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Clinical Research Article

Persistent Deficits in Bone Quality in Treated Acromegaly: Evidence From Assessments of Microstructure

Adriana P. Kuker,[1] Sanchita Agarwal,[1] Elizabeth Shane,[1] Adi Cohen,[1] Thomas L. Nickolas,[1] Emily M. Stein,[2] Tirissa J. Reid,[1] Didier Hans,[3] Serge Cremers,[1,4] Jeffrey N. Bruce,[5] and Pamela U. Freda[1]

[1]Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA
[2]Endocrinology and Metabolic Bone Diseases, Hospital for Special Surgery, New York, NY 10032, USA
[3]Center for Bone Diseases, Bone and Joint Department, Lausanne University Hospital, Lausanne 1011, Switzerland
[4]Pathology and Cell Biology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA
[5]Neurosurgery, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA

Correspondence: Pamela U. Freda, MD, Department of Medicine, Columbia University, Vagelos College of Physicians and Surgeons, 650 W 168th St, 10-1014, New York, NY 10032, USA. Email: puf1@cumc.columbia.edu.

Abstract

Purpose: Fractures are increased in patients with acromegaly, both before and after successful acromegaly treatment. Abnormalities of bone microstructure, which may underlie this fragility, are present in active acromegaly but to what extent these improve with acromegaly treatment or persist despite biochemical remission remains unclear. To examine these questions, we studied the effects of acromegaly treatment and remission on bone quality.

Methods: Sixty-five women and men with acromegaly were studied. Subgroups underwent assessments of areal bone mineral density by dual x-ray absorptiometry, trabecular bone score (TBS), and volumetric bone mineral density, microarchitecture, stiffness and failure load of the distal radius and tibia by high-resolution peripheral quantitative tomography in a longitudinal study before and after acromegaly treatment and in a cross-sectional study in which patients were compared to sex-, age-, and body mass index-matched healthy controls.

Results: In the longitudinal study, significant increases in total, cortical, and trabecular densities at the radius and tibia and increased stiffness and failure load of the tibia occurred with acromegaly treatment. In the cross-sectional study, patients in biochemical remission after surgery had larger bones, lower trabecular and cortical volumetric density, and disrupted trabecular microarchitecture compared to controls. TBS did not change with acromegaly treatment but correlated with some microstructural parameters.

Conclusion: We show, for the first time, that volumetric bone mineral density and microarchitecture of the peripheral skeleton improve with acromegaly treatment but remain abnormal in patients in remission after surgery compared to controls. These abnormalities, known to be associated with fractures in other populations, may play a role in the pathogenesis of persistent fragility in treated acromegaly.

Key Words: acromegaly, HRpQCT, bone

GH and IGF-1 are important regulators of bone metabolism. They are anabolic, regulate bone remodeling, and increase bone strength [1]. In acromegaly, persistently high levels of GH and IGF-1 increase bone remodeling and bone volume [2] and result in appositional bone growth that is clinically apparent in many patients. Until recently, the prevailing view was that these anabolic effects on the skeleton would preserve bone strength in acromegaly. This view stemmed largely from many studies that, overall, have found dual x-ray absorptiometry (DXA)-measured areal bone mineral density (aBMD) to be normal at the lumbar spine (LS) and increased at the femoral neck (FN) [3, 4] in acromegaly. However, recent studies have shown that vertebral fracture (VF) rate is increased in acromegaly and that risk of fracture is not reliably predicted by aBMD [5-8]. While high bone turnover and hypogonadism may be major contributors to the poor bone quality of active acromegaly [9], incident VF rate remains high despite disease control and hypopituitarism treatment [8, 10]. TBS, a predictor of fracture risk in other populations [11, 12], has been found to be low [13] or unchanged [4], overall, in acromegaly. The effects of treatment on TBS or its relationship to bone microstructure in acromegaly remain unclear [4, 13-16]. Further investigation of the effects of acromegaly treatment and disease control on bone quality was needed.

Bone microarchitecture is an important determinant of its strength and fracture risk, independent of aBMD [17-21]. Imaging of this by high-resolution peripheral quantitative tomography (HRpQCT) permits separate, direct analyses of trabecular and cortical microstructural changes that relate to fragility in other populations [17, 21-24]. Recently, HRpQCT was used to cross-sectionally assess bone quality in patients with acromegaly, but it has not been used to assess bone quality prospectively, before and after acromegaly

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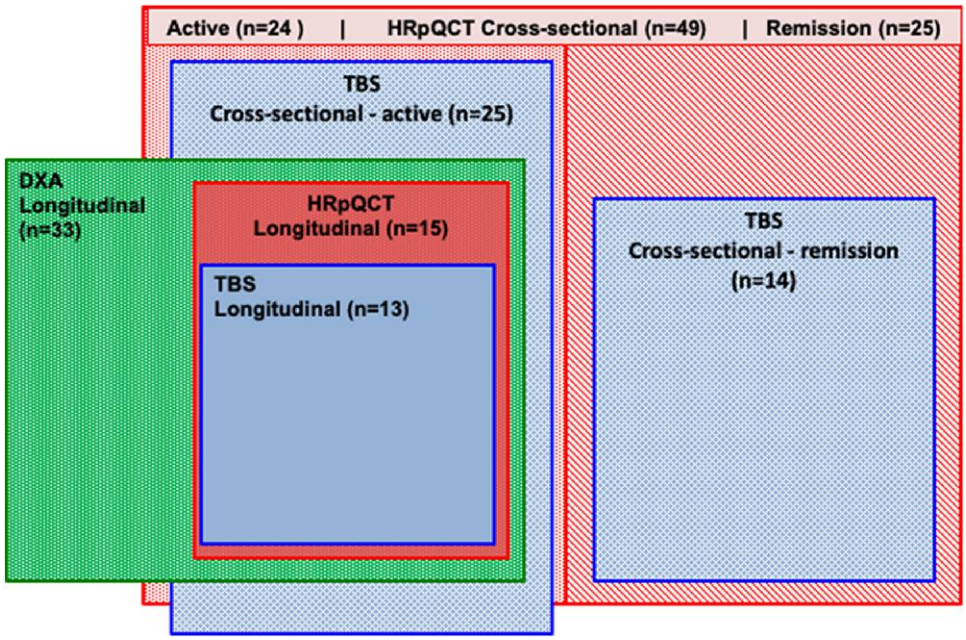

Figure 1. Overview of the relationship between subsets of the study population tested with each method of skeletal assessment. All patients who underwent longitudinal HRpQCT (HRpQCT Longitudinal box), DXA testing (DXA longitudinal box), or all TBS assessments (TBS boxes) were part of the cross-sectional HRpQCT cohort (lHRpQCT Cross-sectional box) except for 15 patients who only participated in the longitudinal DXA study (left side of DXA longitudinal box) and 1 who only underwent cross-sectional TBS assessment (lower edge TBS Cross-sectional active box).
Abbreviations: DXA, dual x-ray absorptiometry; HRpQCT, high-resolution peripheral quantitative tomography; TBS, trabecular bone score.

treatment, or to specifically compare patients in remission to controls. Therefore, our primary objective was to determine the effects of acromegaly treatment on bone quality. To do this, we assessed aBMD by DXA, TBS of the LS, and true volumetric BMD (vBMD), microarchitecture, and stiffness of the distal radius and tibia using HRpQCT in both a prospective, longitudinal study of patients with acromegaly before and after treatment and a cross-sectional study of patients in biochemical remission after surgical treatment compared to controls. We also aimed to examine how clinical and endocrine characteristics relate to parameters of bone quality in treated acromegaly.

Methods

Subjects

Acromegaly patients

Overall cohort. We studied 65 patients with acromegaly (34 women and 31 men) who were between the ages of 18.7 and 72 years (mean 50.2 yr) at baseline testing. All were diagnosed with acromegaly based on an IGF-1 level above the age-adjusted normal range, clinical characteristics of the disease, and eventual pathological confirmation of a GH-secreting pituitary tumor. At baseline testing, they were either newly diagnosed and untreated (n = 29) or had undergone prior surgery, radiotherapy, and/or medical therapies (n = 36). Those with prior therapy were studied ≥3 months after these procedures or the last administration of acromegaly medication. At baseline, 40 had active disease (defined by persistently elevated IGF-1 level) and 25 were in remission (defined as consistently normal IGF-1 level). Patients with hypopituitarism were on stable replacement doses for ≥3 months prior to testing, with the exception that some with hypogonadism were not replaced. DXA testing was performed as part of a longitudinal study that assessed body composition from 2006 to 2014, and HRpQCT was performed as part of a cross-sectional and longitudinal HRpQCT study conducted between 2010 and 2018 [25, 26]. We included all patients in these studies who had skeletal assessment except those who were on medical therapy within 3 months of baseline (n = 2) or had a history of osteoporosis treated with pharmacotherapy (n = 4) or hyperparathyroidism (n = 1). None had an active malignancy, renal or liver disease, hyper- or hypocalcemia, current or prior pharmacotherapy for osteoporosis, recent pregnancy or lactation, or use of supraphysiologic glucocorticoids at baseline or during the period of longitudinal follow-up. Results of these skeletal assessments have not been reported previously.

Acromegaly patient subgroups. Three subgroups of the overall cohort underwent skeletal assessments longitudinally (DXA, HRpQCT, TBS) and two cross-sectionally (HRpQCT, TBS) (Fig. 1). The subgroups overlapped except for 15 patients who underwent longitudinal DXA only and 1 who had cross-sectional TBS only. Characteristics of the subgroups are shown in Table 1 (longitudinal DXA, n = 33), Table 2 (longitudinal HRpQCT, n = 15 and TBS, n = 13), and Table 3 (cross-sectional HRpQCT, n = 49 and TBS, n = 33). The longitudinally studied cohorts were required to have active disease at baseline and only differed from the overall group of active-disease patients by their willingness to be studied longitudinally. For the longitudinal DXA and TBS analysis subgroups, only patients planning surgery participated. For the HRpQCT longitudinal subgroup, patients planning surgery or octreotide LAR therapy as part of their clinical care were invited to participate; 11 who had only surgery (out of 17 eligible) and 4 who received treatment with octreotide LAR (out of 7 eligible) agreed to participate.

Controls

HRpQCT results were compared to those of the same testing performed in healthy controls; 110 women and men who were

Table 1. Longitudinal DXA study: clinical, endocrine, anthropometric, and DXA data at baseline and after surgery in 33 patients

