Bone Mineral Density of the Axial Skeleton in Acromegaly

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Acromegaly is characterized by growth hormone (GH) hypersecretion and insulin-like growth factor-I (IGF-I) excess, both of which stimulate osteoblast proliferation. At diagnosis, GH excess has usually been present for years. Furthermore, impaired gonadotropin secretion with hypogonadism is frequent. To date, studies of changes in bone mineral density (BMD) in acromegaly have been limited and the available data inconsistent. To investigate the effects of GH excess on proximal femur and lumbar spine BMD, a case series of 25 patients with acromegaly (8 eugonadal, 17 hypogonadal) documented by high plasma GH and IGF-I concentrations was studied. BMD was measured using dual-photon absorptiometry, hormonal and biochemical measurements, which included GH, IGF-I, serum calcium, phosphate, alkaline phosphatase, 1,25 dihydroxy vitamin D and urinary calcium and hydroxyproline excretion. Seven patients were re-studied after IGF-I was suppressed for six months by the somatostatin analog 201-995 (five patients) or pituitary adenomectomy (two patients). BMD was normal in 22 patients and was decreased at one site each in one eugonadal and two hypogonadal patients. BMD was similar between the eugonadal and hypogonadal groups at all sites. Urinary hydroxyproline excretion was equally increased in both groups. There was no correlation between any of the hormonal or biochemical parameters and the age, sex, race and body mass index matched Z-scores of BMD at any site. Following normalization of IGF-I for 6 mo in seven patients, there was no significant change of BMD. We conclude that proximal femoral and lumbar spine BMD is normal in most patients with active acromegaly, including those who are hypogonad. Successful treatment of acromegaly does not result in major short-term changes in BMD.

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Osteoporosis, characterized by a decrease in bone mass and strength without mineralization defect, is associated with over 1 million fractures per year in the United States (*1*) and presents a major public health problem. The vertebrae and proximal femur are major sites involved in osteoporotic fractures (*2*). Gonadal steroid deficiency in the postmenopausal period and aging are thought to be two of the major causes (*1*). Treatment of osteoporosis to date has mainly been directed at decreasing bone resorption (*3*). Short-term studies involving the administration of exogenous growth hormone (GH) to patients with osteoporosis have produced variable results (*4–7*) and the long-term efficacy of this approach is yet unknown.

Acromegaly is characterized by GH hypersecretion by a pituitary adenoma. In the peripheral tissues, GH stimulates the production of insulin-like growth factor-I (IGF-I), which is the mediator of many effects of GH. Both GH itself and IGF-I stimulate osteoblast proliferation and contribute to bone formation (*7*). At diagnosis, most acromegalic patients have had prolonged periods (at least 5–15 yr) of supraphysiologic levels of GH, due to the insidious onset of this disease (*8*). A significant percentage of these patients are also hypogonadal, mainly due to impairment of gonadotropin secretion (*8*). Therefore, the combined effects of excess GH and hypogonadism on bone mineral density (BMD) may be manifest in these patients. The changes in BMD in acromegaly are not yet clearly defined. Previous studies have reported normal (*9,10*), decreased (*11*) and increased (*9,10,12–14*) bone mass in acromegaly, as well as differential effects on the axial and appendicular skeleton (*15*).

In this study, we measured the BMD of the proximal femur and lumbar spine using dual-photon absorptiometry in 25 patients with active acromegaly to elucidate the effects of GH excess on bone mineral density at these sites. In addition, the effect of suppressing GH hypersecretion on BMD was studied in seven patients who received the somatostatin analog SMS 201-995 for 6 mo or who underwent selective pituitary adenomectomy.

