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Original Article

Osteopenia Occurs in a Minority of Patients with Acromegaly and is Predominant in the Spine

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Abstract. Acromegaly may induce abnormalities in bone metabolism; however, there are limited data related to bone mineral density (BMD) in this condition. To evaluate the effects of an excess of growth hormone/insulin-like growth fractor I (GH/IGF-I) in the skeleton, we measured the BMD in spine and femoral region, total body calcium and body composition in 45 patients (24 females and 21 males) aged 21–77 years (median 43 years) with acromegaly for 11.4 ± 7.5 years (range 0.5–26 years) using a dual-energy X-ray absorptiometer (Lunar DPX). Thirty-four patients had had hypogonadism for 8.6 ± 6.5 years (1–24 years). Mean serum GH and IGF-I levels were respectively 159 ± 183 μg/l and 843 ± 497 μg/l. Total body calcium was increased in the acromegalics (males: 1272 ± 217 g, range 916–1816 g; females: 1041 ± 223 g, range 739–1609 g) when compared with normal individuals (males: 1115 ± 144 g, range 856–1398 g; females: 909 ± 144 g, range 511–1311 g; $p = 0.01$). The lean body mass was significantly higher in acromegalic patients ($p < 0.001$) compared with normal individuals. There was a tendency for a lower fat percentage in the acromegalics; however, this difference was not significant. Osteopenia (1 Z-score below the mean) was found in the spine in 20% ($n = 9$) of the patients, while BMD was decreased in the femoral region in only 8.8% ($n = 4$). The group with osteopenia had a greater duration of hypogonadism than the normal BMD group (14 ± 11 years vs 4.4 ± 4.0 years; $p = 0.01$). A negative correlation was also found between the duration of hypogonadism and BMD in spine ($r = -0.4$; $p = 0.003$) and femoral region ($r = -0.37$; $p = 0.013$). The hypogonadal patients had a lower BMD in spine ($p < 0.005$), but not in other regions analyzed. No correlation was found between duration of hypersomatotropism, GH/IGF-I levels and BMD. We conclude that the majority of patients with acromegaly have preserved BMD despite the presence of hypogonadism.

Keywords: Acromegaly; Bone mineral density; Hypogonadism; Osteoporosis

Introduction

Abnormalities of calcium homeostasis and bone metabolism have long been described in acromegaly. In earlier reports, acromegaly was associated with vertebral microfractures or was considered as one of the causes of secondary osteoporosis and negative calcium balance [1,2]. More recently, studies have pointed out a positive calcium balance [3] and an enhancement of bone mineral density (BMD) in forearm [4] and femoral region [5], but not in spine [4,5]. Moreover, other authors have shown stimulatory effects of short-term recombinant human growth hormone (GH) on bone metabolism in normal volunteers [6], elderly people [7] and GH-deficient adults [8].

It is well known that GH stimulates directly or indirectly, through production of insulin-like growth factor I (IGF-I), bone turnover by increasing osteoblast number and function [9,10]. Some previous data have shown an increased bone turnover associated with acromegaly, leading to increased serum levels of osteocalcin as well as urinary calcium, hydroxyproline and pyridinoline excretion [5,11]. GH also stimulates the renal 25-hydroxyvitamin D-1α-hydroxylase activity, an

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effect mediated by IGF-I, and therefore enhances calcium and phosphorus absorption in the gut [12].

However, the net effect of GH and/or IGF-I on bone mass is still unclear, especially in the presence of hypogonadism. Some studies have reported a normal [13] or increased [4,5] BMD in hypogonadal patients with acromegaly, while other authors found that the excess of GH and IGF-I is not sufficient to overcome the osteopenia associated with sex hormone deficiency in these patients [11]. To our knowledge, there is no previous study reporting the total body calcium in acromegaly.

In the present study we evaluated the skeletal status in a population with acromegaly with a high prevalence of hypogonadism. We measured BMD in the spine and femoral region and total body calcium and correlated the BMD with duration of hypogonadism and disease activity. We also investigated whether BMD is preserved in acromegaly despite the presence of different degrees of hypogonadism.