	Women (n = 19)			Men (n = 14)			All acromegaly (n = 33)		
	Baseline: active disease	Last follow-up after surgery	*P*-value (pre- vs post-surgery)	Baseline: active disease	Last follow-up after surgery	*P*-value (pre- vs post-surgery)	Baseline: active disease	Last follow-up after surgery	*P*-value (pre- vs post-surgery)
Age at DXA (yr) (range)	47.6 ± 11.8 (23-69)	51.3 ± 12.1 (26-70)	n/a	41.3 ± 11.9 (18-54)	44.3 ± 10.9 (26-57)	n/a	44.9 ± 12.1	48.4 ± 11.9	n/a
Height (cm)	163.2 ± 7.5	163.3 ± 17.2	.61	183.2 ± 7.3	182.5 ± 7.1	.08	171.7 ± 12.4	171.6 ± 12.1	.54
Weight (kg)	76.3 ± 17.1	77.2 ± 19.1	.49	102.4 ± 15.7	100.2 ± 14.1	.11	87.3 ± 20.9	86.9 ± 20.5	.66
BMI (kg/m^2)	29.1 ± 5.9	29 ± 6.7	.97	30.7 ± 5.8	30.1 ± 5.7	.13	29.7 ± 5.9	29.5 ± 6.2	.52
Duration of follow-up (median, range)		2.99 (0.6-13.7 yr)	n/a		2.49 (1.2-8 yr)	n/a		3.44 (0.6-13.7 yr)	n/a
Disease status at follow-up		14 remission, 4 active	n/a		12 remission, 2 active	n/a		26 remission, 6 active	n/a
Newly diagnosed	16		n/a	13		n/a	29		n/a
Prior acromegaly therapy	LAR (2), S/CAB/LAR/PEG (1)		n/a	S (1)		n/a	S (1), LAR (2), S/CAB/LAR/PEG (1)		n/a
Gonadal function and replacements	E (12), PM (5), H (1), HR (1)	E (11), PM (6), HR (2)	ND	E (10), H (3), HR (1)	E (10), HR (4)	ND	E (22), PM (5), H (4), HR (2)	E (21), PM (6), HR (6)	ND
Other hormone replacements (#)			ND	GC (1), T4 (1)	GC (2), T4 (2)	ND			ND
IGF-1 (µg/L)	626 ± 219	243 ± 150	**<.0001**	680 ± 176	224 ± 113	**<.0001**	649 ± 201	235 ± 134	**<.0001**
IGF-1% ULN	246 ± 88.3	96 ± 41	**<.0001**	242 ± 56	87 ± 40	**<.0001**	244 ± 75	105 ± 57	**<.0001**
GH fasting (µg/L) (median, range)	5.96 (1.3-233)	1.81 (.05-7.2)	**<.0001**	10 (1.4-162)	1.31 (0.5-5.3)	**.0001**	8.32 (1.33-233)	0.65 (0.05-7.2)	**.006**
CTX (ng/mL)	0.8 ± 0.5	0.5 ± 0.3	**.0036**	1.5 ± 0.7	0.4 ± 0.2	**.012**	1.1 ± 0.7	0.4 ± 0.3	**.0004**
P1NP (ng/mL)	105 ± 77	64 ± 35	**.034**	123 ± 67	34 ± 22	**.014**	114 ± 71	48 ± 32	**.0005**
N-midOC (ng/mL)	36 ± 24	17 ± 12	**.0007**	48 ± 38	12.5 ± 5	**.004**	41.5 ± 31	15 ± 10	**.0005**
DXA									
Total body									
Z-score	0.6 ± 1	0.9 ± 1	.1	−0.7 ± 0.8	−0.4 ± 0.9	.11	0.1 ± 1.2	0.3 ± 1.2	**.02**
T-score	0.7 ± 1.3	0.9 ± 1.3	.41	−0.1 ± 0.7	0.2 ± 0.8	.1	0.4 ± 1.0	0.6 ± 1.2	.11
aBMD (g/cm^2)	1.18 ± 0.09	1.19 ± 0.11	.45	1.21 ± 0.06	1.24 ± 0.07	**.006**	1.19 ± 0.1	1.21 ± 0.1	**.047**
L1-L4									
Z-score	0.4 ± 1.1	0.5 ± 1.2	.45	−1.1 ± 1.3	−0.7 ± 1.4	**.03**	−0.2 ± 1.4	−0.01 ± 1.4	**.046**
T-score	0.3 ± 1.3	0.1 ± 1.3	.25	−0.7 ± 1.2	−0.4 ± 1.4	**.01**	−0.1 ± 1.3	−0.08 ± 1.4	.63
aBMD (g/cm^2)	1.23 ± 0.16	1.19 ± 0.17	**.03**	1.15 ± 0.14	1.17 ± 0.17	.35	1.19 ± 0.15	1.18 ± 0.17	0.37

(*continued*)

Table 1. Continued

	Women (n = 19)			Men (n = 14)			All acromegaly (n = 33)		
	Baseline: active disease	Last follow-up after surgery	*P*-value (pre- vs post-surgery)	Baseline: active disease	Last follow-up after surgery	*P*-value (pre- vs post-surgery)	Baseline: active disease	Last follow-up after surgery	*P*-value (pre- vs post-surgery)
Total hip									
Z-score	0.7 ± 1.1	0.7 ± 1.1	.54	−0.4 ± 0.7	−0.2 ± 0.9	.06	0.2 ± 1.1	0.3 ± 1.1	.09
T-score	0.4 ± 1.1	0.4 ± 1.2	.8	−0.2 ± 0.7	−0.3 ± 0.8	.92	0.1 ± 1.0	0.1 ± 1.1	.87
aBMD (g/cm^2)	1.03 ± 0.20	1.06 ± 0.16	.45	1.07 ± 0.12	1.07 ± 0.11	.95	1.05 ± 0.17	1.1 ± 0.14	.46
Femoral neck									
Z-score	0.3 ± 0.9	0.3 ± 0.9	.52	−0.6 ± 0.7	−0.1 ± 0.9	.14	−0.06 ± 0.9	0.1 ± 0.9	.12
T-score	−0.2 ± 0.8	−0.2 ± 0.9	.87	−0.2 ± 0.9	−0.3 ± 0.9	.69	−0.2 ± 0.8	−0.2 ± 0.9	.66
aBMD (g/cm^2)	1.01 ± 0.13	0.98 ± 0.14	.06	1.02 ± 0.12	1.01 ± 0.12	.87	1.01 ± 0.12	0.99 ± 0.1	.09
One-third radius									
Z-score	−0.2 ± 1.4	0.1 ± 1.4	.06	−0.4 ± 0.8	−0.3 ± 0.8	.39	−0.3 ± 1.2	−0.03 ± 1.2	**.037**
T-score	−0.6 ± 1.4	−0.4 ± 1.4	.21	−0.7 ± 0.9	−0.3 ± 0.9	**.04**	−0.6 ± 1.2	−0.4 ± 1.2	**.024**
aBMD (g/cm^2)	0.67 ± 0.10	0.64 ± 0.18	.46	0.61 ± 0.55	0.78 ± 0.06	.24	0.64 ± 0.36	0.7 ± 0.2	.39
UDR									
Z-score	0.1 ± 2.1	0.8 ± 1.9	**.01**	0.3 ± 1.5	0.9 ± 1.4	**.007**	0.2 ± 1.8	0.8 ± 1.7	**.0003**
T-score	−0.2 ± 2.1	0.2 ± 1.9	.06	0.2 ± 1.4	0.8 ± 1.6	**.01**	−0.05 ± 1.8	0.5 ± 1.7	**.002**
aBMD (g/cm^2)	0.37 ± 0.08	0.40 ± 0.09	**.02**	0.42 ± 0.06	0.4 ± 0.08	**.0008**	0.39 ± 0.07	0.43 ± 0.09	**<.0001**

Significant *P*-values ($P < .05$) are given in bold text.
Abbreviations: #, number of subjects; aBMD, areal bone mineral density; BMI, body mass index; Cab, cabergoline; CTX, C-telopeptide; DXA, dual x-ray absorptiometry; E, eugonadal; GC, oral glucocorticoid; H, hypogonadal (premenopausal women or men) without replacement therapy; HR, hypogonadal on replacement therapy; LAR, octreotide LAR; n/a, not applicable; ND, not determined, ns, nonsignificant; P1NP, procollagen 1 intact N-terminal propeptide; PEG, pegvisomant; PM, postmenopausal on no replacement therapy; PMR, postmenopausal and on replacement therapy; S, surgery; T4, levothyroxine; UDR, ultradistal radius.

Table 2. Clinical characteristics, endocrine, metabolic, and anthropometric parameters in the 15 acromegaly patients who were studied by HRpQCT before and after surgery or octreotide LAR therapy

	Baseline (n = 15)	Follow-up (n = 15)	*P*-value, (pre- vs post-treatment)
Age (yr) (range)	46.6 ± 12.5 (24.9-69)	49.4 ± 13 (26.7-73)	n/a
Sex (F/M)	7/8	7/8	n/a
Height (cm)	177.5 ± 11.6	177 ± 11.2	.19
Weight (kg)	94.8 ± 15.5	92.3 ± 14.6	.11
BMI (kg/m^2)	30.1 ± 4.2	29.3 ± 4	.07
Duration of follow-up (median, range)		2.04 (1-7 yr)	ND
Newly diagnosed	13		n/a
Surgery	2	11	ND
Surgery and on octreotide LAR		4	n/a
Gonadal function	Females: E (4), PM (3); Males: E (6), HR (1), H (1)	Females: E (4), PM (3); Males: E (5), HR (3)	ND
Hormone replacements (#)		GC (1), T4 (1)	ND
Hypertension (#)	6	6	ND
Sleep apnea (#)	4	3	ND
Diabetes (#)	0	0	ND
Lipid-lowering therapy (#)	5	5	ND
Smoking (#)	3	3	ND
IGF-1 (ng/mL)	625 ± 197	211 ± 74	**<.0001**
IGF-1%ULN	242 ± 56	84 ± 27	**<.0001**
GH fasting (µg/L) (median, range)	3.69 (.31-25)	0.56 (.05-5.5)	**.0001**
Disease status (#)	Active (15)	Remission (13), active (2)	ND
CTX (ng/mL)	1.3 ± 0.8	0.4 ± 0.2	**.014**
P1NP (ng/mL)	85 ± 70	41 ± 29	**.046**
N-midOCN (ng/mL)	44.6 ± 42	15 ± 6.7	**.004**
TBS			
TBS acromegaly (n = 13)	1.327 ± 0.133	1.351 ± 0.142	.13
TBS acromegaly: % normal/% partially degraded/% degraded	46/31/23	54/23/23	ns
TBS controls	1.427 ± 0.103*	1.427 ± 0.103**	

Data are mean ± SD unless otherwise indicated. Significant *P*-values ($P < .05$) are given in bold text. TBS: *$P = .026$, **$P = .097$ acromegaly vs controls. TBS values were categorized as: TBS < 1.23 degraded and TBS 1.23–1.31 as partially degraded microarchitecture and TBS > 1.31 as normal (11).
Abbreviations: #, number of subjects; %ULN, percent upper limit of normal range; BMI, body mass index; CTX, C-telopeptide; E, eugonadal; GC, oral glucocorticoid; H, hypogonadal (premenopausal women or men) without replacement therapy; HR, hypogonadal on replacement therapy; HRpQCT, high-resolution peripheral quantitative tomography; LAR, octreotide LAR; n/a, not applicable; ND, not determined, ns, nonsignificant; N-midOCN, N-mid osteocalcin; P1NP, procollagen 1 intact N-terminal propeptide; PM, postmenopausal on no replacement therapy; T4, levothyroxine; TBS, trabecular bone score.

from 3 cohorts previously studied by Drs. Shane, Cohen, Nickolas, and Stein [27-30]; and 11 men who were studied concurrently as part of this study. Each acromegaly patient was matched to 3 to 5 controls for sex, age ± 5 years, and body mass index (BMI) ± 5 kg/m^2. Male controls were age 50 ± 12 years (mean ± SD; $P = .45$ vs acromegaly) with a mean BMI 30.2 ± 3.1 kg/m^2 ($P = .36$ vs acromegaly). Female controls were age 53 ± 11 years ($P = .59$. vs acromegaly) with a BMI 29.8 ± 3.2 kg/m^2 ($P = .74$ vs acromegaly).

The study was approved by the Institutional Review Board of Columbia University Medical Center. All subjects gave written informed consent before participation.

Design

Patients participated in 1 or more study visit at which they underwent anthropometric measurements (body weight by a digital scale to nearest 0.01 kg and height by a stadiometer to nearest 0.5 cm), fasting (morning) blood sampling, completion of questionnaires about their medical history, and DXA and/or HRpQCT testing. Blood samples from each visit were frozen at −80 °C in multiple aliquots and later assayed for measurements of IGF-1, GH, and markers of bone and mineral metabolism. Patients studied longitudinally participated in 2 to 5 visits that were conducted before and at 1- to 2-year intervals after treatment. Patients studied cross-sectionally participated in 1 visit.

