

Clinical Research Article

# Spine Bone Texture Assessed by Trabecular Bone Score in Active and Controlled Acromegaly: A Prospective Study

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**Abbreviations:** 25OHD, vitamin D; ALP, alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; CT, computed tomography; CTX, carboxyterminal telopeptide; DXA, dual-energy x-ray absorptiometry; FN, femoral neck; GH, growth hormone; GHD, growth hormone deficiency; HR-CBCT, high-resolution-cone beam computed tomography; HRpQCT, high-resolution peripheral quantitative computed tomography; IGF-1, insulin-like growth factor 1; LS, lumbar spine; OGTT, oral glucose tolerance test; PTH, parathyroid hormone; SSA, somatostatin analogue; SQ, semiquantitative visual assessment; TBS, trabecular bone score; VFx, vertebral fractures.

Received: 10 December 2020; Editorial Decision: 6 May 2021; First Published Online: 15 May 2021; Corrected and Typeset: 28 June 2021.

## Abstract

**Context:** Acromegalic patients have an increased vertebral fracture (VFx) risk due to bone quality reduction, independently of bone mineral density (BMD).

**Objective:** The aim of the study is to describe bone quality in acromegaly, measured by trabecular bone score (TBS), a noninvasive index for assessing bone microarchitecture.

**Methods:** We collected data from 18 patients (13 female, age  $56.2 \pm 15$  years) newly diagnosed with acromegaly. Thirty-six age- and sex-matched healthy controls were also recruited. Pituitary function, bone and calcium-phosphorous metabolism, and BMD at spine and femur and TBS (by dual-energy x-ray absorptiometry) were assessed in acromegalic patients at diagnosis and 12 months after the achievement of insulin-like growth factor 1 (IGF-1) normalization.

**Results:** At diagnosis, BMD and the VFx prevalence were comparable between patients and controls ( $28.3 \pm 5.9$  vs  $27.6 \pm 3.7$  and 11% vs 8.3%), whereas TBS was

significantly lower in acromegalic patients ( $1.20 \pm 0.13$  vs  $1.30 \pm 0.06$ ;  $P < .001$ ) and carboxyterminal telopeptide (CTX) and osteocalcin were significantly higher compared to controls ( $707 \pm 365.7$  vs  $371 \pm 104.1$  pg/mL;  $P = .001$  and  $31.6 \pm 15.4$  vs  $17.0 \pm 5.7$  ng/mL;  $P = .001$ , respectively). One year after IGF-1 normalization, a significant reduction of bone turnover indexes was observed in the group of acromegalic patients surgically cured (osteocalcin decrease of 61.2%, CTX decrease of 60.3%) compared to the ones controlled by medical therapy (osteocalcin decrease of 39%, CTX decrease of 40.7%;  $P = .01$  and  $P = .001$ , respectively). Despite these findings, no TBS or BMD variations were observed.

**Conclusion:** Acromegalic patients have impaired bone quality despite normal density. Achieving normal growth hormone secretion rapidly leads to the normalization of bone turnover.

**Key Words:** acromegaly, TBS, bone metabolism, osteoporosis

Acromegaly is a systemic disease characterized by chronic exposure to high growth hormone (GH) and insulin-like growth-factor 1 (IGF-1) serum levels. Both these hormones regulate bone metabolism through life, promoting longitudinal bone growth and mass acquisition during childhood and preserving bone mass and calcium homeostasis during adulthood [1].

In acromegaly, the chronic exposure to elevated GH and IGF-1 concentrations leads to an increase in bone turnover with a negative calcium balance [1-4]. Published data on bone mineral density (BMD) in acromegaly are very heterogeneous, with reports both of decreased and increased BMD [5, 6].

Importantly, acromegalic patients seem to have a higher vertebral fracture (Vfx) risk regardless of BMD, suggesting that GH chronic excess may alter bone quality besides bone density [7-12].

Bone quality can be directly assessed by transiliac crest bone biopsy or by computed tomography (CT) study (high-resolution peripheral quantitative computed tomography, HRpQCT, or high-resolution-cone beam computed tomography, HR-CBCT) [13, 14] and magnetic resonance imaging [15-17]; but these techniques are invasive and not routinely available. The trabecular bone score (TBS) is a new, gray-level, textural measure that can be extracted from the 2-dimensional lumbar spine dual-energy x-ray absorptiometry (DXA) image to estimate trabecular microstructure. TBS is useful, in addition to BMD, to determine patients' fracture risk [18-22]. The relationship between TBS texture and 3-dimensional microarchitecture parameters has been confirmed in several *in vivo* studies, reporting a significant correlation between TBS and bone histology parameters, such as trabecular space and number and trabecular connective density [21, 23, 24]. A higher TBS value may relate to a better skeletal texture, reflecting a strong, fracture resistant microarchitecture, whereas a lower one may reflect weak,

fracture-prone bone microarchitecture. Several studies have reported a link between TBS and fracture risk independently of BMD in primary and secondary osteoporosis and after pharmacological treatment [18, 22, 25, 26].