Patients and Methods

We studied a group of 45 patients (24 females and 21 males; 20 black and 25 white) with a median age of 43 years (range 21–77 years) with clinical and laboratory features of acromegaly. The estimated duration of disease ranged from 0.5 to 34 years (mean 11.4 $\pm$ 7.5 years). Thirty-two patients had been previously submitted to pituitary surgery and/or radiotherapy and 13 patients were studied before any treatment. Thirty-nine patients still had active disease (non-suppressible serum GH and increased IGF-I levels). Gonadal status was determined by menstrual and sexual history, physical examination, and measurement of serum testosterone and gonadotropin levels. Thirty-four patients had been hypogonadal (17 females and 17 males) for 1–24 years (mean 8.5 $\pm$ 6.5 years). Three patients were taking replacement thyroxine therapy and 2 patients were taking prednisone (5 mg/day) because of secondary hypothyroidism and hypocortisolism. No patients were receiving gonadal steroidal therapy or calcium supplementation. All patients had normal serum ionized calcium levels.

Blood samples were drawn in the morning at 08.00 hours after an overnight fast and at 15, 30, 60, 90 and 120 min after a 75 g oral glucose load. Serum samples were stored at -70 °C until assayed. Serum GH concentrations were measured using a monoclonal-antibody-based immunoenzymometric assay (IEMA; sensitivity 0.1 µg/l; IRP-hGH 66/217 used as standard; intra- and interassay coefficients of variation 8.3% and 17.3%, respectively) as described by Vieira et al. [14]. Basal IGF-I levels (recombinant peptide from Amgen used as standard) were measured by conventional radioimmunoassay after extraction [15].

Scans of the lumbar spine and right proximal femur were carried out using a dual-energy X-ray absorptiometer (Lunar Radiation DPX, Madison, WI). All scans were performed and analyzed by the same operator without knowledge of the other data available for the patients. The normal American population reference (n=1211; matched for sex, age and race) provided by bone densitometer's manufacturer was used as reference for the study and the results were expressed as standard deviation Z-scores. A study conducted by Lunar and our own personal data (not shown) concluded that the BMD values of the Brazilian normal population are not significantly different from those of the normal American reference population (data provided by Lunar; not shown). Osteopenia was defined as a BMD more than 1 Z-score below the mean value for age-matched controls. The main regions of interest were L2–L4 in the spine, femoral neck, Ward's region and trochanter. The coefficient of variation of these measurements was 1% for both spine and femur. The total body calcium (TBC), lean mass (g) and fat percentage were also measured by whole body scan. Since normal TBC and body composition values are not provided by the bone densitometer's software, a group of 84 (34 males and 50 females) sex- and age-matched normal individuals were used for analysis of the TBC and body composition. Data on these normal individuals are presented in Table 1.

Table 1. Clinical characteristics of normal individuals (n=84) used for total-body calcium and body composition study and representation of the acromegalic patients (n=45)

	Normal individuals	Acromegalics
Age (median years) (male/female)	45.5/41	46/41
No. of individuals per sex (male/female)	34/50	21/24
No. of individuals per race (white/black)	40/44	20/25
Median body mass index (kg/m^2) (male/female)	25/25	29/28*

*$p < 0.01$.

Statistical Analysis

All data are expressed as mean $\pm$ SD or Z-scores. Data were analyzed by the Mann–Whitney rank sum test and p values less than 0.05 were considered significant. Correlations between variables were determined by Spearman rank-order test. All the patients provided informed consent.

Results

Mean serum GH and IGF-I levels were 159 $\pm$ 183 µg/l (range 0.1–740 µg/l and 843 $\pm$ 497 µg/l (normal values 100–360 µg/l) respectively in the total population of patients. As previously mentioned, 6 patients had suppressed GH levels after oral glucose load and normal IGF-I levels.

The mean BMD values (as mean Z-scores) found in the different regions were: spine, 0.2 (range −2.49 to 3.33); femoral neck, 0.12 (range −1.8 to 3.1); Ward's region, −0.13 (range −2.94 to 3.06); trochanter, 0.24 (range −2.37 to 3.65). The relative BMD values were similar in the two sexes. A percentage of these patients had BMD values 2 Z-scores above the mean (13% in spine; 8.8% in femoral neck and Ward's region; 18% in trochanter).

