Iliac crest bone mass and remodelling in acromegaly

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Abstract. Iliac crest bone biopsies from 18 patients with active acromegaly, of whom 11 had received tetracycline double-labelling, were evaluated by quantitative histomorphometry and compared with age- and sex-matched normal controls. A significant increase (P < 0.01) was found in both cortical (175%) and trabecular (130%) bone mass. In trabecular bone, resorption surfaces and active (tetracycline-labelled) and total formation surfaces were increased (P < 0.05 and P < 0.01, respectively) causing an enhanced bone turn-over at tissue level (P < 0.01). The increased trabecular bone mass indicates a positive net balance per remodelling cycle and, therefore, larger than normal bone remodelling units, which in part may explain the increased bone turn-over at tissue level. The activity of the osteoblasts active in mineralization (the appositional rate) was increased (P < 0.01) and positively related to the fasting serum growth hormone levels (Rs = 0.69, P < 0.05). The average activity of active and inactive osteoblasts (bone formation rate at basic metabolic unit (BMU) level) was insignificantly increased. The proportion of active (tetracycline labelled) to non-active formation surfaces was normal. The bone changes were unrelated to serum levels and urinary excretions of calcium and phosphorus or to renal excretion of total and non-dialyzable hydroxyproline or cAMP.

The metabolic bone disease of acromegaly has over the years been the subject of repeated discussion. Radiological investigations have shown a coarsening of trabecular patterns and increased radiolucency – especially of the vertebral bodies. This finding was interpreted by earlier investigators as evidence for osteoporosis (Scraver & Bryan 1935; Albright & Reifenstein 1948). A recent prestigious textbook also links acromegaly with osteoporosis (Avioli & Raisz 1980).

Erdheim (1931) observed that in spite of radiological evidence of osteoporosis, the surface-near trabecular structures of the vertebral bodies were often thicker than normal. Consequently, he called the bone affection in acromegaly a 'sclerosing osteoporosis'. Remagen (1965) demonstrated that an increase in trabecular size could also be demonstrated in other parts of the skeleton.

Recently the concept of osteoporosis in acromegaly has been challenged. Doyle (1967) and Ikkos et al. (1974) using x-ray morphometry have demonstrated that the bone mass is actually increased in these patients. Using histomorphometry, Roelfsma et al. (1970) found increased values both for cortical and trabecular bone masses – results which were corroborated by Riggs et al. (1972) who studied a number of patients by bone densitometry and microradiography.

Erdheim (1931) pointed to the increase in periosteal and enchondreal bone formation occurring in acromegaly. Riggs et al. (1972) and Delling & Schulz (1977) have presented evidence based on measurements of trabecular bone for an increase in bone turn-over. So far only one case report (Ramsay et al. 1966) has described bone dynamics in acromegaly as evaluated after double tetracycline labelling.

The present study gives the static and dynamic parameters of bone remodelling in transcortical iliac bone biopsies from patients with active acromegaly and the relation to growth hormone levels and other biochemical parameters of calcium/phosphorus metabolism.

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Materials and Methods

The study comprised 13 females and 5 males with a mean age of 47.2 ± 9.4 (SD) years. All patients had active acromegaly as previously defined (Halse & Haugen 1980). Eight patients were untreated prior to the study. The remaining 10 patients had either unsuccessfully been subjected to surgical intervention on the pituitary gland (7 patients) or had been treated with x-ray irradiation not less than 20 years previously (3 patients). At the time of the study, 6 of the patients were on continuous bromocriptine treatment. In none of the patients had the treatment regime been changed during the last year prior to the investigation. Age- and sex-matched controls for bone histomorphometry were selected from a normal Danish population (Melsen & Mosekilde 1978; Melsen et al. 1978).

Trans-iliac bone biopsies (Bordier et al. 1964) were obtained after informed consent from all participants. Eleven of the patients had received tetracycline double-labelling prior to biopsy (Melsen & Mosekilde 1978). A histomorphometric evaluation of bone mass and bone remodelling was carried out on undecalcified stained and unstained bone sections using point-counting and simple measurements. The following parameters were measured or calculated:

In trabecular bone:

\[ V_{f}^{lab} = \frac{\text{volume of trabecular bone}}{\text{area of trabecular bone}} \]

\[ V_{f}^{fract} = \frac{\text{volume of trabecular bone}}{\text{area of trabecular bone}} \]

\[ V_{f}^{fract}(t) = \frac{\text{volume of trabecular bone}}{\text{area of trabecular bone}} \]

\[ V_{f}^{fract}(b) = \frac{\text{volume of trabecular bone}}{\text{area of trabecular bone}} \]

\[ V_{f}^{fract}(BMU) = \frac{\text{volume of bone mineralized in unit time per unit surface}}{\text{unit of bone area}} \]

Thickness \( t \) and \( V_{f}^{(BMU)} \) reflect the activity of the active osteoblasts and the average activity of the active and inactive osteoblasts at bone forming sites, respectively. \( V_{f} \) gives the turnover of bone and is proportional to the birth rate of new remodelling units (BMU = basic metabolic unit (Frost 1969)) and the average size of the remodelling units.