The aim of this study is to describe bone density and quality, as measured by TBS, in acromegalic patients and to assess the effect of disease control on these parameters.

## Material and Methods

### Participants

We screened data from all ( $n = 27$ ) patients newly diagnosed with acromegaly due to a pituitary adenoma at our center between December 2012 and 2015. Acromegaly was diagnosed on the basis of failure of suppression of GH to less than  $0.4 \mu\text{g/L}$  during a standard oral glucose tolerance test (OGTT), in association with serum IGF-1 levels greater than the normal age- and sex-adjusted range. OGTT was performed after an overnight fast and collecting blood samples at 0, 30, 60, 90, and 120 minutes [27].

Based on thinly sliced magnetic resonance imaging or CT scanning of the sellar region, with and without contrast enhancement, a macroadenoma was defined as a pituitary tumor with a maximum diameter greater than or equal to 10 mm and a microadenoma as a pituitary tumor with a maximum diameter of less than 10 mm.

Exclusion criteria at time of diagnosis of acromegaly were 1) diagnosis of multiple endocrine neoplasia type 1; 2) current or past history of secondary forms of osteoporosis, such as isolated hyperparathyroidism, hypogonadism (with the exception of menopausal state), bowel diseases, hyperthyroidism, chronic renal failure, alcoholism or eating disorders, hematological, and rheumatologic diseases; 3) current or past treatments affecting bone metabolism (ie, glucocorticoid treatments, medical therapies for osteoporosis). Eventually, after meeting exclusion criteria,

we enrolled 18 acromegalic patients (13 women, age  $56.2 \pm 15$  years).

Thirty-six nonacromegalic individuals from our outpatient clinics for endocrinological disease with no impact on bone metabolism (ie, thyroid nodes), matched for age, sex, menopausal state, smoking habits, and body mass index (BMI) to the patient group were selected as controls on the basis of the same exclusion criteria used for the acromegalic participants.

As per our protocols, to normalize vitamin D (25OHD) levels, all patients with 25OHD concentration below 30 ng/mL (SI units 74.8 nmol/L) received cholecalciferol supplementation. An oral bolus of 100 000 IU or 300 000 IU of cholecalciferol was administered to patients with 25OHD levels between 10 and 30 ng/mL (SI units 24.9–74.8 nmol/L) and below 10 ng/mL (SI units 24.9 nmol/L), respectively. Subsequently, in all patients a cholecalciferol supplementation of 50 000 IU monthly and 400 IU daily was recommended [28], and in those with a calcium intake of less than 1000 mg/day also an oral calcium carbonate supplementation (500 mg/day or 1000 mg/day in patients with an estimated calcium intake above or below 500 mg/day, respectively) was prescribed [29, 30].

The study protocol was approved by the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Ethical Committee (protocol No. 1755).

All patients signed an informed consent to participate in the study according to the indications for Good Clinical Practice.

## Study Protocol

We recorded and analyzed data from patients at 2 standard points: at the diagnosis of acromegaly and 12 months after the achievement of cure or control of the disease.

Patients were considered cured after achievement of normal serum IGF-1 levels, sex- and age-standardized, in association with nadir GH after OGTT below 0.4 mcg/L without concomitant use of medical therapy. Biochemical control was defined as the presence of normal serum IGF-1 levels and basal GH levels (mean of at least 3 samples) below 1 mcg/L during medical therapy with somatostatin analogues (SSAs) [27].

The data of matched controls were analyzed only at the study enrollment.

Pituitary function was assessed both at diagnosis and follow-up by measuring basal hormone levels (IGF-1, thyroid and gonadal function) or by both basal and dynamic testing (GH, adrenal function). Hypopituitarism was defined for each axis as follows: hypoadrenalism, by low morning cortisol ( $< 5$  mcg/dL/SI units 138 nmol/L) and/or an insufficient response to an adrenocorticotropin stimulation test (peak cortisol  $< 18$   $\mu$ g/dL/SI units 500 nmol/L);

hypothyroidism, by low free plasma thyroxine with normal or low plasma thyrotropin levels; GH deficiency (GHD) by insufficient response to growth hormone–releasing hormone plus arginine test (adjusted by BMI) performed in patients with IGF-1 below the 50th percentile in the age- and sex-matched range [31], and hypogonadism, by low serum total testosterone in the presence of low or inappropriately normal serum luteinizing hormone and follicle-stimulating hormone in men and by amenorrhea or by low or normal luteinizing hormone and follicle-stimulating hormone in women of menopausal age. The presence of hyperprolactinemia was documented. Hyperprolactinemia was defined as prolactin levels higher than 15 mcg/L in men and 25 mcg/L in women.