METHODS

Patients

The study subjects consisted of 25 patients (13M, 12F; 23–69 yr) with active acromegaly. The diagnosis was made clinically and confirmed biochemically by elevated plasma GH concentration (mean of 25 to 145 samples taken at regular intervals over 24 hr in 17 patients, of hourly samples for 4 hr in 5 patients, or of several morning fasting samples in 3 patients) and elevated plasma IGF-I concentration. The duration of disease was esti-

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mated from clinical history and review of past photographs of the patients. Patients were otherwise in good health. Specifically, none had a history of bone disease or other condition known to cause osteopenia, such as chronic renal failure, hyperthyroidism or hyperparathyroidism. Five patients (4 male, 1 female) were eugonadal (defined as normal serum testosterone concentration in men or normal menstrual cyclicity in women). Three patients (2 males, 1 female) had been diagnosed with hypogonadism 4–7 yr prior to the study, and since then had been receiving testosterone or estradiol replacement therapy adequate to maintain normal serum concentrations of the respective sex steroids. Untreated hypogonadism was present in 7 men and in 10 women (for 1–26 yr, 10 ± 2 yr, range, mean ± s.e.). Of the latter, five women had a history of natural menopause, three had undergone bilateral ovariectomy and two had amenorrhea with suppressed serum estradiol levels secondary to concomitant hyperprolactinemia.

Protocol

The protocol was approved by the local institutional review board and informed consent was obtained from every patient. Bone mineral density (g/cm^2) of the hip on the nondominant side and of lumbar vertebrae was assessed in each patient by dual-photon absorptiometry (Lunar DP3 Dual Photon Absorptiometer, Madison, WI) of the femoral neck, Ward's triangle, greater trochanter and lumbar vertebral L2-4 regions. The precision and accuracy of the procedure were 3%–6% and 2%–3%, respectively. Serum calcium, albumin, phosphate, alkaline phosphatase and 1,25-dihydroxy vitamin D concentrations, and 24-hr urinary calcium and hydroxyproline excretion were measured using standard clinical assays. Patients were on a normal diet and none were taking any medications known to affect the parameters measured.

Dual-photon absorptiometry was repeated in seven patients (3M, 4F, 34–65 yr) after GH secretion had been suppressed, either after 6 mo of treatment with SMS 201-995 (Sandostatin, Sandoz, E. Hanover, NJ), 100 or 250 μg subcutaneously three times a day (five patients), or at 7–9 mo post-transsphenoidal selective pituitary adenomectomy (two patients).

Assays

Plasma GH was assayed by double-antibody RIA (*16*). Assay detectability limit was 0.3 ± 0.1 μg/liter. Intraassay coefficient of variation was 6.2% ± 0.6%. Plasma IGF-I was measured using the method of Furlanetto (*17*). All other blood and urine tests were performed using standard clinical pathology protocols by the Department of Pathology at the University of Michigan Medical Center.

Data Analysis

The Z-score of BMD measurements were compared with the age-, sex-, race- and weight-matched normal control data bank which formed part of the dual-photon absorptiometer software package. Eugonadal patients (n = 5) and those on long-term gonadal steroid replacement (n = 3) were combined and analyzed as a single group. Mann-Whitney U-test was used to compare the eugonadal and hypogonadal patients. Fisher's exact test was used to compare sex distributions between groups. Results pre- and post-treatment were compared using Wilcoxon matched-pairs signed-ranks test. Results were expressed as mean ± s.e. Statistical significance was assessed at $p < 0.05$.

RESULTS

The majority of patients (70%) were hypogonadal and had not received any sex steroid replacement therapy. Age, sex distribution, body mass index and duration of acromegaly were similar in the eu- and hypogonadal groups (Table 1).

Mean plasma GH and IGF-I concentrations were similarly elevated in both groups (Table 2). Serum calcium, albumin, phosphate, 1,25-dihydroxy vitamin D and alkaline phosphatase concentrations were within normal limits and not significantly different between groups. Mean urinary calcium excretion was mildly elevated in the patients as a whole (7.76 ± 1.02 mmol/d) and in the eugonadal group, and was in the upper range of normal in the hypogonadal group (Table 2). There was, however, no significant difference in the degree of calciuria between groups. Urinary hydroxyproline excretion was elevated and similar in both groups (Table 2).