Imaging Methods

aBMD of the total body, LS, total hip, FN, one-third (1/3R), and ultradistal radius (UDR) of the nondominant forearm were measured by DXA (software version 11.4; GE Lunar Prodigy Advance, Madison WI, USA) in the Metabolic Bone Disease Unit. The same densitometer with the same software and scan speed was used for all visits, and scanning was conducted by

Table 3. Cross-sectional HRpQCT cohort: clinical characteristics, endocrine, metabolic, and anthropometric parameters in 25 women and 24 men with acromegaly studied in active disease or in remission and the full HRpQCT cohort

	Women			Men			All acromegaly
	Active (n = 13)	Remission (n = 12)	*P*-value, active vs remission	Active (n = 11)	Remission (n = 13)	*P*-value, active vs remission	Women (n = 25), Men (n = 24)
Age (yr) (range)	51.4 ± 13.6 (26-69)	57.6 ± 11.7 (34-72)	.27	50.2 ± 13.9 (32-72)	51.8 ± 15.6 (20-71)	.79	52.5 ± 13.7
Height (cm)	164.7 ± 6.3	160.9 ± 7.3	.19	181.6 ± 7.5	184.7 ± 6.1	.28	173.4 ± 12.2
Weight (kg)	80.8 ± 17.6	76.1 ± 12.9	.48	103.1 ± 15.1	104.8 ± 17.8	.81	91.7 ± 20.3
BMI (kg/m^2)	29.8 ± 6.8	29.3 ± 3.8	.82	31.3 ± 4.7	30.9 ± 6.2	.86	30.4 ± 5.5
Newly diagnosed	9		n/a	6		n/a	15
Prior therapy (#)	S (2), S/Som (1), S/BC/LAR (1)	S (9), Sx2/RT (1), LAR/S (1), S/BC/Cab/PEG/S(1)	ND	S (1), S/BC (1), S/Cab (1), S/Cab/LAR (1), S/LAR (1)	S (12), Sx2 (1)	ND	S (24), Sx2 (1), Sx2/RT (1), S/Cab (1), LAR/S (2), S/BC (1), S/Som (1), S/BC/LAR (1), S/Cab/LAR (1), S/BC/Cab/PEG/S (1),
Years after surgery at bone testing	7.4 ± 7.2 (1-17)	8.9 ± 7.5 (1.8-23)	.74	6.1 ± 7.6 (0.5-18)	5.9 ± 5 (1.1-15.7)	.95	7.05 ± 6.3
Hormone replacements (#)		GC (1), T4 (5)	ND		GC (1), T4 (1)	ND	GC (2), T4 (6)
Gonadal function	PM (7), E (5), H (1)	PM (7), E (3), HR (1), H (1)	ND	E (8), H (2), HR (1)	E (9), HR (4)	ND	PM (14), E (25), HR (6), H (4)
Hypertension (#)	4	4	ND	5	5	ND	18
Sleep apnea (#)	2	1	ND	4	3	ND	10
Lipid-lowering therapy (#)	2	2	ND	5	5	ND	14
Diabetes (#)	1	0	ND	2	1	ND	4
Smoking	3 active	2 active, 3 former	ND	3 active, 3 former	5 active, 6 former	ND	13 active, 12 former
IGF-1 (ng/mL)	556 ± 195	169 ± 47	**<.0001**	610 ± 331	192 ± 90	**.0002**	385.9 ± 278
IGF-1%ULN	223 ± 69	75 ± 21	**<.0001**	238 ± 134	75 ± 22	**.0003**	154.2 ± 107.7
GH fasting (µg/L) (median, range)	4.45 (1.5-31.6)	1.16 (0.35-2.3)	**.0002**	7.02 (0.92-114)	0.48 (.05-4.8)	**<.0001**	1.756 (.05-114)
Calcium (#)	9.227 ± 0.46(12)	9.829 ± 0.39 (7)	.2	9.656 ± 0.35 (9)	9.457 ± .45(7)	.34	9.512 ± 0.4624
Vitamin D (#)	24.84 ± 6.95(10)	29.80 ± 2.775 (5)	.15	24.83 ± 14.83(9)	32.60 ± 9.236(5)	.31	27.03 ± 10.09
CTX (ng/mL)	1.05 ± 0.53	0.63 ± 0.39	**.06**	1.121 ± 0.57	0.408 ± 0.27	**.002**	0.8305 ± 0.54
P1NP (ng/mL)	68 ± 35.3	52.09 ± 20.9	.07	73.9 ± 35	52.15 ± 60.4	**.04**	62 ± 41
N-midOC (ng/mL)	39.9 ± 27	19.2 ± 9.85	**.01**	42.19 ± 36.4	24.30 ± 40.6	**.0007**	31.87 ± 31.73
Vitamin D status (%)	Low (19), borderline (36), normal (45)	Borderline (23), normal (77)	ND	Low (45), borderline (33), normal (22)	Low (12), borderline (54), normal (34)	ND	Low (18), borderline (37), normal (45)
Osteoporosis (%)	23	8.3	ns	9	7.6	ns	12

(*continued*)

Table 3. Continued

	Women			Men			All acromegaly
	Active (n = 13)	Remission (n = 12)	*P*-value, active vs remission	Active (n = 11)	Remission (n = 13)	*P*-value, active vs remission	Women (n = 25), Men (n = 24)
TBS	n = 13	n = 8	n/a	n = 12	n = 6	n/a	n = 39
TBS acromegaly	1.339 ± 0.111	1.217 ± 0.12	**.03**	1.348 ± 0.154	1.336 ± 0.125	.87	1.31 ± 0.13
TBS acromegaly: % normal/% partially degraded/% degraded	54/23/23	13/13/75	n/a	58/17/25	33/50/17	ns	44/23/33
TBS controls	1.373 ± 0.121*	1.344 ± 0.115**	n/a	1.410 ± 0.087*	1.388 ± 0.092*	n/a	1.38 ± .11***

Data are mean ± SD unless otherwise indicated. Significant *P*-values ($P < .05$) are given in bold text. Vitamin D status: low < 20 ng/mL, borderline 20-30 ng/nL, normal > 30 ng/mL. TBS: * P = ns, ** P = .028, *** P = .018 acromegaly vs controls. TBS values were categorized as: TBS <1.23 degraded and TBS 1.23-1.31 partially degraded microarchitecture and TBS > 1.31 normal (11).
Abbreviations: #, number of patients; %ULN, percent upper limit of normal range; aBMD, areal bone mineral density; BC, bromocriptine; BMI, body mass index; Cab, cabergoline; CTX, C-teleopeptide; E, eugonadal; GC, oral glucocorticoid; H, hypogonadal (premenopausal women or men) without replacement therapy; HR, hypogonadal on replacement therapy; HRpQCT, high-resolution peripheral quantitative tomography; LAR, octreotide LAR; n/a, not applicable; ND, not determined; ns, nonsignificant; P1NP, procollagen 1 intact N-terminal propeptide; PAS, pasireotide; PEG, pegvisomant; PM, postmenopausal on no replacement therapy; PMR, postmenopausal and on replacement therapy; RT, radiotherapy; S, surgery; Som, somatuline depot; T4, levothyroxine; TBS, trabecular bone score.

International Society for Clinical Densitometry-certified and trained technicians who matched identical regions of interest for baseline and follow-ups. Coefficient of variation (CV) is 0.68% for the spine, 1.36% for the total hip, and 0.70% for the radius.

Trabecular bone score (TBS) was calculated from DXA images of the LS utilizing TBSiNsight software (Version 1.9, Medimaps, Geneva, Switzerland). 3D structure is estimated based upon the amplitude of pixel value variation in a 2D projection [31]. For analysis of TBS, data were compared to controls (described earlier) and to published normative data that has established TBS <1.23 as degraded, TBS 1.23-1.31 as partially degraded, and TBS > 1.31 as normal microarchitecture [11].

Vertebral fracture analysis was performed in a consecutively enrolled, in the later years of our study, subset of patients (20 cross-sectional and 6 longitudinal). Lateral images of the thoracolumbar spine were acquired at time of DXA with the patient in the left lateral decubitus position. Images were inspected to rule out nonosteoporotic deformities. VF were diagnosed on visual inspection using the semiquantitative technique of Genant et al [32]. and graded as: grade 1 (mild): 20% to 25% reduction in height and 10% to 20% reduction in vertebral body area; grade 2 (moderate): >25% to 40% reduction in height with ≥ 20% to 40% reduction in area; and grade 3 (severe): ≥ 40% reduction in height and area [32].

HRpQCT was performed using the first-generation (XCT1; 82 µm; n = 56 scans) and subsequently the second-generation scanner (XCT2; 61 µm; n = 8 scans; Scanco Medical AG, Switzerland). Scans are acquired at the nondominant distal radius and tibia unless there is contraindication. Briefly, the region of interest is defined on a scout film by placing the reference line at the distal endplate of the radius or tibia and a series of parallel slices are acquired at a fixed offset. Attenuation data are converted to equivalent hydroxyapatite densities. Manufacturer's phantom is scanned regularly for quality control. Scans are scored for motion on a scale of 1 (no motion) to 5 (significant blurring of the periosteal surface, discontinuities in the cortical shell or streaking in the soft tissue). Images with a motion score of 4 to 5 are excluded from analyses. The standard HRpQCT analysis methods we use have been described, validated [33, 34], and applied in publications [24, 30, 35-38]. We use the manufacturer's standard method to filter and binarize the HRpQCT images [39]. To segment the cortical and trabecular regions, we use an automatic segmentation algorithm [40]. Due to differences in scanner generations, all data from XCT2 were calibrated to XCT1 using equations from an extensive cross-calibration study at our center [41]. Our in vivo short-term reproducibility (RMS-CV) for XCT1 measures is <1.06% for all density and <5.20% for all structural parameters [38]. Bone strength was also estimated from HRpQCT images by finite element analysis (FEA) based on the voxel conversion approach [42, 43]. We simulated uniaxial compression on each radius and tibia model up to 1% strain using a homogeneous Young's modulus of 6829 MPa and Poisson's ratio of 0.3 [44]. We use a custom FEA solver (FAIM, Version 6.0; Numerics88, Calgary, Alberta, Canada) on a desktop workstation (Linux Ubuntu 12.10, 2 × 6-core Intel Xenon, 64GB RAM) to solve the models [45, 46]. We estimated bone stiffness (stiffness, N/mm), a surrogate for bone strength, and failure load (F.load, N). Cortical porosity, bone stiffness, and F.load were measured only in acromegaly patients.

Hormone Assays

GH was measured by a 2-site, 22 kD GH specific chemiluminescence immunoassay (IDS-iSYS, Immunodiagnostic Systems, Tyne & Ware, UK; RRID:AB_2811291) calibrated to IRS 98/574 [47] that has intra- and inter-assay CVs of 2% to 4% and 5% to 7%, respectively, at GH concentrations of 1.7 to 27.5 μg/L. Assay sensitivity in our laboratory is 0.05 μg/L. IGF-1 was measured by a chemiluminescent immunoassay (IDS-iSYS; RRID:AB_2756880) calibrated to recombinant standard 02/254 [48] and has intra- and inter-assay CVs of 1.3% to 3.7% and 3.4% to 8.7%, respectively. IGF-1 levels were compared to the manufacturer's age- and sex-specific normative ranges [48]. Regarding mineral metabolism and bone turnover, intact procollagen type 1 N-terminal propeptide, C-telopeptide (CTX), and N-mid osteocalcin were measured by chemiluminescence assays (IDS-iSYS) on morning, fasting samples. Available data from clinical records on calcium and vitamin D levels were collected.

Statistical Analysis

Continuous variables were summarized by mean ± SD for normally distributed and as median and range for nonnormally distributed variables. Categorical variables were summarized by counts and percentages. For the cross-sectional analyses, HRpQCT parameters were compared in acromegaly patients to matched controls and in active vs remission groups by independent *t*-test. For the longitudinal study analyses, baseline to follow-up aBMD, TBS, and HRpQCT data were compared by paired *t*-test. Clinical and endocrine data were compared for the cross-sectional analyses by independent *t*-test or Mann-Whitney test as appropriate. Longitudinal clinical and endocrine data were compared by paired *t*-test or Wilcoxon signed-rank test. Fisher's exact test was used to compare proportions of patients with osteoporosis or osteopenia across groups. Spearman correlation was performed to examine the relationships between changes, percent and absolute, in HRpQCT parameters and those of TBS and bone markers and length of follow-up in the longitudinal study and between values of TBS, bone markers, HRpQCT parameters, and aBMD in the cross-sectional study. Using the cross-sectional data, simple linear and logistic regression models were constructed to examine potential predictors of HRpQCT parameters including presence of hypogonadism (defined as unreplaced low testosterone levels in men or secondary amenorrhea in premenopausal and postmenopausal state in women), newly diagnosed vs postoperative status, bone marker levels, and TBS score. *P*-values < .05 were considered significant. Statistical analyses were performed using GraphPad Prism version 9 for Mac.