An increase in the mean TBC was also found in the acromegalic group (males: 1272 ± 217 g, range 739–1816 g; females: 1041 ± 223 g, range 739–1609 g) compared with normal individuals (males: 1115 ± 183 g, range 856–1398 g; females: 909 ± 144 g, range 511–1311 g; p=0.01) (Fig. 1). The mean lean body mass was significantly higher in acromegalics (males: 66370 ± 7982 g, females: 47323 ± 7635 g; $p<0.001$) when compared with normal individuals (males: 51362 ± 11657 g, females: 35084 ± 7670 g; $p<0.001$). A tendency to a lower mean fat percentage was found in the acromegalics (males: mean 21%, range 5.7–30%; females: mean 31%, range 13%–48%) when compared with normal individuals (males: mean 24%, range 7–34%; females: mean 35%, range 12.9%–55%); however, this difference was not significant.

Lumbar osteopenia was present in 9 patients (2 females and 7 males) and in 4 patients (2 females and 2 males) in the femoral region. However, the TBC was within the normal range (798–1381 g; 1060 ± 168 g) in all osteopenic patients and did not differ significantly from patients with normal BMD (739–1816 g; 1170 ± 264 g). The duration of hypogonadism was significantly greater in patients with osteopenia when compared with those with normal BMD (p = 0.01) (Table 2). All patients with osteopenia had hypogonadism. When all patients were divided according to their gonadal status (hypogonadal and eugonadal), the group with hypogonadism had a significant lower BMD in spine (p = 0.005) but not in the femoral region (Fig. 2). There was a negative correlation between duration of hypogonadism and BMD in both spine (r = −0.4; p = 0.003) and femoral area (r = −0.3; p = 0.013) (Fig. 3).

Table 2. Clinical and hormonal parameters of the patients divided according to their BMD status

	Normal BMD	Low BMD
Acromegaly duration (years)	8.62±5.4 (range 0.5–26)	18±4.4** (range 11.5–23)
Hypogonadism duration (years)	4.4 ±4 (range 0–20)	14±11* (range 1.5–34)
GH levels (μg/ml)	191±191	175±154 (NS)
IGF-I levels (μg/ml)	918±451	1292±498 (NS)

Values are the mean ± SD.
GH, growth hormone; IGF-I, insulin-like growth factor I.
*P=0.01; **$p<0.001$.

The duration of acromegaly activity was also significantly greater in the low BMD group ($p<0.001$) (Table 2). However, when all patients were separated according to the estimated disease duration (less than 5 years; 5–10 years and more than 10 years), the BMD was not different between groups. Hormonal parameters of the patients with normal and low BMD were similar and are also presented in Table 2. Among those patients with inactive acromegaly (n = 6), 2 had osteopenia and the others had normal BMD. These 2 patients with osteopenia had been cured for 20 years; however, they had persisted with untreated hypogonadism throughout this time. There was no correlation between duration of disease activity, GH or IGF-I levels and BMD.

Discussion

This study indicates a predominant site for osteopenia associated with acromegaly. The reduction of bone mass