Mean BMD was normal or near normal in both patient groups (Table 3). All patients had BMD Z-scores between −2 and 2 except for three patients: Two hypogonadal patients had Z-scores of −2.3 and −2.8 for Ward's triangle, and one patient who had been receiving testosterone replacement therapy for 4 yr had a Z score of −2.8 for lumbar vertebrae L2-4. There was no significant difference in BMD (in g/cm^2 or Z-scores) between the eugonadal and hypogonadal groups at any site. In the five truly eugonadal patients who were not taking any sex steroids, Z-scores in all areas of interest were between −1.2 and 1.5 (0.1 ± 0.2), except for a single measurement of 3.3 in the lumbar vertebrae L2-4. No significant correlation was found between bone mineral density Z-scores and mean GH, IGF-I, duration of acromegaly, serum calcium, phosphate, 1,25-dihydroxy vitamin D, or urinary hydroxyproline or calcium excretion.

In the seven patients who received SMS 201-995 or underwent selective pituitary adenomectomy, actual values of mean GH (from 18.4 ± 7.1 to 4.9 ± 2.0 μg/liter) and IGF-I (from 898 ± 131 to 259 ± 57 μg/liter) decreased

TABLE 1
Demographic Characteristics of Patients with Acromegaly

	Eugonadal or on sex steroid replacement for ≥ 4 yr (n = 8)	Hypogonadal and on no replacement (n = 17)
Age (yr)	40 ± 4	48 ± 3
Sex	6M, 2F	7M, 10F
Body mass index (kg/m^2)	28.9 ± 0.8	30.9 ± 2.0
Duration of acromegaly (yr)	9 ± 2	14 ± 2
Duration of untreated hypogonadism (yr)	0	10 ± 2

Data are mean ± s.e.

TABLE 2
Biochemical Parameters of Patients with Acromegaly

	Eugonadal or on sex steroid replacement for ≥ 4 yr (n = 8)	Hypogonadal and on no replacement (n = 17)	Reference range
Mean GH (μg/liter)	27.6 ± 7.2	20.6 ± 6.2	<5
IGF-I (μg/liter)	1091 ± 133	930 ± 81	M 90–318 F 116–270
Calcium (mmol/liter)	2.30 ± 0.02	2.38 ± 0.02	2.14–2.60
Albumin (g/liter)	39 ± 1	41 ± 1	35–49
Phosphate (mmol/liter)	1.40 ± 0.05	1.40 ± 0.05	0.80–1.60
Alkaline phosphatase (μkat/liter)	1.8 ± 0.3	1.7 ± 0.1	0.5–2.2
1,25-dihydroxy vitamin D (pmol/liter)	112 ± 22	114 ± 10	38–148
Urinary Ca (mmol/d)	8.3 ± 2.5	7.3 ± 1.4	2.5–7.5
Urinary hydroxyproline (μmol/d)	560 ± 120	380 ± 30	110–340

Data are mean ± s.e.
$p > 0.05$ for all comparisons.

substantially and remained at those levels for 6–9 mo. No significant change in any of the other biochemical parameters was found. There was no significant change in absolute BMD or in the Z-scores at any bony site in the group as a whole (Table 4) or in four patients who completely normalized their IGF-I concentrations.

DISCUSSION

The effects of GH and IGF-I excess in acromegaly on BMD are not yet clearly defined. Early studies, based on visual assessment of bone in x-ray films (*11*) and on the finding of hypercalciuria and negative calcium balance in some patients (*18*), suggested that acromegaly was associated with osteoporosis. However, more recent studies have generally found normal or increased bone mass in acromegaly. Increased cortical bone thickness in acromegaly has been demonstrated morphometrically (*12*), while normal to high distal appendicular bone mass has also been found (*9,15*). Animal studies have shown that exogenous GH increases cortical bone mass via an increase in endosteal and periosteal bone formation and a decrease in endosteal resorption (*19*).