Results

Longitudinal Testing

aBMD

Longitudinal assessment of aBMD was performed from before to after surgical treatment in 33 patients. Duration of follow up was ~3 years in the 19 women and ~ 2.5 years in the 14 men (Table 1). Eighty-two percent were in remission after surgery. In women, UDR aBMD ($P = .02$) and Z-score ($P = .01$) increased, but LS aBMD ($P = .03$) decreased. One woman, who became menopausal during the follow-up, transitioned from a LS T-score in the normal to osteopenic range. Two others transitioned from a UDR T-score in the osteoporotic to osteopenic range. Osteoporosis was present at 1 or more sites in 21% of women at baseline and 10.5% at follow-up ($P = .66$), and osteopenia was present in 47% at baseline and 42% at follow-up ($P = .99$).

Men had increases in total body aBMD ($P = .006$), LS Z-score ($P = .03$) and T-score ($P = .01$), 1/3R T-score ($P = .04$), and UDR Z-score ($P = .007$), T-score ($P = .01$), and aBMD ($P = .0008$). T-score at the 1/3R transitioned from the osteoporotic to osteopenic range in 1 man and from the osteopenic to normal range in another. UDR T-score transitioned from the osteopenic to normal range in 1 man and from the osteoporotic to osteopenic range in another. In 1 man, LS T-score transitioned from the normal to osteopenic range. Osteoporosis was present at 1 or more sites in 14.2% of men at baseline and 7% at follow-up ($P = .99$), and osteopenia was present in 64% at baseline as well as at follow-up ($P = .99$). The percentages of women, men, or patients overall with osteoporosis or osteopenia at each site before and after surgery did not differ.

TBS

TBS was analyzed on longitudinally acquired LS DXA images from 13 consecutive patients. TBS was lower than controls at baseline and showed a trend to be lower than controls after acromegaly surgery (Table 2). Neither TBS values nor the proportions that were normal, partially degraded, or degraded changed with acromegaly treatment.

HRpQCT

Fifteen patients underwent HRpQCT longitudinally, from before to ~ 2 years (median, range 1-7 yr) after surgical (n = 11), or long-acting somatostatin analog (n = 4) therapy (Table 2). Before and after treatment HRpQCT data are shown in Table 4, and Fig. 2 shows the posttreatment HRpQCT data expressed as a percentage of the baseline, pretreatment values. At the radius, treatment resulted in significant increases in total volumetric BMD (Tot.vBMD) ($P = .017$), cortical volumetric BMD (Ct.vBMD) ($P = .023$), and trabecular volumetric BMD (Tb.vBMD) ($P = .04$); an increase in trabecular number (Tb.N) ($P = .023$); and a lowering of trabecular separation (Tb.Sp) ($P = .016$). At the tibia, significant increases in Tot.vBMD ($P = .002$), Ct.vBMD ($P < .0001$), Tb.vBMD ($P = .009$), trabecular bone volume fraction (Tb.BV/TV) ($P = .008$), stiffness ($P = .0008$), and F.load ($P = .0008$) occurred with acromegaly treatment. Patterns of change for all HRpQCT parameters were similar in the surgically and octreotide LAR- treated patients.

Bone markers

Markers of bone formation (procollagen 1 intact N-terminal propeptide, N-mid osteocalcin) and resorption (CTX) fell significantly with treatment of acromegaly (Tables 1 and 2). The markers did not differ in their percentage of change with therapy ($P = .23$, ANOVA).

Associations between longitudinal changes

Changes in TBS, HRpQCT parameters, and bone markers with acromegaly treatment did not correlate with one another. Length of follow-up did not correlate with changes in HRpQCT parameters.

Table 4. HRpQCT parameters in 15 acromegaly patients studied longitudinally before, in active acromegaly, and after treatment with surgery or octreotide LAR therapy

	Baseline, pre-treatment active acromegaly (n = 15)	Follow-up, post-treatment acromegaly (n = 15)	Percent difference, baseline vs follow-up acromegaly	*P*-value, pre- vs post- treatment
Radius				
Total area (mm2)	333 ± 109	332 ± 109	−0.08	.49
Ct.area (mm2)	71 ± 18	72 ± 19	1.5	.069
Tb.area (mm2)	261 ± 99	259 ± 99	−0.6	.06
Ct.perimeter (mm)	82 ± 14	68 ± 34	0.2	.17
Tot.vBMD (mgHA/cm3)	311 ± 72	319 ± 74	2.4	**.017**
Ct.vBMD (mgHA/cm3)	834 ± 79	855 ± 78	2.6	**.023**
Tb.vBMD (mgHA/cm3)	139 ± 46	149 ± 10	2.1	**.04**
Tb.BV/TV (%)	12 ± 3	13 ± 3	1.9	.09
Ct.thickness (μm)	1.08 ± 0.25	1.05 ± 0.24	3.2	.19
Tb.number (1/mm)	1.87 ± 0.34	2.09 ± 0.35	13.2	**.023**
Tb.thickness (μm)	0.066 ± 0.01	0.061 ± 0.01	−4.9	.16
Tb.separation (μm)	0.49 ± 0.09	0.44 ± 0.10	−9.8	**.016**
Tb.separation SD (μm)	0.21 ± 0.05	0.14 ± 0.08	−5.7	**.04**
Ct.porosity (%)	2.1 ± 1	2.2 ± 1	23.8	.82
Stiffness (n/mm)	65 682 ± 18 569	66 346 ± 20 415	0.8	.71
F.load (n)	2770 ± 673	2812 ± 736	1.4	.49
Tibia				
Total area (mm2)	906 ± 182	906 ± 182	0.03	.66
Ct.area (mm2)	136 ± 18	136 ± 19	0.4	.66
Tb.area (mm2)	770 ± 178	769 ± 180	−0.2	.65
Ct.perimeter (mm)	118 ± 13	114 ± 37	1.9	.49
Tot.vBMD (mgHA/cm3)	267 ± 48	274 ± 50	2.7	**.002**
Ct.vBMD (mgHA/cm3)	825 ± 56	848 ± 54	2.9	**<.0001**
Tb.vBMD (mgHA/cm3)	156 ± 44	159 ± 46	2.6	**.009**
Tb.BV/TV (%)	12 ± 4	13 ± 4	2.6	**.008**
Ct.thickness (μm)	1.32 ± 0.24	1.33 ± 0.26	0.07	.79
Tb.number (1/mm)	1.93 ± 0.57	1.98 ± 0.49	6.3	.21
Tb.thickness (μm)	0.068 ± 0.01	0.067 ± 0.01	−0.01	.77
Tb.separation (μm)	0.57 ± 0.52	0.49 ± 0.27	−3.9	.28
Tb.separation SD (μm)	0.20 ± 0.08	0.13 ± 0.09	2.6	.09
Ct.porosity (%)	4.7 ± 2	4.7 ± 2	1.4	.85
Stiffness (n/mm)	170 356 ± 43 104	177 845 ± 44 898	4.4	**.0008**
F.load (n)	7450 ± 1368	7726 ± 1439	3.7	**.0008**

Significant *P*-values ($P < .05$) are given in bold text.
Abbreviations: Ct.area, cortical area; Ct.perimeter, cortical perimeter; Ct.porosity, cortical porosity; Ct.thickness, cortical thickness; Ct.vBMD, cortical volumetric bone mineral density; F.load, estimated failure load; HA, hydroxyapatite; HRpQCT, high-resolution peripheral quantitative tomography; LAR, octreotide LAR; Tb.area, trabecular area; Tb.separation, trabecular separation; Tb.BV/TV, trabecular bone volume/total volume; Tb.number, number of trabeculae; Tb.separation SD, trabecular separation heterogeneity; Tb.thickness, trabecular thickness; Tb.vBMD, trabecular volumetric bone mineral density; Tot.vBMD, total volumetric bone mineral density.

Cross-sectional Testing

HRpQCT

Characteristics of the cross-sectional HRpQCT study group are shown in Table 3. Acromegaly patients' HRpQCT parameters compared to those in matched healthy controls are shown in Table 5 and expressed as a percentage of those of controls in Fig. 3.

For acromegaly in remission see Fig. 3, left, and Table 5, left. Acromegaly patients in remission had significant differences in bone size, volumetric density, and trabecular microarchitecture compared to controls.

Men with acromegaly in remission had significantly larger bones with greater total area (Tot.A) ($P = .03$) and cortical perimeter (Ct.Pm) ($P = .004$) at the radius (Fig. 3A). Acromegaly men in remission had lower Tot.vBMD ($P = .011$) and ~ 20% lower Tb.vBMD ($P = .004$) and Tb.BV/TV ($P = .0005$) than controls (Fig. 3B). Tb.N ($P = .03$) and thickness (Tb.Th) ($P = .02$) were lower and Tb.Sp ($P = .03$) was higher than controls (Fig. 3C). At the tibia men in remission had greater Tot.A ($P = .003$), trabecular area (Tb.A) ($P = .002$), and Ct.Pm ($P = .0006$) (Fig. 3A) but lower Tot.vBMD($P = .006$) and Ct.vBMD($P = .008$)(Fig. 3B) than controls.