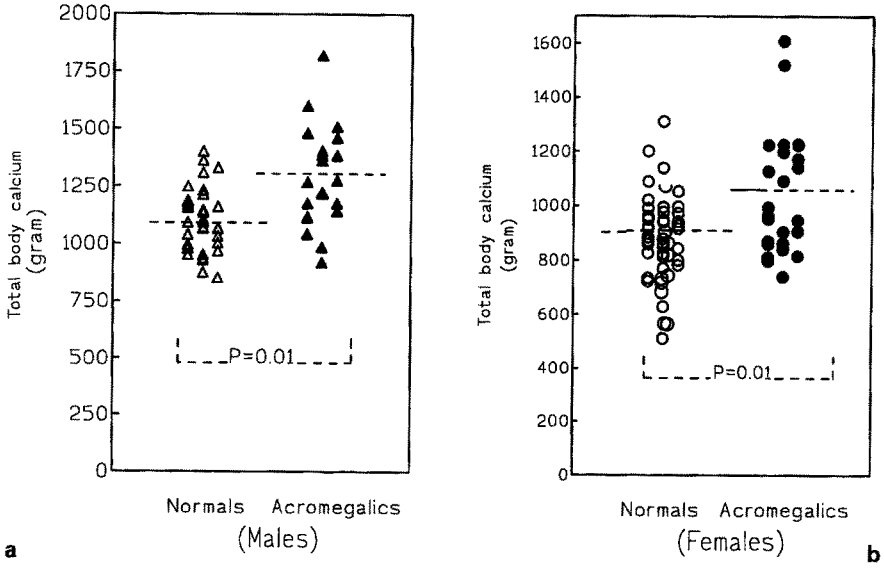

Fig. 1a,b. Representation of total body calcium (TBC) in normal individuals and acromegalics. *Dashed lines* represent the mean TBC values in each group. The mean TBC is higher in acromegalics compared with normal individuals (p=0.01). **a** Representation of TBC in normal (*open triangles*) and acromegalic (*filled triangles*) men. Mean TBC values are 1115 ± 183 g and 1272 ± 217 respectively. **b** Representation of TBC in normal (*open circles*) and acromegalic (*filled circles*) women. Mean TBC values are 909 ± 144 g and 1115 ± 183 g respectively.

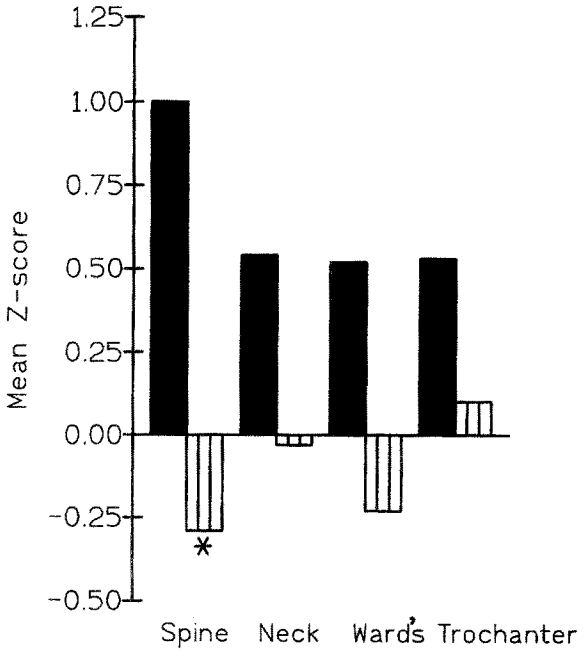

Fig. 2. Mean BMD values (as Z-scores) in the spine and femoral region. The patients were divided according to their gonadal status. *Black bars* represent eugonadal patients and *hatched bars* represent hypogonadal patients. The group with hypogonadism had lower BMD in spine (*p=0.005), but not in the femoral region.

occurred in spine in 20% of the population studied and in approximately 9% of the patients in the femoral region. The majority of our patients had preserved BMD in all regions studied (including the spine), despite the condition of prolonged hypogonadism found in some cases. Moreover, a fraction of the patients had a BMD 2 Z-scores above the mean and many of them had long-standing hypogonadism.

The known anabolic and lipolytic effects of GH with consequent changes in body composition were confirmed in our study. There was an increase in lean body mass and a tendency to a decrease in the fat mass in the acromegalics. An important finding of our study, which has not been described before, was a mean increase in TBC. We found a preservation of TBC even in those patients with osteopenia. This suggests that an excess of GH and IGF-I actually promotes a general increase in bone mass despite the presence of hypogonadism; however, for some reason the spine in particular is not fully protected from osteopenia. Discrepancies between vertebral and cortical (forearm and femur) bone measurements have been reported with other endocrine disorders such as hypogonadism [16], hypercortisolism [13], hyperthyroidism [13] and hyperparathyroidism [13]. In these conditions, the BMD decrease is more pronounced in vertebral cancellous bone, because of its more rapid turnover. Unlike these high bone remodelling diseases that are usually associated with progressive bone loss, the increased bone mass with high bone turnover seen in acromegaly indicates that GH/IGF-I excess might achieve a positive bone balance at each remodelling cycle.

This study shows that in the majority of patients the positive effects of GH and IGF-I on osteoblastic activity override the negative effects of hypogonadism in the femoral region. Diamond et al. [4] also showed that vertebral bone density was lower in acromegalics and that vertebral values correlated with the gonadal status. However, these authors found an increase in forearm bone mass, leading to the conclusion that forearm and vertebral BMD change in opposite directions in acromegaly. Another study, which evaluated only the vertebral BMD in 27 patients with acromegaly [11], using quantitative computed tomography, also showed a subnormal BMD in a substantial percentage of patients. Kotzmann et al. [5] evaluated both the lumbar and femoral BMD in 16 patients with active acromegaly and did not find osteopenia in any site analyzed.