The heterogeneous changes of BMD in acromegaly suggests that bone formation and resorption may be stimulated to variable extents in individual patients. The increased urinary excretion of hydroxyproline in our patients is consistent with increased bone collagen turnover, and indirectly, bone resorption, since hydroxyproline is not recycled for collagen synthesis once it is released from bone (*20*). This is consistent with an earlier study that found an elevated urinary hydroxyproline excretion which correlated with the GH concentration in acromegaly (*21*). Increased bone resorption in acromegaly has also been demonstrated by bone biopsy in previous studies (*9,22*). In contrast, serum alkaline phosphatase, an index of bone formation, was normal in our patients, although a moderate increase in the bone-specific fraction of this enzyme cannot be excluded (*23*). Indeed, increased bone formation in acromegaly has been demonstrated by other methods. Plasma concentration of osteocalcin (bone Gla protein), a noncollagenous bone matrix protein synthesized by osteoblasts, is believed to more specifically reflect the rate of bone formation (*20*). It is increased in acromegaly (*24*), correlates with plasma IGF-I concentrations (*25*) and decreases after pituitary adenomectomy (*24*). Bone apposi-

TABLE 3
BMD in Patients with Acromegaly

	Eugonadal or on sex steroid replacement for ≥ 4 yr (n = 8)	Hypogonadal, not on sex steroid replacement (n = 17)
Femoral neck		
BMD (g/cm²)	1.043 ± 0.046	0.949 ± 0.025
(Z-score)	0.3 ± 0.3	0.2 ± 0.2
Ward's triangle		
BMD (g/cm²)	0.870 ± 0.061	0.788 ± 0.037
(Z-score)	−0.4 ± 0.3	−0.3 ± 0.3
Greater trochanter		
BMD (g/cm²)	0.880 ± 0.037	0.805 ± 0.031
(Z-score)	0.4 ± 0.3	0.2 ± 0.3
Lumbar vertebrae L2–4		
BMD (g/cm²)	1.347 ± 0.083	1.223 ± 0.054
(Z-score)	0.3 ± 0.7	−0.2 ± 0.4

Data are mean ± s.e.
$p > 0.05$ for all comparisons.

TABLE 4
Effects of Treatment of Acromegaly on BMD

	Baseline	Post-treatment*
Plasma GH (μg/liter)	18.4 ± 7.1	4.9 ± 2.0
Plasma IGF-I (μg/liter)	898 ± 131	259 ± 57†
Femoral neck		
BMD (g/cm²)	0.961 ± 0.050	0.927 ± 0.062
(Z-score)	0.4 ± 0.5	0.1 ± 0.6
Ward's triangle		
BMD (g/cm²)	0.777 ± 0.061	0.733 ± 0.073
(Z-score)	−0.3 ± 0.6	−0.8 ± 0.5
Greater trochanter		
BMD (g/cm²)	0.826 ± 0.044	0.816 ± 0.046
(Z-score)	0.5 ± 0.5	0.5 ± 0.5
Lumbar vertebrae L2–4		
BMD (g/cm²)	1.167 ± 0.064	1.178 ± 0.080
(Z-score)	−0.5 ± 0.5	−0.3 ± 0.5

Data are mean ± s.e., n = 7.
* Six months of SMS 201-995, n = 5; 6 mo post-pituitary adenomectomy, n = 2.
† $p < 0.05$ vs. baseline.

tional rate is increased in acromegaly, as shown by tetracycline double-labelling and quantitative histomorphometry (*14*). Our results thus indicate that while bone resorption was accelerated in this group of patients with active acromegaly, bone formation must also have increased to a similar extent to balance resorption, since bone mineral density was not significantly reduced.

The normal serum calcium and phosphate in our patients are consistent with several previous studies (*15,26*). The high urinary calcium excretion in some of our patients may reflect increased bone resorption. It may also be secondary to increased intestinal calcium absorption (*27*), due to increased gut sensitivity to 1,25-hydroxy vitamin D or stimulation of 1α-hydroxylase by excess GH (*26*). The normal 1,25-dihydroxy vitamin D levels in this group of patients suggests the former mechanism and is in contrast to other studies which found increased serum levels of the compound (*26,28*).