Both at diagnosis and the end of the follow-up we evaluated parathyroid hormone (PTH), 25OHD, serum, and 24-hour urinary calcium, serum and 24-hour urinary phosphate, carboxyterminal telopeptide (CTX), osteocalcin and total alkaline phosphatase (ALP) levels, BMD by DXA (Hologic Discovery, software version 13.3:3; Hologic) at lumbar spine (LS, precision 1.0%), femoral neck (FN, precision 1.8%), and total femur (precision 1.7%) and TBS automatically calculated from the DXA lumbar scan [20]. LS TBS was derived for each DXA examination using TBS iNsite software (Medimaps SASU). The mean value of the vertebrae from L1 to L4 was calculated, and vertebrae affected by fracture were excluded DXA from analysis [18, 20]. TBS data were reported as absolute value and classified as grade 1 (TBS  $\geq 1.350$ , normal), grade 2 (TBS 1.200–1.350, mildly decreased), and grade 3 (TBS  $\leq 1.200$ , frankly decreased) reduction [18–32].

Vfx were diagnosed on visual inspection using the semiquantitative visual assessment (SQ) previously described by Genant and colleagues, and fractures assessed on lateral thoracolumbar spine radiographs were defined in the presence of a greater than 20% reduction in anterior, middle, or posterior vertebral height: 13 vertebrae (from thyroxine to L4) were evaluated visually and classified as intact (SQ grade 0) or as having mild (20%–25% compression), moderate (25%–40% compression), or severe ( $> 40\%$  compression) deformity (SQ grades 1, 2, and 3, respectively) [33].

Radiographic fracture scoring was assessed by an individual scorer who is part of our dedicated team of endocrinologists expert in bone metabolism. In the longitudinal scoring the x-rays were individually evaluated and, because of the study design, the scorer was not blinded.

Outcomes of the study were to assess bone mineral and quality, as measured by TBS, and prevalence of Vfx in active acromegalic patients. We analyzed these data in a cross-sectional evaluation (primary outcome) and in a longitudinal evaluation after disease control or cure (secondary outcome).

## Hormonal Assays

GH was assayed with a chemiluminescence method (Immulite 2000, Siemens Medical Solutions Diagnostics) with a detection limit of 0.01 mg/L. Standards were calibrated to the World Health Organization international standard IS 98/574. IGF-1 levels were measured by a chemiluminescent immunometric assay (Immulite 2000 IGF-I; Siemens Medical Solutions Diagnostics), with an intra-assay and interassay coefficient of variation of 2.9 and 7.4%, respectively. Standards were calibrated to the World Health Organization international standard IRR87/518. IGF-1 values were compared with those from an appropriate age- and sex-adjusted range and expressed as SD scores (SDS) as previously described [28].

Serum and urinary calcium, albumin, and phosphate were measured by standard colorimetric techniques. Serum intact PTH was measured by electrochemiluminescence immunoassay (normal values, 15-65 pg/mL). The serum 25OHD concentration was measured by chemiluminescent immunoassay (normal values  $\geq 30$  ng/mL/SI units 74.8 nmol/L). Serum osteocalcin (normal values, 5-65 ng/mL) was measured by the Invitrogen human Osteocalcin Enzyme Amplified Sensitivity Immunoassay (Life Technologies) and serum CTX was determined by the Serum CrossLaps enzyme-linked immunosorbent assay (Immunodiagnostic System Ltd) according to the manufacturer's assay procedure.

## Statistical Analysis

Data are expressed as mean  $\pm$  SD) unless otherwise stated. Statistical analysis was carried out using paired or unpaired 2-tailed *t* test as appropriate. Categorical variables were compared by Fisher exact test or chi-square test as appropriate. Logistic analysis was carried out by SPSS (version 17.0). *P* values less than .05 were considered statistically significant.

## Results

### Patient Demographics and Pituitary Function at Baseline

As shown in Table 1, 72% of patients were female and the mean age at diagnosis was  $56.2 \pm 15$  years. The estimated duration of the disease prior to diagnosis was  $8.5 \pm 7.2$  years. Neuroradiological imaging revealed a macroadenoma in 55.5% of cases. At diagnosis GH concentration was  $16.1 \pm 47.4$  mcg/L while the mean nadir GH after OGTT was  $13.5 \pm 38.6$  mcg/L. The mean IGF-1 serum levels were  $656 \pm 251$  ng/mL ( $6.8 \pm 4.1$  SDS). No concomitant hypersecretions were observed. Pituitary deficiencies were found in 3 patients (16.6%), all presenting

with hypoadrenalism. Fifty-four percent (6/13) of female patients were postmenopausal and none of them underwent hormonal replacement. Five patients (28%) were diagnosed with diabetes at diagnosis. All patients were in optimal glycemic control without medical therapy (average glycated hemoglobin  $A_{1c}$ ,  $6.6 \pm 0.6\%$  SI units 49 mmol).