In cortical bone:

MCW, \( \mu m \), as the mean width of the inner and outer cortical lamellae.

Serum growth hormone (GH) concentrations were measured by radioimmunoassay using a kit from Cambridge Nuclear, Mass., USA. Except in patients receiving bromocriptine, the mean of three fasting GH values was used as an assessment of the GH status. In those receiving bromocriptine a representative mean value was calculated from GH levels obtained 3, 3.5 and 4 h after the first daily dose of medication (Halse et al. 1977). GH values greater than 50 \( \mu g/l \) were re-assayed in the same batch and ranked according to \( CPM \) values in the statistical evaluation. Fasting blood samples were also obtained for measurement of serum concentrations of calcium, phosphate, creatinine and total protein. Standard laboratory methods were used for these analyses. All patients received a collagen free diet for 3 days and two 24 h urine portions were sampled from the second day on. The urine was analyzed for total and non-dialyzable hydroxyproline (Gordeladze et al. 1978; Halse & Gordeladze 1981) as well as calcium, phosphate and creatinine. Urinary 3',5'-cyclic adenosine monophosphate (cAMP) was measured using a competitive protein binding method (kit from the Radiochemical Centre, Amersham, England) (Halse & Gordeladze 1979; Halse 1980).

Statistical evaluation was performed with non-parametric methods (Wilcoxon’s test for group comparison and Spearman’s rank test for correlation analysis). Mean values for each parameter in the individual patient were used whenever possible.

Results

The static and dynamic histomorphometric values for patients and controls are shown in Tables 1 and 2. Both cortical and trabecular bone volumes were significantly \( P < 0.01 \) increased in the patients. The mean cortical width (MCW) was 175% of the respective control value and only one of the patients had a MCW value lower than normal mean. The mean trabecular bone volume \( (V_{f}^{(BMU)}) \) in the patient group was 130% of normal mean and, again only one patient had an individual value lower than normal mean. The mean extent of both formative \( (S_{fract}(f)) \) and resorptive \( (S_{fract}(r)) \) surfaces
Bone mass and static parameters of bone turn-over in acromegals and age and sex matched controls.

<table>
<thead>
<tr>
<th></th>
<th>MCW (µm)</th>
<th>Vfrac (b) (µm²/µm³)</th>
<th>Sfrac (f) (µm²/µm³)</th>
<th>Sfrac (r) (µm²/µm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acromegals</td>
<td>1517</td>
<td>0.264</td>
<td>0.278</td>
<td>0.067</td>
</tr>
<tr>
<td>Mean</td>
<td>(15)</td>
<td>(18)</td>
<td>(18)</td>
<td>(18)</td>
</tr>
<tr>
<td>Controls</td>
<td>864</td>
<td>0.203</td>
<td>0.191</td>
<td>0.043</td>
</tr>
<tr>
<td>Mean</td>
<td>(14)</td>
<td>(17)</td>
<td>(17)</td>
<td>(17)</td>
</tr>
<tr>
<td>P-values</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

MCW: mean cortical width; Vfrac (b): fraction of trabecular bone of total narrow space; Sfrac (f): fraction of trabecular bone surface covered with osteoid; Sfrac (r): fraction of trabecular bone surface demonstrating evidence of osteoclastic resorption.

The extent of active bone formation surfaces in trabecular bone (Sfract(lab)) was significantly increased in the patients with acromegaly (P < 0.01). The proportion of active (labelled) to total (osteoid covered) surfaces was normal (0.70 ± 0.33 in the patient group vs 0.61 ± 0.26 in the control group) showing that a normal proportion of the formative surfaces was active in mineralization. The bone formation rate at tissue level (SVf) was markedly increased (P < 0.01) in the patient group indicating an enhanced bone turnover. This increase was caused by an increase in the activity of the osteoblasts (µM/t) and by the greater extent of active bone formation surfaces (Sfract(lab)). The appositional rate (µM/t) was significantly correlated to the serum GH levels (R = 0.69, P < 0.05) (Fig. 1). The mean bone formation rate at BMU level (SVf(BMU)) was increased compared to normal. The difference, however, was not significant because of a great scatter of the results.