Hypogonadism is relatively common in patients with acromegaly due to hyperprolactinemia or to tumor-induced or iatrogenic (surgery, radiation) pituitary damage, as well as incidental menopause (a common cause in this study). Therefore, hypogonadism may also effect changes in BMD in some patients with acromegaly. Seeman et al. (*10*) reported that BMD was increased in the lumbar spine in acromegaly and suggested that osteopenia was probably rare in acromegaly per se, and that if it occurred, other factors such as hypogonadism might be involved. Diamond et al. (*15*) found increased bone mineral content in the forearm and decreased BMD in the vertebrae. They postulated that the axial and appendicular skeletons were differentially affected by GH excess and hypogonadism because trabecular bone has a greater surface area that is more susceptible to resorption than cortical bone (*10*). In contrast, we showed that BMD in the proximal femur and lumbar vertebrae (both of which consist mainly of trabecular bone) was normal in our acromegalic patients, including those who had been hypogonadal for a number of years.

The difference between the normal BMD of the lumbar spine in our group of acromegalic patients and the decreased BMD in an earlier study (*15*) may be explained by differences in the duration of GH hypersecretion and of hypogonadism between the two studies. The average duration of acromegalic symptoms in the present study was 14 ± 2 yr, and that of hypogonadism, 10 ± 2 yr. Moreover, as hypogonadism is more likely to be symptomatic than mild GH hypersecretion, our hypogonadal patients probably had had a considerable period of GH hypersecretion prior to the onset of hypogonadism. A similar comparison cannot be made for the earlier study (*15*), for though the average duration of acromegalic symptoms (4.7 ± 1.8 yr) was shorter, that of hypogonadism is not available.

In our eugonadal acromegalic subjects, no significant increase in BMD was found in either the proximal femur or the lumbar spine. This may be due to the small number of eugonadal patients in our study, or the mildness of the effect of excess GH, and cannot be verified by this study. However, it suggests that GH itself may not be effective in significantly increasing BMD in eugonadal subjects, and/or that the proposed therapeutic effect of GH in osteoporosis is modest. Indeed, in a recent study, administration of GH to healthy older men for 6 mo resulted in a small increase in BMD only in the lumbar vertebrae but no change in five other axial or appendicular sites that were examined, whereas in postmenopausal females there was a reduction in BMD (*6,13,29*). Our data represent a large series of consecutively presenting patients with active acromegaly in whom axial skeletal BMD was studied using modern methodology. We, like others, express the data as BMD (g/cm^2) rather than bone mineral content or projected bone area as the normative data for these parameters was not assessable.

In the small subset of patients with successfully treated acromegaly, each patient was compared with themselves during the active phase of the disease and no obvious change was demonstrable over the 6–9-mo study interval. Given the limited size of the study series and the precision of the methodology, only major changes could have been detected. With seven subjects, it would require a change of 1.3 standard deviations to achieve 80% power using a paired t-test at a two-sided 5% level of significance (e.g., in the femoral neck, a 7.9% change from baseline). Our data do not exclude a more subtle or gradual change. Nevertheless, the lack of change in BMD is in striking contrast to the rapid and obvious change in soft tissue overgrowth (e.g., coarseness of facial features and hand volume) that successfully treated patients demonstrate (*8,30*).

In summary, we conclude that acromegaly is associated with evidence for increased bone turnover, but abnormal BMD in the proximal femur and lumbar spine is uncommon. This may indicate an equal balanced enhancement of bone formation and resorption of trabecular bone in this disease. Successful treatment of acromegaly did not result in any obvious major short-term changes in BMD.

NOTE ADDED IN PROOF

Recent studies in monkeys have shown that GH may protect against the osteoporosis of hypogonadism (Mann DR, Rudman CG, Akinbami MA, Gould KG. Preservation of bone mass in hypogonadal female monkeys with recombinant human growth hormone administration. *J Clin Endocrinol Metab* 1992; 74:1263–1269).

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