As per the inclusion criteria of the study, controls were recruited by age, sex, BMI, smoking habit, and menopausal state matched to patient's group. No significant differences in terms of alteration of glucose metabolism were observed between control individuals and patients.

### Cross-sectional study

The clinical and biochemical characteristics of patients and controls are reported in Table 1. Age, sex distribution, BMI, PTH, serum phosphate, ALP, vitamin D, spinal and femur BMD and of VFX were comparable between patients and controls. In particular, 2 patients showed VFX (1 patient with a grade 1 anterior wedge deformity in L1, and 1 patient with 2 fractures, a grade 1 anterior wedge deformity in L1, and a grade 2 anterior wedge deformity in D12).

At variance were serum and urinary calcium levels, osteocalcin, and CTX, whereas TBS was lower in patients than in controls. The prevalence of patients with a TBS grade 3 reduction was higher in patients than in controls (Fig. 1). In the whole group of patients, the logistic regression analysis showed that the presence of acromegaly and age was inversely associated with TBS grade 3 regardless of sex, BMI, and gonadal status (Table 2).

The 2 acromegalic patients with prevalent VFX at diagnosis were older than acromegalic patients without fractures, while no significant differences were observed in terms of BMI, diagnostic delay, hormonal and glycemic status, smoking habits, calcium metabolism, and BMD between acromegalic patients with and without VFX (data not shown).

### Prospective observational study

Twelve patients out of 18 underwent transsphenoidal surgery as a first treatment for acromegaly. Six patients (33.3%) were cured after surgery. Among the 6 patients not cured by surgery, 2 patients (11%) needed a second surgical approach, and subsequent radiosurgery with Gamma Knife. All patients not cured by surgery started SSA therapy.

The remaining 6 patients (33.3%) began SSA therapy as a first treatment for acromegaly. In summary, 6 patients (33.3%) were cured of acromegaly by surgery and 12 patients (66.7%) were controlled in therapy with SSA. Four out of 6 patients cured were female (67%), and 9 out of the 12 patients controlled were female (75%).

After surgery 2 patients developed new pituitary deficits. One patient developed hypoadrenalism, hypothyroidism,

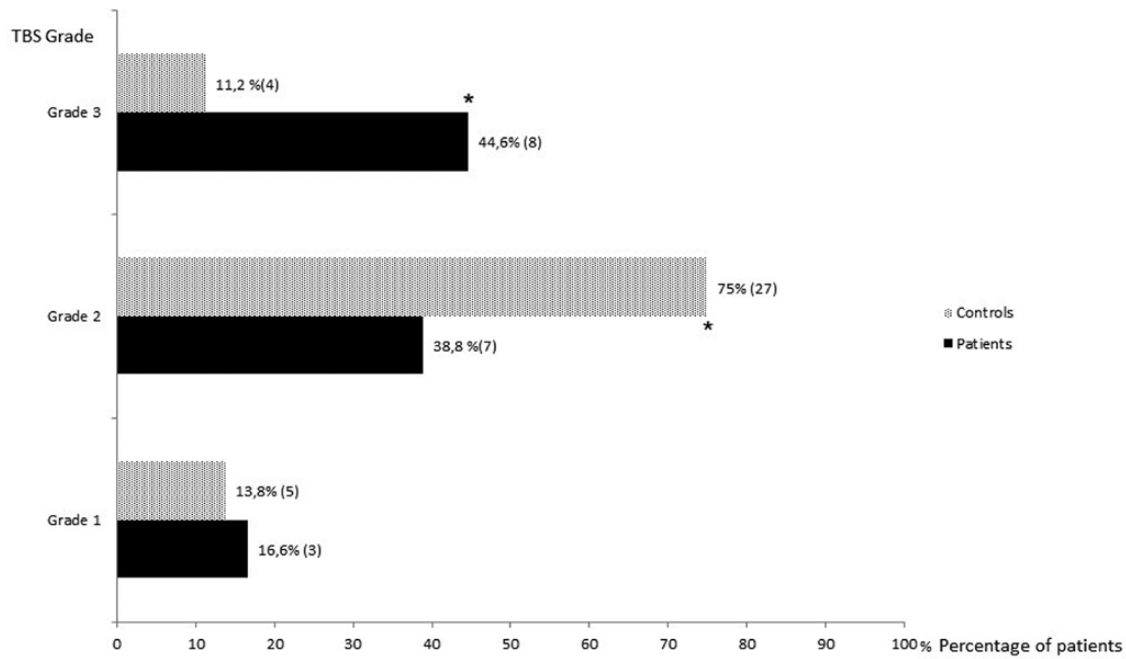
**Table 1.** Calcium phosphorus metabolism of patients and controls. Patient data at diagnosis and at follow-up