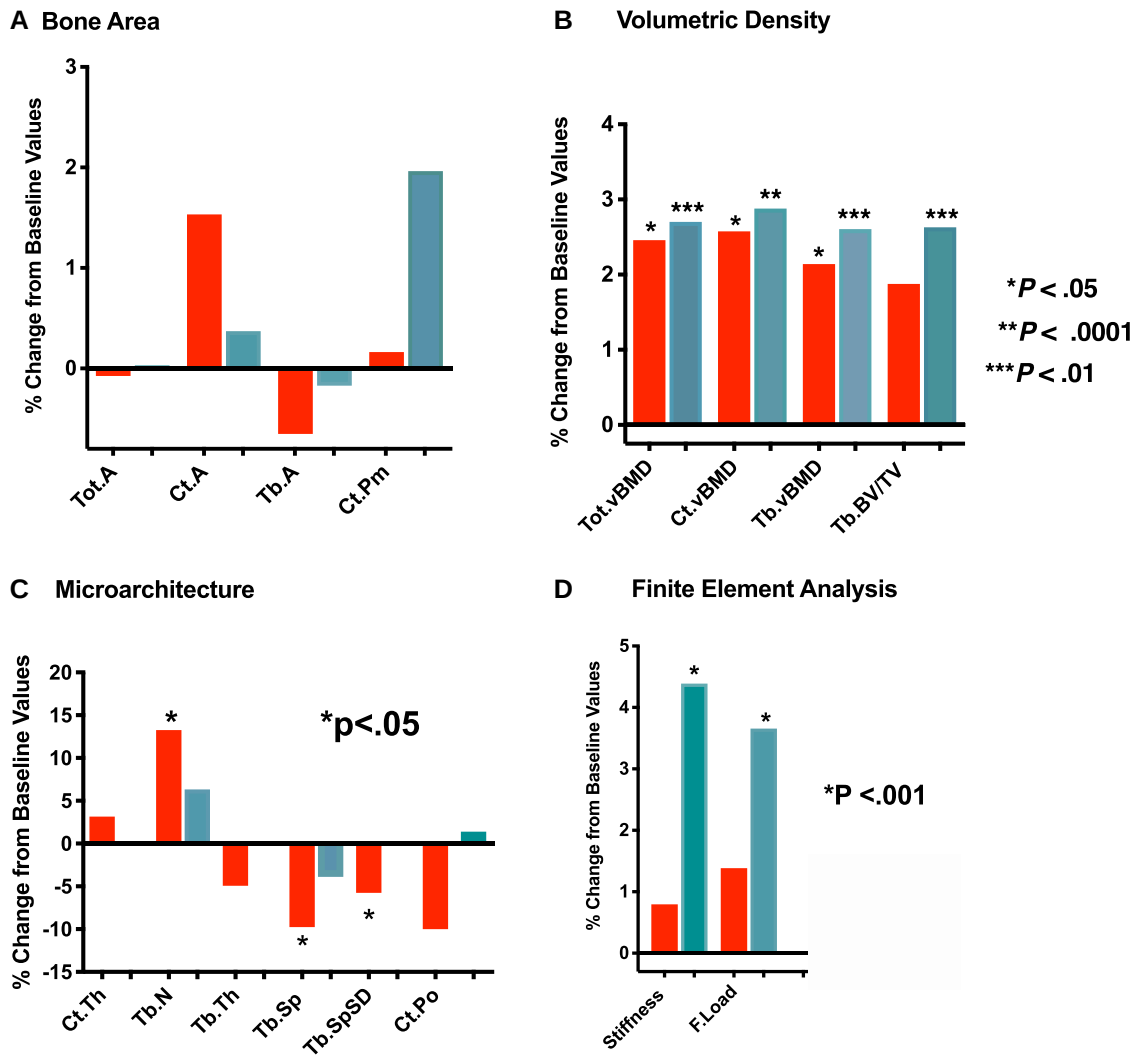

Figure 2. Longitudinal HRpQCT testing results. Percentage change from baseline to after surgical or medical therapy of parameters of bone area (A), volumetric density (B), microarchitecture (C), and finite element analysis of the radius (red) and tibia (teal) (D).
Abbreviations: Ct.A. cortical area; Ct.Pm, cortical perimeter; Ct.Po, cortical porosity, Ct.Th, cortical thickness; Ct.vBMD, cortical volumetric bone mineral density; F.load, estimated failure load; HRpQCT, high-resolution peripheral quantitative tomography; Tb.A, trabecular area; Tb.BV/TV, trabecular bone volume/total volume; Tb.N, number of trabeculae; Tb.Sp, trabecular separation; Tb.SpSD, trabecular separation heterogeneity; Tb.Th, trabecular thickness; Tb.vBMD, trabecular volumetric bone mineral density; Tot.A, total area; Tot.vBMD, total volumetric bone mineral density.

Women with acromegaly in remission had larger bones with greater cortical area (Ct.A) ($P = .009$) at the radius (Fig. 3A). At the radius, they had ~ 18% lower Tb.vBMD ($P = .039$) and Tb.BV/TV ($P = .038$) (Fig. 3B), higher cortical thickness (Ct.Th) ($P = .002$), and lower Tb.Th ($P = .0005$) than controls (Fig. 3C). In the tibia, women with acromegaly in remission had ~18% lower Tb.vBMD ($P = .026$) and Tb.BV/TV ($P = .026$) (Fig. 3B) and higher Ct.Th ($P = .021$) but lower Tb.Th ($P = .006$) than controls (Fig. 3C).

For active acromegaly, see Fig. 3, right, and Table 5, right. Patients with active acromegaly had significant differences in bone size, volumetric density, and trabecular microarchitecture compared to controls, and these differences tended to be greater than those in patients in remission. Men with active acromegaly had, at the radius, greater Ct.A ($P = .004$) and Ct.Pm ($P = .008$), ~25% lower Tb.vBMD ($P = .0003$) and Tb.BV/TV ($P = .0003$), ~6% lower Ct.vBMD ($P = .019$), higher Ct.Th ($P = .03$), lower Tb.N ($P = .004$), and greater Tb.Sp. ($P = .006$) than controls. At the tibia, men with active acromegaly had greater Tb.A ($P = .036$) and Ct.Pm ($P = .012$), ~11% lower Tot.vBMD ($P = .005$), and ~6% lower Ct.vBMD($P = .0006$) than controls. Women with active acromegaly had, at the radius, greater Ct.A ($P = .009$) and Ct.Pm ($P = .016$), ~ 27% lower Tb.vBMD ($P = .003$) and Tb.BV/TV ($P = .003$), higher Ct.Th ($P = .005$), and lower Tb.N ($P = .006$) than controls. In the tibia, women with active acromegaly had ~ 28% lower Tb.vBMD ($P = .003$) and Tb.BV/TV ($P = .003$), higher Ct.Th ($P = .011$), and lower Tb.Th ($P = .033$) than controls.

In a post hoc analysis, HRpQCT parameters were compared in active vs remission groups. Ct.Pm ($P = .002$) was greater in the active group, but we found no other significant differences, including none in cortical porosity or FEA results.

Associations between HRpQCT parameters, TBS, bone markers, gonadal function, and disease status were tested in the cross-sectional data. TBS correlated positively with LS T score ($r = 0.7$, $P < .0001$), LS BMD($r = 0.7$, $P < .0001$), FN T-score ($r = 0.405$, $P = .014$), FN BMD ($r = 0.409$, $P = .014$), Tb.vBMD ($r = 0.319$, $P = .048$), and BV/TV ($r = 0.319$, $P = .048$) of the radius and Tot.vBMD ($r = 0.403$, $P = .011$),

Table 5. Cross-sectional HRpQCT data in 49 patients with acromegaly compared to controls

	Acromegaly in remission								Active acromegaly								All acromegaly		
	Women				Men				Women				Men						
	Acromegaly (n = 12)	Controls	% diff., acro vs ctls	*P*-value, acro vs ctls	Acromegaly (n = 13)	Controls	% diff., acro vs ctls	*P*-value, acro vs ctls	Acromegaly (n = 13)	Controls	% diff., acro vs ctls	*P*-value, acro vs ctls	Acromegaly (n = 11)	Controls	% diff. acro vs ctls	*P*- value, acro vs ctls	Acromegaly (n = 49)	Controls	*P*-value, acro vs ctls
Radius																			
Total area (mm2)	267 ± 44	241 ± 16	10.8	.066	426 ± 95	363 ± 19	17.6	**.03**	259 ± 40	237 ± 20	9.3	.088	409 ± 81	369 ± 27	11	.13	339 ± 104	301 ± 67	**.03**
Ct.area (mm2)	59 ± 6	53 ± 5	11.9	**.009**	85 ± 18	76 ± 4	11.2	.11	68 ± 16	55 ± 4	23.1	**.009**	92 ± 17	75 ± 4	22.8	**.004**	76 ± 194	65 ± 11	.0009
Tb.area (mm2)	208 ± 46	188 ± 17	10.7	.17	341 ± 99	286 ± 4	19.3	.061	192 ± 46	181 ± 22	6.2	.43	318 ± 77	294 ± 28	7.9	.35	263 ± 96	235.± 57	.09
Ct.perimeter (pm)	69 ± 6	67 ± 2	4.5	.11	93 ± 9	81 ± 8	13.9	**.004**	70 ± 5	66 ± 3	6.3	**.016**	93 ± 10	83 ± 4	11.6	**.008**	81 ± 14	74 ± 9	**.004**
Tot.vBMD (mgHA/cm3)	302 ± 72	333 ± 38	−9.3	.2	293 ± 59	340 ± 19	−13.9	**.011**	323 ± 89	350 ± 46	−7.6	.34	306 ± 53	339 ± 15	−9.9	.057	308 ± 69	341 ± 32	**.003**
Ct.vBMD (mgHA/cm3)	858 ± 49	877 ± 25	−2.1	.27	812 ± 76	853 ± 18	−4.8	.072	861 ± 79	893 ± 29	−3.6	.18	805 ± 62	855 ± 23	−5.9	**.019**	835 ± 72	870 ± 29	**.002**
Tb.vBMD (mgHA/cm3)	128 ± 42	157 ± 17	−18.3	**.039**	145 ± 34	181 ± 23	−19.9	**.004**	117 ± 42	161 ± 25	−27.2	**.003**	144 ± 34	192 ± 13	−25.2	**.0003**	133 ± 39	172 ± 24	**<.0001**
Tb.BV/TV (%)	11 ± 4	13 ± 1	−18.7	**.038**	12 ± 3	15 ± 1	−22.1	**.0005**	9 ± 4	13 ± 2	−27.3	**.003**	12 ± 3	16 ± 1	−25.1	**.0003**	11 ± 3	14 ± 2	**<.0001**
Ct.thickness (μm)	0.99 ± 0.17	0.81 ± 0.10	23.8	**.002**	1.05 ± 0.25	0.93 ± 0.06	13	.105	1.14 ± 0.32	0.85 ± 0.10	33.2	**.005**	1.12 ± 0.27	0.94 ± 0.07	20.9	**.03**	1.08 ± 0.26	0.88 ± 0.09	**<.0001**
Tb.number (1/mm)	1.93 ± 0.49	2.01 ± 0.17	−3.9	.6	1.97 ± 0.35	2.20 ± 0.11	−10.3	**.03**	1.58 ± 0.02	2.018 ± 0.27	−21.1	**.006**	1.85 ± 0.41	2.26 ± 0.10	−18.2	**.004**	1.83 ± 0.44	2.12 ± 0.21	**.0001**
Tb.thickness (μm)	0.056 ± 0.01	0.066 ± 0.01	−14.1	**.0005**	0.062 ± 0.01	0.071 ± 0.01	−11.5	**.02**	0.061 ± 0.02	0.066 ± 0.01	−6.6	.39	0.066 ± 0.01	0.071 ± .01	−7.2	.21	0.061 ± 0.01	0.068 ± 0.01	**.0009**
Tb.separation (μm)	0.51 ± 0.21	0.45 ± 0.06	12.8	.36	0.47 ± 0.12	0.39 ± 0.02	21.1	**.03**	0.64 ± 0.28	0.46 ± 0.12	36.9	**.05**	0.50 ± 0.13	0.37 ± 0.02	33.7	**.006**	0.53 ± 0.21	0.42 ± 0.08	**.0007**
Tb.separation SD (μm)	0.25 ± 0.17	0.22 ± 0.08	16	.53	0.23 ± 0.12	0.16 ± 0.01	44.4	**.044**	0.33 ± 0.25	0.23 ± 0.11	52.3	.16	0.24 ± 0.13	0.15 ± 0.03	60.9	**.028**	0.26 ± 0.18	0.19 ± 0.08	**.006**
Tibia																			
Total area (mm2)	714 ± 138	667 ± 30	7.1	.26	1017 ± 129	893 ± 44	13.9	**.003**	743 ± 139	662 ± 38	12.2	.054	979 ± 120	904 ± 31	8.3	.057	862 ± 188	779 ± 124	**.01**
Ct.area (mm2)	116 ± 18	111 ± 12	5.2	.37	148 ± 19	160 ± 16	−7	.12	130 ± 20	118 ± 11	10.4	.065	146 ± 19	158 ± 17	−7.9	.12	135 ± 23	136 ± 27	.83
Tb.area (mm2)	598 ± 140	556 ± 40	7.4	.34	869 ± 131	733 ± 49	18.4	**.002**	614 ± 149	545 ± 45	12.6	.12	834 ± 128	746 ± 26	11.8	**.036**	727 ± 183	643 ± 104	**.006**
Ct.perimeter (pm)	104 ± 10	102 ± 3	1.3	.65	127 ± 88	118 ± 3	8.1	**.0006**	107 ± 107	1017 ± 37	5.5	.068	125 ± 8	118 ± 2	6.1	**.012**	116 ± 14	109 ± 9	**.01**
Tot.vBMD (mgHA/cm3)	262 ± 64	287 ± 29	−8.6	.24	264 ± 42	308 ± 31	−14.3	**.006**	260 ± 78	302 ± 32	−13.9	.083	265 ± 33	299 ± 15	−11.5	**.005**	263 ± 57	299 ± 28	**.0001**
Ct.vBMD (mgHA/cm3)	846 ± 78	858 ± 33	−1.4	.63	805 ± 49	848 ± 23	−5.1	**.008**	839 ± 79	877 ± 33	−4.3	.12	796 ± 40	854 ± 26	−6.8	**.0006**	822 ± 66	859 ± 30	**.0005**
Tb.vBMD (mgHA/cm3)	133 ± 42	164 ± 16	−18.9	**.026**	163 ± 35	182 ± 2	−10.8	.097	122 ± 48	171 ± 20	−28.4	**.003**	164 ± 28	175 ± 7	−6.2	.24	145 ± 43	173 ± 18	**<.0001**
Tb.BV/TV (%)	11 ± 4	3 ± 1	−18.8	**.026**	13 ± 3	15 ± 2	−10.5	.1	10 ± 4	14 ± 2	−28.6	**.003**	13 ± 2	14 ± 1	−6.8	.22	12 ± 3	14 ± 1	**<.0001**