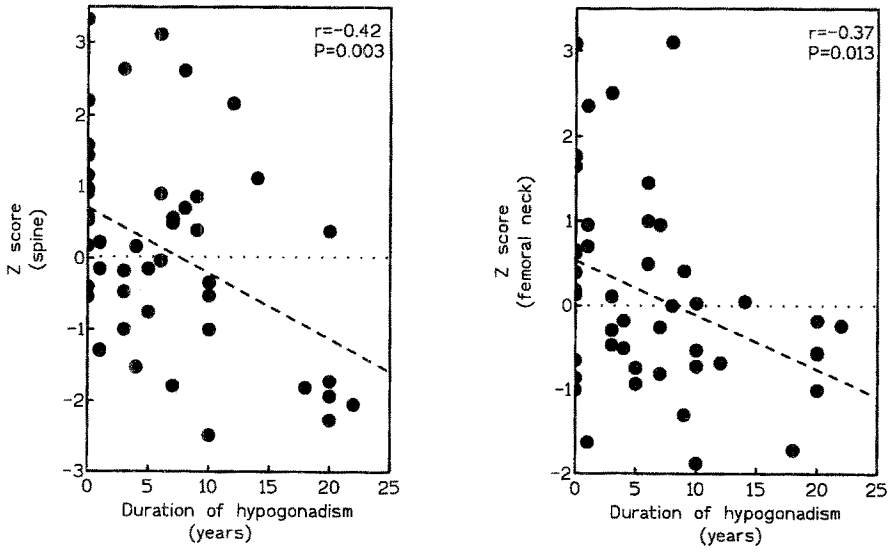

Fig. 3. Correlation between duration of hypogonadism and BMD (as Z-scores) in spine (*left-hand panel*) and femoral neck (*right-hand panel*). The duration of hypogonadism was negatively correlated with BMD values in both sites.

In accordance with previous data [4,17], we also found a positive correlation between the duration of hypogonadism and the BMD decrease. About 76% of our patients were hypogonadal and this group had a spinal BMD lower than that of the eugonadal group. However, femoral BMD was similar in the two groups and showed less dependence on the gonadal status than the spinal BMD. The group with osteopenia also had a greater duration of hypogonadism.

The population in our study was heterogeneous with a large range in age, serum GH/IGF-I levels and duration of disease and of hypogonadism. Therefore, we had to analyze our data using subgroups. When patients were divided according to the duration of disease, the BMD did not differ. The degree of present hypersomatotropism also did not correlate with BMD. In fact, the group with osteopenia had a longer duration of disease. However, the low BMD group had a longer duration of hypogonadism, suggesting that prolonged hypogonadism might have been the factor responsible for the appearance of osteopenia. Therefore, it seems that at least in the spine, GH/IGF-I excess only partially protects the bone mass from the increased bone resorption promoted by decreased gonadal steroids.

It is well known that bone formation and resorption markers such as serum osteocalcin and urinary pyridinolines are increased in acromegaly [5,11,18]. On the other hand, a decrease in the concentration of these parameters is found in GH-deficient children and adults [19,20] and a clear decrease in BMD has been reported in adults with long-standing GH deficiency [20]. Previous data in acromegalics shows a correlation of serum osteocalcin and urinary hydroxyproline with sreum IGF-I levels but not with serum GH levels [18]. Recently, a correlation between femoral BMD and serum osteocalcin levels was also shown [5]. Another study [4] demonstrated that forearm BMD was linearly correlated with the degree of GH excess and in patients followed over time an increase in BMD of 1.5% was observed in active acromegaly. In our study we could not find a linear correlation between GH/IGF-I levels and BMD, probably because of the population's heterogeneity.

According to our data, it seems that GH/IGF-I excess is sufficient to overcome the osteopenia associated with sex hormone deficiency in most patients with acromegaly, particularly in the femoral region. The majority of patients with acromegaly have preserved skeletal BMD and all them have normal or even increased TBC. Acromegaly per se does not seem to be a risk factor for developing osteoporosis, with the exception of the occurrence of a predominantly spinal osteopenia in a minority of patients, especially those with prolonged hypogonadism.

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