	Baseline		P ( <sup>α</sup> vs <sup>γ</sup> )	Follow-up		P ( <sup>β</sup> vs <sup>α</sup> )
	Patients <sup>α</sup> 18	Controls <sup>γ</sup> 36		Patients <sup>β</sup> 18		
Age, y	56.2 ± 15.0 (38-82)	58.0 ± 13.1 (38-82)	.67	57.6 ± 13.7 (39-83)	.81	
Sex, F %	13 (72.2)	26 (72.2)	1.00	13	1.00	
BMI	28.3 ± 5.9 (19.1-43.6)	27.6 ± 3.7 (19.9-38)	.58	27.9 ± 4.6 (20.7-35)	.61	
PTH, ng/L	49.2 ± 25.5 (11.6-81)	49.8 ± 13.0 (16-70)	.90	41 ± 22. (14.9-82.4)	.06	
Serum calcium levels (mg/dL)/ (mmol/l)	9.3 ± 0.4/2.3 (8.9-10.5)/(2.2-2.62)	9.1 ± 0.3/72.2 (8.5-9.6)/(2.1-2.4)	.05	9.3 ± 0.4/2.3 (8.8-10.2)/(2.2-2.5)	.91	
24-h urinary calcium levels (mg/ kg/24h) (mmol/kg/24)	3.5 ± 3/0.08 (0.4-10.9) (0.01-.27)	2.1 ± 1.1/3/0.05 (0.3-2.4) (0.01-0.06)	.05	2.4 ± 2.5/0.06 (1-4) (0.02-0.1)	.12	
Serum phosphate levels (mg/dL)/ (mmol/L)	3.9 ± 0.4/1.25 (3.1-4.6)/(1-1.4)	3.7 ± 0.4/1.1 (2.6-4.5)/(0.8-1.4)	.16	3.3 ± 0.5/1.0 (2.7-4.8) (0.8-1.5)	.001	
24-h urinary phosphate levels, g/24 h	0.49 ± 0.23 (0.13-0.97)	0.7 ± 0.27 (0.2-1.6)	.32	0.87 ± 0.37 (0.18-1.6)	.001	
ALP, U/L	71 ± 28.0 (37-135)	67.3 ± 15.5 (49-105)	.65	62 ± 20.7 (32-98)	.06	
25-hydroxvitamin D (ng/mL)/ (nmol/L)	22.5 ± 17.1/56.1 ± 42.6 (6.2-59.7)/ (15.4-149)	24.9 ± 11.7/62.1 ± 29.2 (6.4-65.8)/ (15.9-164.2)	.57	28.3 ± 12.7/70.6 ± 31.7 (8.8-56.7)/ (21.9-141.5)	.08	
Osteocalcin, ng/mL	31.6 ± 15.4 (16.7-67.4)	17.0 ± 5.7 (8-31)	.001	17.6 ± 6.9 (11.1-31.8)	.009	
CTX, pg/mL	707.5 ± 365.7 (218-1550)	371.0 ± 104.1 (170-560)	.001	387.0 ± 224.9 (161-962)	.01	
LS BMD, T score	-0.37 ± 1.34 (-3.5 + 2.5)	-0.50 ± 1.19 (-2.6 + 2.8)	.79	-0.41 ± 1.21 (-3.1 + 2.4)	.77	
FN BMD, T score	-0.48 ± 1.07 (-2.5 + 0.9)	-0.60 ± 1.33 (-2.6 + 3.2)	.73	-0.47 ± 1.11 (-2.1 + 1.3)	.78	
FT BMD, T score	0.09 ± 1.09 (-2.0 + 1.9)	-0.31 ± 1.07 (-2.4 + 1.2)	.15	0.14 ± 1.10 (-1.8 + 2.4)	.46	
TBS	1.20 ± 0.13 (0.97-1.42)	1.30 ± 0.06 (1.17-1.43)	<.001	1.22 ± 0.13 (0.95-1.42)	.37	
TBS Z score	-2.2 ± 1.9 (-5.9 + 0.96)	-0.5 ± 1.3 (-1.9 + 1.9)	<.001	-2.0 ± 1.9 (-6.4 + 0.51)	.46	
TBS grade 1 (%)	3 (16.6)	5 (13.8)	1.00	2 (11.1)	1.00	
TBS grade 2 (%)	7 (38.8)	27 (75)	.01	11 (61.1)	.31	
TBS grade 3 (%)	8 (44.6)	4 (11.2)	.01	5 (27.8)	.48	
VFx, %	2 (11)	3 (8.3)	1.00	3 (16.6)	1.00	

Data are expressed in mean ± SD (range) or absolute number (percentage). Significant *P* less than or equal to .005. Values in bold are statistically significant analysis (*P* < .05).

Abbreviations: ALP, alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; CTX, carboxyterminal telopeptide; F, female; FN, femoral neck; FT, femoral total; LS, lumbar spine; PTH, parathyroid hormone; TBS, trabecular bone score; VFx, vertebral fractures.

TBS data were reported as absolute value and classified as grade 1 (TBS ≥ 1.350, normal), grade 2 (TBS 1.200-1.350, mildly decreased), and grade 3 (TBS ≤ 1.200, frankly decreased).