(*continued*)

Table 5. Continued

	Acromegaly in remission								Active acromegaly								All acromegaly		
	Women				Men				Women				Men						
	Acromegaly (n = 12)	Controls	% diff., acro vs ctls	*P*-value, acro vs ctls	Acromegaly (n = 13)	Controls	% diff., acro vs ctls	*P*-value, acro vs ctls	Acromegaly (n = 13)	Controls	% diff., acro vs ctls	*P*-value, acro vs ctls	Acromegaly (n = 11)	Controls	% diff. acro vs ctls	*P*- value, acro vs ctls	Acromegaly (n = 49)	Controls	*P*-value, acro vs ctls
Ct.thickness (μm)	1.29 ± 0.26	1.08 ± 0.14	19.3	**.021**	1.34 ± 0.18	1.38 ± 0.17	−2.5	.64	1.42 ± 0.31	1.17 ± 0.13	21.8	**.011**	1.34 ± 0.24	1.38 ± 0.15	−2.7	.67	1.35 ± 0.25	1.25 ± 0.19	**.03**
Tb.number (1/mm)	1.71 ± 0.50	1.85 ± 0.14	−7.5	.37	2.04 ± 0.48	2.13 ± 0.11	−4.2	.52	1.60 ± 0.64	1.92 ± 0.18	−16.4	.11	2.09 ± 0.40	2.15 ± 0.11	−2.9	.63	1.86 ± 0.55	2.01 ± 0.19	.06
Tb. thickness (μm)	0.066 ± 0.01	0.074 ± 0.01	−11.2	**.006**	0.067 ± 0.01	0.071 ± 0.01	−5.6	.29	0.065 ± 0.01	0.075 ± 0.01	−13.2	**.033**	0.066 ± 0.01	0.067 ± .01	−2.9	.57	0.066 ± 0.01	0.072 ± 0.01	**.002**
Tb.separation (μm)	0.58 ± 0.23	0.49 ± 0.05	18.2	.19	0.47 ± 0.22	0.41 ± 0.03	14.8	.33	0.73 ± 0.56	0.47 ± 0.07	55.7	.12	0.44 ± 0.13	0.41 ± 0.03	6.8	.49	0.56 ± 0.34	0.44 ± 0.05	**.03**
Tb. separation SD (μm)	0.35 ± 0.22	0.24 ± 0.05	48.6	.093	0.22 ± 0.17	0.18 ± 0.02	22.7	.4	0.53 ± 0.69	0.22 ± 0.05	142.8	.14	0.19 ± 0.09	0.18 ± 0.02	9.2	.57	0.33 ± 0.39	0.21 ± 0.04	**.03**

Data are given for 25 women and men with acromegaly in remission, 24 women and men with active acromegaly, and all 49 acromegaly patients combined. Significant *P*-values ($P < .05$) are given in bold text.
Abbreviations: % diff, percent difference; acro, acromegaly; Ct.area, cortical area; ctls, controls; Ct.perimeter, cortical perimeter; Ct.porosity, cortical porosity; Ct.thickness, cortical thickness; Ct.vBMD, cortical volumetric bone mineral density; HA, hydroxyapatite; HRpQCT, high-resolution peripheral quantitative tomography; LAR, octreotide LAR; Tb.area, trabecular area; Tb.separation, trabecular separation; Tb.BV/TV, trabecular bone volume/total volume; Tb.number, number of trabeculae; Tb.separation SD, trabecular separation heterogeneity; Tb.thickness, trabecular thickness; Tb.vBMD, trabecular volumetric bone mineral density; Tot.vBMD, total volumetric bone mineral density.

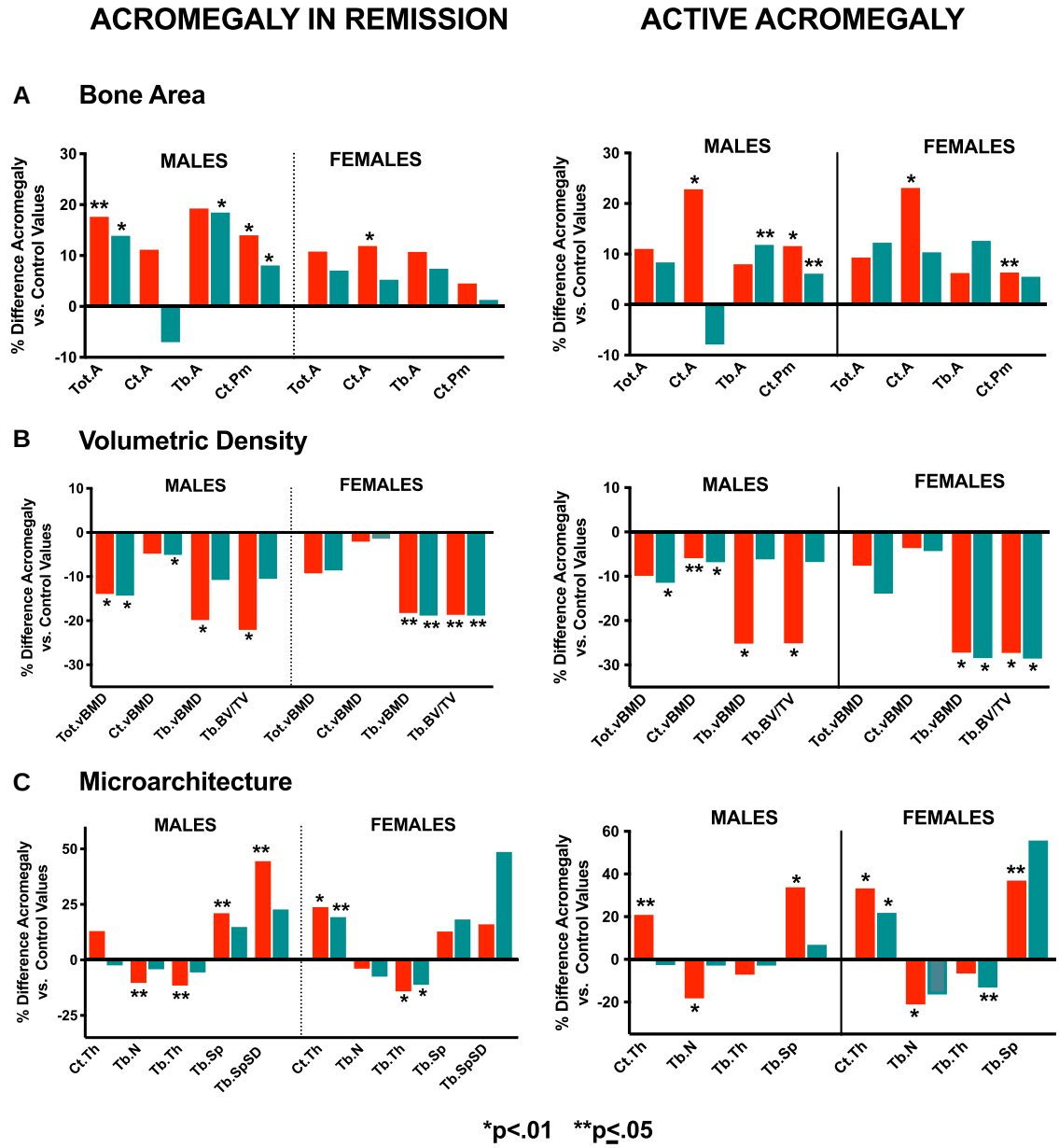

Figure 3. Cross-sectional HRpQCT testing results: Percentage difference in parameters of bone area (A), density (B), and microarchitecture of the radius (red) and tibia (teal) (C) in patients with acromegaly in remission (left) or active acromegaly (right) compared to controls.
Abbreviations: Ct.A, cortical area; Ct.Pm, cortical perimeter; Ct.Po, cortical porosity, Ct.Th, cortical thickness; Ct.vBMD, cortical volumetric bone mineral density; F.load, estimated failure load; HRpQCT, high-resolution peripheral quantitative tomography; Tb.A, trabecular area; Tb.BV/TV, trabecular bone volume/total volume; Tb.N, number of trabeculae; Tb.Sp, trabecular separation; Tb.SpSD, trabecular separation heterogeneity; Tb.Th, trabecular thickness; Tb.vBMD, trabecular volumetric bone mineral density; Tot.A, total area; Tot.vBMD, total volumetric bone mineral density.

Tb.vBMD (r = 0.462, $P = .003$), BV/TV (r = 0.462, $P = .003$), and Tb.N (r = 0.404, $P = .011$) of the tibia. TBS correlated negatively with Tb.Sp (r = −0.405, $P = .009$) of the tibia and CTX (r = −.338, $P = .038$). In regression analysis, neither disease status (active vs remission or newly diagnosed vs postoperative) nor time from surgical treatment to bone assessment or bone marker values were predictors of HRpQCT parameters. Hypogonadism was a negative predictor of some HRpQCT parameters including density, area, stiffness, and F.load of the radius and tibia (Table 6) and of TBS (β= −12 (SE 3.98), $P = .0025$).

Vertebral fractures

Of the 20 patients in the cross-sectional analysis who were assessed for VF, 4 patients with active disease had fractures: 1 hypogonadal, premenopausal woman had a grade 1 fracture and 2 men, 1 eugonadal and 1 on testosterone replacement, each had 1 grade 1 fracture. One eugonadal man had 2 fractures, 1 grade 1 and 1 grade 2. Of the 6 patients who were followed longitudinally from before to after surgery, none had a VF at baseline or in follow up. X-rays were not done to confirm VFs.

Discussion

In this study, the first to longitudinally assess bone quality using HRpQCT in patients with acromegaly, we found improvements in volumetric BMD, microarchitecture, biomechanical stiffness (strength), and F.load of the peripheral skeleton

Table 6. Associations between hypogonadism and microstructural parameters measured by HRpQCT in the cross-sectional HRpQCT cohort (n = 49)

	Radius		Tibia	
	β coefficient (SE)	*P*-value	*β* coefficient (SE)	*P*-value
Total area (mm2)	−.013 (.004)	**.001**	−.004(.002)	**.03**
Ct. area (mm2)	−.051 (.02)	**.004**		ns
Tb.area (mm2)	−.012 (.005)	**.004**	−.004(.002)	**.032**
Ct.perimeter (mm)	−.099 (.034)	**<.001**	−.047 (.02)	**.026**
Tot.vBMD (mgHA/cm3)	−.0037 (.007)	**.001**		ns
Tb.vBMD (mgHA/cm3)	−.0167 (.008)	**.04**	−.019 (.008)	**.017**
Tb.BV/TV (%)	−.0137 (.0087)	**.04**	−23 (9)	**.017**
Tb.number (1/mm)		ns	−1.15 (.59)	**.04**
Tb.thickness (μm)		ns		ns
Tb.separation (μm)		ns	2.96 (1.5)	**.013**
Stiffness (n/mm)	−.00007 (.00002)	**<.001**	−.00003(.00019)	**.003**

Significant *P*-values ($P < .05$) are given in bold text.
Abbreviations: Ct.area, cortical area; Ct.perimeter, cortical perimeter; HA, hydroxyapatite; HRpQCT, high-resolution peripheral quantitative tomography; ns, nonsignificant; Tb.area, trabecular area; Tb.vBMD, trabecular volumetric bone mineral density; Tb.BV/TV, trabecular bone volume/total volume; Tb.number, number of trabeculae; Tb.separation, trabecular separation; Tb.thickness, trabecular thickness; Tot.vBMD, total volumetric bone mineral density.

with acromegaly treatment. We also found increases in aBMD (by DXA) at some sites and a trend for TBS to improve after surgical treatment. However, we also newly show that patients in remission after surgery have lower volumetric BMD and disrupted microarchitecture compared to controls. Similar deficits were present, most to a greater degree, in patients with active disease. These data suggest that despite improvements in acromegaly treatment, deficits in bone quality persist. Since these associate with skeletal fragility and VF in other populations, they may play a role in promoting VF in acromegaly.

