 (52.31)	44 (24.04)	<0.001
Use of bone active agents	13 (20.00)	39 (21.31)	0.823
Use of calcium supplements	16 (24.62)	52 (28.42)	0.555
Use of vitamin D3	52 (80.00)	140 (76.50)	0.562
Follow up (months)	48 (12-120)	48 (12-132)	0.922

Categorical data are presented as n/n or n (%) and were compared using the chi-square test.
Continuous data are presented as either mean ± SD or median and ranges, and the comparisons
were carried out using parametric and nonparametric tests, respectively.
Abbreviations: F, female; M, male; VF, vertebral fracture.

Table 3.

Results of univariate and multivariate logistic regression analyses assessing the determinants of incident vertebral fractures (VFs) in the entire population of 248 acromegalic patients

	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.01 (0.99-1.03)	.528		
Sex (M vs F)	1.63 (0.92-2.88)	.094		
Active acromegaly at the study entry	2.52 (1.41-4.51)	.002	2.48 (1.29-4.79)	.007
Duration of active acromegaly	1.01 (1.00-1.01)	.008	1.01 (1.00-1.01)	.042
Treated hypoadrenalism	2.55 (1.41-4.58)	.002	2.50 (1.31-4.77)	.005
Treated hypothyroidism	0.83 (0.45-1.51)	.534		
Untreated hypogonadism + postmenopausal status	1.46 (0.80-2.67)	.220		
Diabetes mellitus	1.45 (0.81-2.63)	.214		
Prevalent VFs	3.46 (1.91-6.27)	<.001	3.75 (1.97-7.14)	<.001

	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Bone active drugs	0.92 (0.46-1.86)	.823		
Calcium supplements	0.82 (0.43-1.57)	.556		
Vitamin D3	1.23 (0.61-2.47)	.563		

Abbreviations: CI, confidence interval; F, females; M, males; OR, odds ratio; VFs, vertebral fractures.

Figure 1.

Incidence of vertebral fractures in acromegaly patients stratified for activity of disease and treatment with bone active drugs.