**Figure 1.** Trabecular bone score (TBS) value at diagnosis: grade of TBS expressed as a percentage of total in patients and controls.

**Table 2.** Factors independently associated with a trabecular bone score grade 3 in the whole group of patients assessed by logistic regression analysis

	OR	95% CI	<i>P</i>
Acromegaly, yes/no	7.40	1.47-37.2	<b>.015</b>
Age, y	1.08	1.02-1.14	<b>.008</b>
BMI	0.89	0.78-1.02	.113
Female sex	1.03	0.09-10.83	.976
Hypogonadism, yes/no	0.29	0.38-2.34	.245

Values in bold are statistically significant analysis ( $P < .05$ ).

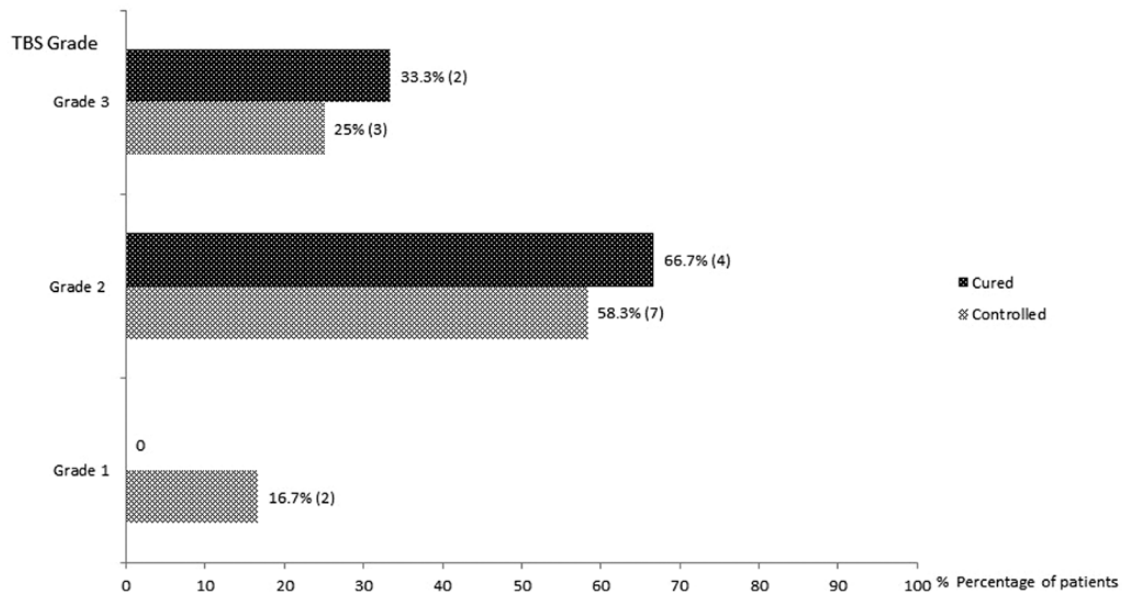
Abbreviations: BMI, body mass index; OR, odds ratio.

and hypogonadism, and one patient GHD plus diabetes insipidus. All pituitary deficits were replaced with the exception of GHD.

All diabetic patients maintained optimal glycometabolic control at last follow-up (average glycated hemoglobin  $A_{1c}$ ,  $5.9 \pm 1.2\%$ ). No new diagnosis of diabetes occurred.

In acromegalic patients, 1 year after the biochemical cure or control of disease, we observed a reduction of bone turnover indexes (even though a statistically significant difference was not reached for ALP) and serum phosphorus levels, whereas urinary phosphorous levels increased (see [Table 1](#)). On the contrary, BMI, mean TBS values, BMD, serum and urinary calcium and 25OHD levels did not vary. Interestingly, 3 patients improved their TBS value, moving from grade 3 to grade 2 ([Fig. 2](#)). No other relevant fractures were reported.

The comparison of baseline and end of follow-up data between cured patients and controlled individuals is reported in [Table 3](#). The changes in PTH, calcium 25OHD, serum and urinary calcium, ALP, TBS, and BMD between baseline and the end of follow-up were not significant and were not different between cured and controlled patients. The 2 groups also did not differ for incident VFX, BMI, and IGF-1 levels at baseline and end of follow-up. At variance, we found that osteocalcin and CTX levels decreased significantly in cured patients but not in controlled ones: osteocalcin showed a 61.2% decrease in cured patients from diagnosis to last follow-up ( $35.1 \pm 17.9$  ng/mL vs  $13.6 \pm 3.4$  ng/mL,  $P = .01$ ) and a 39% decrease in controlled patients ( $30.9 \pm 16.1$  ng/mL vs  $18.8 \pm 6.6$  ng/mL,  $P = .06$ ); CTX showed a decrease in cured patients of 60.3% from diagnosis to last follow-up ( $719 \pm 166.4$  pg/



**Figure 2.** Trabecular bone score (TBS) grade at diagnosis and 12 months after cured or controlled definition in acromegalic patients. Grades of TBS are expressed as a percentage of total number of patients.