We longitudinally assessed the effects of acromegaly treatment on aBMD by DXA, TBS, and vBMD and microarchitecture of the distal radius and tibia by HRpQCT. With surgical treatment alone, aBMD improved at the radius but deteriorated at the spine in women and improved at the total body, spine, and radius sites in men. Very few other longitudinal studies have reported the effects of surgical/medical therapy on aBMD. In 1 study, aBMD did not change [49], and in another increases in aBMD of the LS and UDR and trends for increases in aBMD of the 1/3R and hip were observed [50]. aBMD seemed to improve more in men in our study, possibly because of the relatedly lower rate of hypogonadism among them in our cohort. Others have reported greater increases in aBMD in eugonadal patients [50]. We found no change in TBS after acromegaly surgery, but scores were closer to controls at follow-up suggesting an improvement. The small sizes of our TBS analysis groups could have led to underestimation of its change with treatment. However, prior studies conflict with regard to the effect of acromegaly treatment on TBS; TBS rose [15], was unchanged [51, 52], or decreased [50].

On longitudinal HRpQCT testing we found increases in volumetric density and estimates of strength and improvements in microarchitecture with acromegaly treatment. Specifically, at the radius, Tot.vBMD, Ct.vBMD, Tb.vBMD, and Tb.N increased and Tb.Sp was lowered and at the tibia, Tot.vBMD, Ct.vBMD, Tb.vBMD, and Tb.BV/TV increased with acromegaly treatment. FEA also demonstrated improvements in stiffness and F.load of the tibia. These surrogate measures of strength relate to fragility fractures, independent of DXA, in other populations [17, 35, 53, 54] and could be markers of fracture risk in acromegaly. Most of the patients in the prospective HRpQCT study were surgically treated, but 4 were tested before and after octreotide LAR therapy. HRpQCT parameters changed similarly with both treatments. Although octreotide suppressed osteoblasts in 1 vitro study [55], prior cross-sectional HRpQCT studies, which included 57% [56], 67% [57], or unspecified [58, 59] percentages of somatostatin receptor ligand-treated patients did not report differential effects of surgical vs somatostatin receptor ligand treatment, and a recent study found VF rate to be independent of type of acromegaly medical therapy [60]. These data do not suggest that inclusion of octreotide LAR-treated patients biased our longitudinal studies' results. However, the potential differential effects of acromegaly therapies on bone quality warrants further study.

Given prior reports of an increased rate of incident VF among treated acromegaly patients, we aimed to determine the extent to which microstructural abnormalities persist in patients in remission after surgery. We found that men and women in remission had larger bone size, lower trabecular density, and disrupted microarchitecture at the radius and lower trabecular density at the tibia compared to controls. Men also had larger bone size and lower cortical volumetric density and women disrupted microarchitecture at the tibia. Since no prior HRpQCT study specifically compared patients in remission to controls, ours is novel evidence of these deficits in successfully surgically treated patients. In this study, we also cross-sectionally evaluated patients with active disease compared to controls using HRpQCT as did 2 prior studies [56, 58], but 2 others reported data from combined active and controlled disease cohorts [57, 59]. Overall, ours and prior studies found that bone size is increased [56-58], volumetric density is reduced, and bone microarchitecture is disrupted [56-59] in active acromegaly. We, as did others, found similar microstructural parameters in active and remission/controlled acromegaly groups [56, 57, 59, 61], and disease activity did not predict these parameters in our regression analysis.

However, since we separately compared active and remission groups to controls in the same study, we were able to appreciate that the degree of deviation from controls seemed greater in the active compared to remission groups. This is consistent with the improvements that we observed in our longitudinal study.

We also explored the potential relationships of abnormal microarchitecture in acromegaly to treatment stage and gonadal function. Of our active disease patients, 62% were newly diagnosed and untreated whereas this percentage was only 3% [56], 1.5% [57] or unspecified [58, 59] in other studies. Newly diagnosed vs prior treatment status was not a predictor of microstructural parameters in our regression analysis. However, hypogonadism was a negative predictor of a number of these parameters. This finding is consistent with prior studies in which, using a variety of techniques, hypogonadal patients had lower vBMD and more disrupted microarchitecture in the peripheral skeleton [59, 61] as well as reduced spinal volumetric trabecular bone mass [62]. Importantly, however, microarchitectural abnormalities persisted in eugonadal patients in prior studies [58, 59], and the men in remission in our HRpQCT cross-sectional study group, who were all eugonadal, had significantly reduced vBMD and disrupted microarchitecture. Thus, although hypogonadism accentuates the abnormalities of bone structure in acromegaly, it does not appear to be the only etiology of this. A strength of our study is our sex-specific analyses of HRpQCT data; normal values for these are sex specific [11]. Prior HRpQCT studies examined just men [58], women [56] or both sexes combined [57, 59], but we could appreciate sex differences in microstructural abnormalities. For example, in men the tibia appeared less affected than the radius and than the tibia in women, suggesting less protection from weight bearing in the tibia of women. VF risk is higher in men than women with acromegaly, and characterizing sex-specific abnormalities is relevant to understanding this difference in risk.

TBS has been found to be overall lower in acromegaly regardless of disease activity and gonadal function [13] or to not differ [4] from nonacromegaly populations. In our study, TBS was lower than controls at baseline in our longitudinal group and in women tested cross-sectionally in remission, who were mostly postmenopausal and, overall, had lower LS aBMD than other groups. We found positive relationships of TBS to aBMD of the LS and FN, as expected from data in other populations [11, 63]. Interestingly, TBS correlated positively with some volumetric density and microarchitectural parameters of the radius and tibia. Since in other data lower TBS signifies worse microarchitecture that relates to fragility fractures [64, 65], low TBS is likely to be evidence of disrupted vertebral trabecular microarchitecture in acromegaly. This may relate to higher bone remodeling, which negatively impacts microstructure, leading to trabecular perforation and dropout. TBS and bone marker values did not correlate in our study, but we found, as expected, higher bone marker levels in active disease than remission and a lowering of them with acromegaly treatment [4].

A limitation of our study is that it was not designed to evaluate VF rate. We assessed for VF in only a third of our cohort and did this by vertebral fracture analysis, which has a lower sensitivity for grade 1 than grade 2 and 3 fractures [66]. This limitation needs to be considered in the interpretation of our findings of no incident VF in the 6 longitudinally followed patients and a low VF rate among patients assessed cross-sectionally. In prior studies, rates of prevalent and incident VF remained increased in treated acromegaly patients [5-8, 10] and some of the peripheral microstructural abnormalities we found in patients in remission were associated with VF in 1 [61], but not another [56] study. However, the improvements in density, microstructure, and strength estimates we detected could have mitigated VF risk. Also, our cohort seemed to differ from those of prior VF studies with regard to factors that increase fracture risk in that ours had a lower proportion of patients with hypogonadism and receiving glucocorticoid replacement [10]. Less hypopituitarism in our cohort may partially explain why we detected improvements in bone quality with acromegaly treatment. With our study size, we could not test for an association of VF with microstructural abnormalities, and additional studies are needed to examine whether HRpQCT findings predict VF in acromegaly.

Other limitations of our study should be considered. Interpretation of our results should consider that our longitudinal studies were small in size and patients varied in their length of follow-up. Some of our patients had vitamin D deficiency, and in some this was corrected at the time of longitudinal follow-up, which could have been a factor in our findings. However, other studies have reported similar microarchitectural changes in patients who appeared to be vitamin D replete [56, 58]. Prior studies found more disrupted microarchitecture in acromegaly patients with than without type 2 diabetes, but our study included only a small number of patients with diabetes. The fact that some of our subgroups included very few hypogonadal patients limited our ability consider gonadal function in all analyses. Also, acromegaly is a heterogeneous disease, so factors that we could not adjust for may have contributed to our results.

In conclusion, we show, for the first time in a longitudinal study of bone structure assessed by HRpQCT, that acromegaly treatment is associated with improvements in vBMD and microarchitecture, stiffness, and F.load. However, patients in remission after surgery have persistently reduced vBMD and microarchitectural abnormalities. We did not assess VF in the majority of our patients, but the abnormalities we found are associated with lower bone strength and prevalent fractures in other populations. TBS did not clearly change with acromegaly treatment but did relate to a number of microstructural abnormalities in these patients. Further studies are warranted to understand how to identify, potentially by HRpQCT abnormalities, those patients with continued poor bone quality despite successful acromegaly treatment.

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Disclosures

The authors have nothing to disclose.

Data Availability

Original data generated and analyzed during this study are included in this published article.

Clinical Trial Information

NCT01809808, NCT03225040.