No significant correlation was found between the histomorphometric data and the serum levels of calcium and phosphate or the renal excretion rates of calcium, phosphate, total or non-dialyzable hydroxyproline or cAMP. None of the histomorphometric data showed age dependency.

Dynamic parameters of trabecular bone remodelling in acromegals and ages and sex matched controls.

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>uM (µm/day)</th>
<th>Sfract (lab) (µm²/µm³)</th>
<th>SVf (µm³/µm²/day)</th>
<th>SVf (BMU) (µm³/µm²/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acromegals</td>
<td>46.5</td>
<td>0.87</td>
<td>0.231</td>
<td>0.198</td>
<td>0.66</td>
</tr>
<tr>
<td>Mean</td>
<td>10.3</td>
<td>0.30</td>
<td>0.077</td>
<td>0.113</td>
<td>0.40</td>
</tr>
<tr>
<td>(n)</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Controls</td>
<td>44.4</td>
<td>0.60</td>
<td>0.112</td>
<td>0.067</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean</td>
<td>7.5</td>
<td>0.11</td>
<td>0.058</td>
<td>0.034</td>
<td>0.17</td>
</tr>
<tr>
<td>(n)</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>P-values</td>
<td>n.s.</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

uM: appositional rate; Sfract (lab): tetracycline labelled trabecular surface; SVf: bone formation rate at tissue level; SVf(BMU): bone formation rate at BMU level.
The correlation between mean growth hormone level (GH) and appositional rate ($\mu_{M}$) as determined after double tetracycline labelling.

Discussion

The present study has demonstrated an increase in both cortical and trabecular bone mass in patients with acromegaly. None of the patients showed any evidence of osteopenia in spite of the various previous treatment and the varying length of the disease. The observed increase in cortical bone mass corroborates a previous radiogrammatic study by Dequecker (1971) who found a greater mean cortical bone area in acromegaly than in sex age and skeletal size-matched controls. The reason for the increased cortical width is an enhanced periosteal bone formation (Erdheim 1931; Garn 1970; Dequecker 1971).

The increase in trabecular bone volume may theoretically be explained by formation of new bone without previous bone resorption (modelling), by a reduction in bone turnover (Parfitt 1976) or by larger than normal bone remodelling units or packets. In polarized light the trabecular showed a normal structure with packets close to the surfaces and interstitial bone more centrally. Furthermore, the normal proportion of formation to resorption surfaces indicates a normal remodelling without modelling process. The dynamic data and the static parameters showed an increased bone turnover. The most likely explanation for the observed increase in trabecular bone volume, therefore, is a larger than normal mean size of the remodelling units.

The bone formation rate at tissue level was markedly increased followed by excess bone resorption and bone formation surfaces. This enhanced bone turnover at tissue level is in accordance with kinetic studies of skeletal calcium exchange rates in acromegalic patients (Eisenberg & Gordan 1961). The significant positive correlations found between serum levels of GH and bone remodelling estimated by microradiography on one hand (Riggs et al. 1972) and urinary excretion of hydroxyproline on the other (Halse & Gordeladze 1978, 1981), indicate that the effect of GH on bone turnover is proportional to the serum concentration of the hormone. The increase in formation rate at tissue level may in part be explained by larger packets. The bone formation rate, however, was three times normal in the acromegalic patients so it seems unlikely that this increase is caused by larger packets alone. Some of the increase in bone turnover may, therefore, be explained by an enhanced activation frequency of new remodelling units.

The present finding of a significant positive correlation between serum GH levels and the appositional rate, which represents the metabolic output of the active osteoblasts at cellular level, indicates that GH has an effect – probably indirectly via the somatomedin system – on the osteoblasts themselves. Morphologically the osteoblasts are enlarged and show evidence of increased activity in acromegaly (Remagen 1965).

The present results indicate that the effects of excess GH in the adult are similar to the effects of normal serum GH concentrations in the growing organism with activation of periosteal growth, trabecular bone remodelling and an increase in both cortical and trabecular bone mass. In acromegaly there is an increase in parathyroid function (Halse & Haugen 1980; Halse 1980) and in the serum levels of the ultimate active vitamin D metabolite, 1,25-dihydroxyvitamin D (Esikldsen et al. 1979; Brown et al. 1980). How these secondary changes in the main hormones regulating calcium-phosphorus metabolism affect bone remodelling in acromegaly is unknown. It is known, however, that parathyroid hormone increases bone remodelling without
and decreases bone mass (Parfitt 1976). The main effect of the active vitamin D metabolite is to enhance the intestinal calcium and phosphate absorption. Increased serum levels may therefore secure a sufficient amount of bone mineral for the mineralization process.

References


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