**Table 3.** Calcium-phosphorus metabolism at diagnosis and 12 months after acromegaly remission

	Cured patients (N = 6)			Controlled patients (N = 12)		
	Baseline	Follow-up	P	Baseline	Follow-up	P
IGF-1 SDS	6.36 ± 5.0	-0.48 ± 0.74	<b>.007</b>	6.58 ± 4.1	0.46 ± 0.52	<b>.001</b>
Age, y	60.6 ± 14.9		NA	53.6 ± 7.0		NA
Sex, F %	4 (66.6)		NA	9 (75)		NA
PTH	58.3 ± 28.2	46.4 ± 28.1	.6	49.3 ± 25.5	39.9 ± 21.3	0.4
Serum calcium	9.15 ± 0.24	9.23 ± 0.35	.4	9.27 ± 0.28	9.27 ± 0.39	.9
Serum phosphorus	3.8 ± 0.47	2.9 ± 0.42	<b>.005</b>	4.0 ± 0.5	3.4 ± 0.2	<b>.01</b>
25-hydroxyvitamin D	17.1 ± 10.5	27.7 ± 12.6	.14	20.1 ± 17.1	27.8 ± 15.1	.3
24-h urinary calcium, g/kg/24 h	3.6 ± 3.5	2.7 ± 2.6	.67	2.7 ± 1.9	1.15 ± 0.85	.07
24-h urinary phosphorus, g/L	0.4 ± 0.1	0.9 ± 0.4	<b>.03</b>	0.9 ± 0.4	0.8 ± 0.3	<b>.03</b>
Osteocalcin	35.1 ± 17.9	13.6 ± 3.4	<b>.01</b>	30.9 ± 16.1	18.8 ± 6.6	.06
CTX	719.1 ± 166.4	285.5 ± 109.3	<b>.001</b>	684.8 ± 394.8	405.1 ± 202.8	.07
ALP	74.1 ± 24.5	62.2 ± 22.3	.42	65.1 ± 0.5	57.2 ± 19.8	.49
LS BMD, T score	-1.15 ± 1.27	-1.05 ± 1.17	.9	-0.2 ± 1.2	-0.2 ± 1.07	.9
FN BMD, T score	-0.13 ± 1.31	-0.15 ± 1.3	.9	-0.8 ± 0.9	-0.85 ± 0.94	.9
FT BMD, T score	0.43 ± 1.2	0.5 ± 1.08	.9	-0.08 ± 1.1	-0.07 ± 1.1	.9
TBS Z score	-3.0 ± 2.4	-2.9 ± 2.3	.9	-1.9 ± 1.7	-1.63 ± 1.8	.7
TBS	1.170 ± 0.17	1.170 ± 0.15	.9	1.197 ± 0.1	1.230 ± 0.13	.5
VFX	1 (16.6)	1 (16.6)	1	1 (8.3)	2 (16.6)	1

Data are expressed in mean ± SD (range) or absolute number (percentage). Significant *P* less than or equal to .005. Values in bold are statistically significant analysis (*P* < .05).

Abbreviations: ALP, alkaline phosphatase; BMD, bone mineral density; CTX, carboxyterminal telopeptide; F, female; FN, femoral neck; FT, femoral total; IGF-1, insulin like growth factor 1; LS, lumbar spine; NA, not applicable; PTH, parathyroid hormone; SDS, SD score; TBS, trabecular bone score; VFX, vertebral fractures.

mL vs 285.5 ± 109.3 pg/mL, *P* = .001) and in controlled patients of 40.7% (684.8 ± 394.8 pg/mL vs 405.1 ± 202.8 pg/mL, respectively, *P* = .07).

The only patient with documented postsurgical GHD showed stable parameters at last follow-up (data not shown).

## Discussion

Bone reabsorption and formation are coupled processes to maintain bone homeostasis and, in both, GH and IGF-1 are involved [1, 28, 34]. In acromegaly, chronic exposure to elevated GH and IGF-1 concentrations leads to increase bone turnover and negative calcium balance. A recent meta-analysis showed that biochemical markers of bone formation and bone resorption increased in active acromegaly, with bone resorption being more enhanced than bone apposition. Moreover, some authors pointed out that a disproportion in bone resorption in relation to bone formation could reflect the degree of observed bone loss. [1, 35-37]. Our study further confirms this evidence, showing a significant difference in markers of bone turnover (CTX and osteocalcin), which resulted higher in active acromegalic patients compared to controls.

The impact of GH and IGF-1 on bone turnover appeared clearly in our data, according to previous published data stating the improvement of bone turnover indexes after IGF-1 normalization [7, 38]. Indeed we showed that, after normalization of GH and IGF-1 levels, bone turnover markers significantly decreased.