References

1. Giustina A, Mazziotti G, Canalis E. Growth hormone, insulin-like growth factors, and the skeleton. *Endocr Rev*. 2008;29(5):535-559.
2. Halse J, Melsen F, Mosekilde L. Iliac crest bone mass and remodelling in acromegaly. *Acta Endocrinol (Copenh)*. 1981;97(1):18-22.
3. Mazziotti G, Biagioli E, Maffezzoni F, *et al*. Bone turnover, bone mineral density, and fracture risk in acromegaly: a meta-analysis. *J Clin Endocrinol Metab*. 2015;100(2):384-394.
4. Ribeiro de Moura C, Campos Lopes S, Monteiro AM. Determinants of skeletal fragility in acromegaly: a systematic review and meta-analysis. *Pituitary*. 2022;25(6):780-794.
5. Mazziotti G, Bianchi A, Bonadonna S, *et al*. Prevalence of vertebral fractures in men with acromegaly. *J Clin Endocrinol Metab*. 2008;93(12):4649-4655.
6. Bonadonna S, Mazziotti G, Nuzzo M, *et al*. Increased prevalence of radiological spinal deformities in active acromegaly: a cross-sectional study in postmenopausal women. *J Bone Miner Res*. 2005;20(10):1837-1844.
7. Wassenaar MJ, Biermasz NR, Hamdy NA, *et al*. High prevalence of vertebral fractures despite normal bone mineral density in patients with long-term controlled acromegaly. *Eur J Endocrinol*. 2011;164(4):475-483.
8. Mazziotti G, Bianchi A, Porcelli T, *et al*. Vertebral fractures in patients with acromegaly: a 3-year prospective study. *J Clin Endocrinol Metab*. 2013;98(8):3402-3410.
9. Scillitani A, Battista C, Chiodini I, *et al*. Bone mineral density in acromegaly: the effect of gender, disease activity and gonadal status. *Clin Endocrinol (Oxf)*. 2003;58(6):725-731.
10. Claessen KM, Kroon HM, Pereira AM, *et al*. Progression of vertebral fractures despite long-term biochemical control of acromegaly: a prospective follow-up study. *J Clin Endocrinol Metab*. 2013;98(12):4808-4815.
11. McCloskey EV, Oden A, Harvey NC, *et al*. A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. *J Bone Miner Res*. 2016;31(5):940-948.
12. Briot K, Paternotte S, Kolta S, *et al*. Added value of trabecular bone score to bone mineral density for prediction of osteoporotic fractures in postmenopausal women: the OPUS study. *Bone*. 2013;57(1):232-236.
13. Bioletto F, Barale M, Prencipe N, *et al*. Trabecular bone score as an index of bone fragility in patients with acromegaly: a systematic review and meta-analysis. *Neuroendocrinology*. 2023;113(4):395-405.
14. Hong AR, Kim JH, Kim SW, Kim SY, Shin CS. Trabecular bone score as a skeletal fragility index in acromegaly patients. *Osteoporos Int*. 2016;27(3):1123-1129.
15. Calatayud M, Perez-Olivares Martin L, Librizzi MS, *et al*. Trabecular bone score and bone mineral density in patients with long-term controlled acromegaly. *Clin Endocrinol (Oxf)*. 2021;95(1):58-64.
16. Kuzma M, Vanuga P, Sagova I, *et al*. Non-invasive DXA-derived bone structure assessment of acromegaly patients: a cross-sectional study. *Eur J Endocrinol*. 2019;180(3):201-211.
17. Stein EM, Liu XS, Nickolas TL, *et al*. Abnormal microarchitecture and reduced stiffness at the radius and tibia in postmenopausal women with fractures. *J Bone Miner Res*. 2010;25(12):2572-2581.
18. Stein EM, Liu XS, Nickolas TL, *et al*. Abnormal microarchitecture and stiffness in postmenopausal women with ankle fractures. *J Clin Endocrinol Metab*. 2011;96(7):2041-2048.
19. Shane E. Improving fracture risk assessment in older adults. *Lancet Diabetes Endocrinol*. 2019;7(1):5-7.
20. Samelson EJ, Broe KE, Xu H, *et al*. Cortical and trabecular bone microarchitecture as an independent predictor of incident fracture risk in older women and men in the bone microarchitecture international consortium (BoMIC): a prospective study. *Lancet Diabetes Endocrinol*. 2019;7(1):34-43.
21. Boutroy S, Khosla S, Sornay-Rendu E, *et al*. Microarchitecture and peripheral BMD are impaired in postmenopausal white women with fracture independently of total hip T-score: an international multicenter study. *J Bone Miner Res*. 2016;31(6):1158-1166.
22. Biver E, Durosier-Izart C, Chevalley T, van Rietbergen B, Rizzoli R, Ferrari S. Evaluation of radius microstructure and areal bone mineral density improves fracture prediction in postmenopausal women. *J Bone Miner Res*. 2018;33(2):328-337.
23. Langsetmo L, Peters KW, Burghardt AJ, *et al*. Osteoporotic fractures in men study research G. Volumetric bone mineral density and failure load of distal limbs predict incident clinical fracture independent HR-pQCT BMD and failure load predicts incident clinical fracture of FRAX and clinical risk factors among older men. *J Bone Miner Res*. 2018;33(7):1302-1311.
24. Stein EM, Liu XS, Nickolas TL, *et al*. Microarchitectural abnormalities are more severe in postmenopausal women with vertebral compared to nonvertebral fractures. *J Clin Endocrinol Metab*. 2012;97(10):E1918-E1926.
25. Reid TJ, Jin Z, Shen W, *et al*. IGF-1 levels across the spectrum of normal to elevated in acromegaly: relationship to insulin sensitivity, markers of cardiovascular risk and body composition. *Pituitary*. 2015;18(6):808-819.
26. Kuker AP, Shen W, Jin Z, Chen J, Bruce JN, Freda PU. Long-term outcome of body composition, ectopic lipid, and insulin resistance changes with surgical treatment of acromegaly. *J Endocr Soc*. 2023;7(5):bvad028.
27. Kepley AL, Nishiyama KK, Zhou B, *et al*. Differences in bone quality and strength between Asian and Caucasian young men. *Osteoporos Int*. 2017;28(2):549-558.
28. Levy RV, McMahon DJ, Agarwal S, *et al*. Comprehensive associations between acidosis and the skeleton in patients with kidney disease. *J Am Soc Nephrol*. 2023;34(4):668-681.
29. Liu XS, Cohen A, Shane E, *et al*. Individual trabeculae segmentation (ITS)-based morphological analysis of high-resolution peripheral quantitative computed tomography images detects abnormal trabecular plate and rod microarchitecture in premenopausal women with idiopathic osteoporosis. *J Bone Miner Res*. 2010;25(7):1496-1505.
30. Cohen A, Dempster DW, Muller R, *et al*. Assessment of trabecular and cortical architecture and mechanical competence of bone by high-resolution peripheral computed tomography: comparison with transiliac bone biopsy. *Osteoporos Int*. 2010;21(2):263-273.
31. Silva BC, Leslie WD, Resch H, *et al*. Trabecular bone score: a noninvasive analytical method based upon the DXA image. *J Bone Miner Res*. 2014;29(3):518-530.
32. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;8(9):1137-1148.
33. Laib A, Ruegsegger P. Calibration of trabecular bone structure measurements of in vivo three-dimensional peripheral quantitative computed tomography with 28-microm-resolution microcomputed tomography. *Bone*. 1999;24(1):35-39.
34. Muller R, Hildebrand T, Hauselmann HJ, Ruegsegger P. In vivo reproducibility of three-dimensional structural properties of noninvasive bone biopsies using 3D-pQCT. *J Bone Miner Res*. 1996;11(11):1745-1750.
35. Liu XS, Stein EM, Zhou B, *et al*. Individual trabecula segmentation (ITS)-based morphological analyses and microfinite element analysis of HR-pQCT images discriminate postmenopausal fragility fractures independent of DXA measurements. *J Bone Miner Res*. 2012;27(2):263-272.

36. Nickolas TL, Stein EM, Dworakowski E, *et al.* Rapid cortical bone loss in patients with chronic kidney disease. *J Bone Miner Res*. 2013;28(8):1811-1820.
37. Agarwal S, Shiau S, Kamanda-Kosseh M, *et al.* Teriparatide followed by denosumab in premenopausal idiopathic osteoporosis: bone microstructure and strength by HR-pQCT. *J Bone Miner Res*. 2023;38(1):35-47.
38. Nishiyama KK, Cohen A, Young P, *et al.* Teriparatide increases strength of the peripheral skeleton in premenopausal women with idiopathic osteoporosis: a pilot HR-pQCT study. *J Clin Endocrinol Metab*. 2014;99(7):2418-2425.
39. Laib A, Hauselmann HJ, Ruegsegger P. In vivo high resolution 3D-QCT of the human forearm. *Technol Health Care*. 1998;6(5-6):329-337.
40. Buie HR, Campbell GM, Klinck RJ, MacNeil JA, Boyd SK. Automatic segmentation of cortical and trabecular compartments based on a dual threshold technique for in vivo micro-CT bone analysis. *Bone*. 2007;41(4):505-515.
41. Agarwal S, Rosete F, Zhang C, *et al.* In vivo assessment of bone structure and estimated bone strength by first- and second-generation HR-pQCT. *Osteoporos Int*. 2016;27(10):2955-2966.
42. Muller R, Ruegsegger P. Three-dimensional finite element modelling of non-invasively assessed trabecular bone structures. *Med Eng Phys*. 1995;17(2):126-133.
43. van Rietbergen B, Weinans H, Huiskes R, Odgaard A. A new method to determine trabecular bone elastic properties and loading using micromechanical finite-element models. *J Biomech*. 1995;28(1):69-81.
44. Macneil JA, Boyd SK. Bone strength at the distal radius can be estimated from high-resolution peripheral quantitative computed tomography and the finite element method. *Bone*. 2008;42(6):1203-1213.
45. Macdonald HM, Nishiyama KK, Kang J, Hanley DA, Boyd SK. Age-related patterns of trabecular and cortical bone loss differ between sexes and skeletal sites: a population-based HR-pQCT study. *J Bone Miner Res*. 2011;26(1):50-62.
46. Nishiyama KK, Macdonald HM, Buie HR, Hanley DA, Boyd SK. Postmenopausal women with osteopenia have higher cortical porosity and thinner cortices at the distal radius and tibia than women with normal aBMD: an in vivo HR-pQCT study. *J Bone Miner Res*. 2010;25(4):882-890.
47. Manolopoulou J, Alami Y, Petersenn S, *et al.* Automated 22-kD growth hormone-specific assay without interference from pegvisomant. *Clin Chem*. 2012;58(10):1446-1456.
48. Bidlingmaier M, Friedrich N, Emeny RT, *et al.* Reference intervals for insulin-like growth factor-1 (igf-i) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. *J Clin Endocrinol Metab*. 2014;99(5):1712-1721.
49. Tamada D, Kitamura T, Onodera T, *et al.* Rapid decline in bone turnover markers but not bone mineral density in acromegalic patients after transsphenoidal surgery. *Endocr J*. 2014;61(3):231-237.
50. Godang K, Olarescu NC, Bollerslev J, Heck A. Treatment of acromegaly increases BMD but reduces trabecular bone score: a longitudinal study. *Eur J Endocrinol*. 2016;175(2):155-164.
51. Kuzma M, Vanuga P, Sagova I, *et al.* Vertebral fractures occur despite control of acromegaly and are predicted by cortical volumetric bone mineral density. *J Clin Endocrinol Metab*. 2021;106(12):e5088-e5096.
52. Sala E, Malchiodi E, Carosi G, *et al.* Spine bone texture assessed by trabecular bone score in active and controlled acromegaly: a prospective study. *J Endocr Soc*. 2021;5(8):bvab090.
53. Boutroy S, Van Rietbergen B, Sornay-Rendu E, Munoz F, Bouxsein ML, Delmas PD. Finite element analysis based on in vivo HR-pQCT images of the distal radius is associated with wrist fracture in postmenopausal women. *J Bone Miner Res*. 2008;23(3):392-399.
54. Vilayphiou N, Boutroy S, Sornay-Rendu E, *et al.* Finite element analysis performed on radius and tibia HR-pQCT images and fragility fractures at all sites in postmenopausal women. *Bone*. 2010;46(4):1030-1037.
55. Vitali E, Palagano E, Schiavone ML, *et al.* Direct effects of octreotide on osteoblast cell proliferation and function. *J Endocrinol Invest*. 2022;45(5):1045-1057.
56. Silva PPB, Pereira RMR, Takayama L, *et al.* Impaired bone microarchitecture in premenopausal women with acromegaly: the possible role of wnt signaling. *J Clin Endocrinol Metab*. 2021;106(9):2690-2706.
57. Duan L, Yang S, Wang LJ, *et al.* The negative impacts of acromegaly on bone microstructure not fully reversible. *Front Endocrinol (Lausanne)*. 2021;12:738895.
58. Silva PPB, Amlashi FG, Yu EW, *et al.* Bone microarchitecture and estimated bone strength in men with active acromegaly. *Eur J Endocrinol*. 2017;177(5):409-420.
59. Madeira M, Neto LV, de Paula Paranhos Neto F, *et al.* Acromegaly has a negative influence on trabecular bone, but not on cortical bone, as assessed by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab*. 2013;98(4):1734-1741.
60. Chiloiro S, Mazziotti G, Giampietro A, *et al.* Effects of pegvisomant and somatostatin receptor ligands on incidence of vertebral fractures in patients with acromegaly. *Pituitary*. 2018;21(3):302-308.
61. Maffezzoni F, Maddalo M, Frara S, *et al.* High-resolution-cone beam tomography analysis of bone microarchitecture in patients with acromegaly and radiological vertebral fractures. *Endocrine*. 2016;54(2):532-542.
62. Battista C, Chiodini I, Muscarella S, *et al.* Spinal volumetric trabecular bone mass in acromegalic patients: a longitudinal study. *Clin Endocrinol (Oxf)*. 2009;70(3):378-382.
63. Khosla S, Riggs BL, Atkinson EJ, *et al.* Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive in vivo assessment. *J Bone Miner Res*. 2006;21(1):124-131.
64. Boutroy S, Hans D, Sornay-Rendu E, Vilayphiou N, Winzenrieth R, Chapurlat R. Trabecular bone score improves fracture risk prediction in non-osteoporotic women: the OFELY study. *Osteoporos Int*. 2013;24(1):77-85.
65. Winzenrieth R, Michelet F, Hans D. Three-dimensional (3D) microarchitecture correlations with 2D projection image gray-level variations assessed by trabecular bone score using high-resolution computed tomographic acquisitions: effects of resolution and noise. *J Clin Densitom*. 2013;16(3):287-296.
66. Lewiecki EM, Laster AJ. Clinical review: clinical applications of vertebral fracture assessment by dual-energy x-ray absorptiometry. *J Clin Endocrinol Metab*. 2006;91(11):4215-4222.