Interestingly, we found that patients controlled by medical therapy were less likely to normalize bone turnover compared to patients cured by surgery. To explain these findings, we can hypothesize that a complete cure of the disease leads to a physiological hormonal balance that may be not comparable to the biochemical control obtained by medical therapy. Moreover, a direct effect of SSAs on bone metabolism cannot be excluded.

This hypothesis is also supported by the study by Rubeck and colleagues showing that, despite similarly normalized IGF-1 serum levels, SSA treatment was associated with less-suppressed GH levels compared with surgery alone [39]. The authors explained this discordance through the specific suppression of hepatic IGF-1 production by SSAs [39]. In fact, treatment with SSAs reduces not only pituitary GH secretion, but also hepatic IGF-1 production. This secondary effect may result in biochemical IGF-1 normalization despite persistent disease activity induced by circulating GH, which can have an effect on bone metabolism [39]. Furthermore, another study demonstrated that the rapid fall of GH levels after transphenoidal surgery was associated with a rapid decline in bone turnover markers [40].

In acromegalic patients, the increase of bone resorption associated with GH renal effects induces bone loss and skeletal fragility [1]. In the present study, we did not observe a significant alteration in BMD in our population, as previously reported [36]. In acromegaly, BMD is affected by several factors such as morphological and volumetric skeletal changes. Moreover, DXA is not able to discriminate between

cortical and trabecular bone. GH has an opposite effect on these tissues, exerting an anabolic role on the former and a catabolic effect on the latter [36]. Nevertheless, in our series we did not find significant differences in BMD among the different skeletal segments examined.

Previous studies demonstrated that, regardless of BMD values, acromegalic patients have an increased prevalence of morphometric VFX and a higher fracture risk compared to controls [8-11]. Disease duration is the main predictor of fracture risk, and patients with uncontrolled disease have a 3-fold greater risk than controlled or treated patients [11]. Other studies reported an increased VFX risk after GH normalization due to the onset of pituitary deficiencies, especially hypogonadism and GHD [11, 41]. In our population morphometric VFX were comparable between acromegalic patients and controls. One year after biochemical normalization, we did not find new fractures or significant BMD variations. As suggested by previous studies, a longer follow-up is probably needed to evaluate the effects of treatment and disease control on BMD and VFX [11, 40]. However, in the present study only 1 out of 18 patients (5.6%) experienced an incidental fracture, a figure that is definitely lower than that recently reported (33%) [42]. As in other forms of secondary osteoporosis, acromegalic patients seem to have an increased VFX risk that is not entirely explained by the reduction of BMD, suggesting that, besides bone density, the chronic GH excess may alter also bone quality. This hypothesis has been demonstrated *in vivo* by 2 recent studies conducted with HRpQCT and HR-CBCT showing a reduction in trabecular density and a deterioration of bone microarchitecture in acromegalic patients [10, 12]. Published data on TBS in acromegaly are few. A recent Korean series evaluated TBS in 33 newly diagnosed acromegalic patients showing that LS TBS was lower in acromegalic patients than in controls, in particular in hypogonadal patients [43]. In a Norwegian longitudinal study of 48 patients, TBS was significantly decreased 12 months after treatment [44]. In our study, we evaluated both cross-sectional and prospective data. As in the Korean series, we found that acromegalic patients had a significantly lower TBS than the control population. In addition, we were able to demonstrate that acromegaly is associated with a reduced TBS regardless of age, sex, BMI, and gonadal status. This finding reinforces the idea that the increased fracture risk in acromegaly is due to a reduction of bone quality, as indirectly measured by TBS. Nevertheless, we observed that TBS did not change 12 months after disease remission in contrast to the Norwegian series [44].

The present study has several limitations mainly due to the small sample size and to the short duration of the follow-up. Indeed, these 2 aspects did not allow us to

estimate the effect of the curing of acromegaly on the risk of incident fractures and on possible changes of bone quality.

Notwithstanding these considerations, our data confirm that acromegalic patients have impaired bone quality as measured by TBS in the presence of normal bone density, which is also consistent with the HRpQCT findings. Achieving hormonal control, bone turnover indexes improve. They improve rapidly and more significantly in cured patients than in individuals controlled with SSA therapy. Conversely, a longer follow-up may be needed to detect significant variation of bone mass and quality.

## Acknowledgments

We thank Prof Giovanni Vitale and Dr Letizia Fatti for the provided data.

**Financial Support:** This work was supported by AIRC (Associazione Italiana Ricerca Cancro; grant No. IG 2014-15507 to G.M.) and Ricerca Corrente Funds from the Italian Ministry of Health to Fondazione IRCCS Ca Granda, Ospedale Maggiore Policlinico, Milan.

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**Disclosures:** The authors have nothing to disclose.

**Data Availability:** The data that support the findings of this study are available from the corresponding author on reasonable request.

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