The reduction of bone mineral density in postmenopausal women with primary hyperparathyroidism is higher in the presence of concomitant GH secretion impairment

Elisabetta Cecconi, Maurizio Gasperi, Maura Genovesi, Fausto Bogazzi, Lucia Grasso, Filomena Cetani, Massimo Procopio, Claudio Marroccoli, Luigi Bartalena, and Enio Martino

Department of Endocrinology and Metabolism, University of Pisa, Ospedale, Cisanello, Via Paradisa 2, 56124 Pisa, Italy; Division of Endocrinology, University of Turin, Turin, Italy, and Chair and Division of Endocrinology, University of Insubria, 21100 Varese, Italy

(Correspondence should be addressed to M Gasperi; Email: mgasperi@endoc.med.unipi.it)

Abstract

Objective: To investigate, in a large group of postmenopausal primary hyperparathyroidism (PHP) women, whether the concomitance of GH deficiency (GHD) may contribute to the development of changes in bone mineral density (BMD).

Design: GH secretion, bone status and metabolism were investigated in 50 postmenopausal women with PHP and in a control group of 60 women with no evidence of PHP, matched for age, age at menopause and body mass index (BMI).

Methods: GH response to growth hormone-releasing hormone (GHRH) + arginine (Arg), femoral neck BMD (g/cm²) by dual energy X-ray absorptiometry, BMI, serum-ionized calcium, parathyroid hormone (PTH) and markers of bone remodelling were evaluated in all patients and controls.

Results: Among PHP patients, GH secretion was reduced (8.8 ± 4.2 μg/l, range 1.1–16.5 μg/l) in 34 patients and normal (28.7 ± 11.8 μg/l, range 17.9–55.7 μg/l) in the remaining 16 (P < 0.05), no women in the control group had GHD (peak GH 33.8 ± 10.9 μg/l, range 21.7 ± 63.2 μg/l).

Osteoporosis (T-score < -2.5) and osteopenia (T-score > -2.5 and < -1) were found in 73.5 and 17.6% of GHD patients, in 37.5 and 43.7% of patients with normal GH secretion and 3.1 and 27% of controls. T-score and BMD were not correlated with ionized calcium, age, age at menopause, BMI, GH peak and IGF-I but were correlated with serum PTH levels in both groups. T-score was correlated with serum levels of markers of bone remodelling only in PHP patients with GHD.

Conclusions: Concomitant impairment of GH secretion may play a pathogenetic role in the occurrence of changes in bone mass observed in PHP and contribute to make them more severe.

Introduction

It is well established that primary hyperparathyroidism (PHP), due to excessive parathyroid hormone (PTH) secretion usually by a parathyroid adenoma, is responsible for changes in bone metabolism leading to a reduction in bone mineral density (BMD) (1–4). We recently reported that many patients with untreated PHP due to parathyroid adenoma have an impaired growth hormone (GH) secretion, as assessed by a blunted GH response to maximal stimulation by growth hormone-releasing hormone (GHRH) + arginine (Arg) test and by the assessment of 24-h GH secretion (5, 6). Improvement of GH deficiency (GHD) is achieved in PHP patients after parathyroidectomy (7). The observation that a reduced GH response to provocative stimuli is found in members of families with familial hypocalciuric hypercalcaemia (FHH), whose serum PTH levels are normal, underscores the concept that hypercalcaemia rather than increased PTH is likely the factor responsible for GHD in PHP (8), as confirmed by the observation that no abnormality of GH secretion was found in secondary hyperparathyroidism (9). Both childhood-onset and adult-onset GHD show a reduction in BMD, which improves following GH replacement therapy (10–12). Thus, both conditions (PHP and GHD) have negative effects on bone mass.

The aim of the present study was to investigate, in a large group of postmenopausal PHP women, whether the concomitance of GHD may contribute to the development of changes in BMD.

Patients and methods

Subjects

Fifty consecutive PHP postmenopausal women (mean age 62.5 yr, range 48–85, body mass index (BMI) 26 ± 0.2) referred to our Institution during 4 years were
enrolled in this study. PHP was in all cases due to a single parathyroid adenoma. Diagnosis was based on the increase in serum total and ionized calcium and PTH levels, and supported by the presence of a hypoechoic posterior nodule in the thyroid bed by ultrasonography, and by a positive sestamibi parathyroid scan. No patients had history of head trauma; pituitary magnetic resonance imaging was normal in all patients. No clinical and biochemical thyroid, adrenal and gonadal dysfunction, as well as renal, liver and cardiac abnormalities were found. No patients were taking drugs known to affect GH secretion or bone mineral metabolism, including estroprogestins. Sixty postmenopausal women matched for age, age at menopause, BMI 25.9 (95% CI 24.1–27.7) g/l, range 17.9–55.7 g/l, P=0.0001 vs PHP with GHD) suggestive of normal GH secretion (PHP-no GHD). Mean GH values after GHRH + Arg in controls were significantly higher than those in PHP-GHD (P<0.0001), but not different from PHP-no GHD (Table 1). No difference was found between the two groups for age, age at menopause, BMI, serum ionized calcium, PTH and IGF-I concentrations.

### Assays

Serum ionized calcium, PTH, GH, insulin-like growth factor-I (IGF-I) were measured as previously reported (5, 6). Stimulated GH secretion was evaluated after i.v. administration of GHRH + Arg, as previously reported (5, 6). Briefly, serum GH concentrations were measured at baseline and 30, 60, and 90 min after the simultaneous i.v. 30-min infusion of Arg hydrochloride (0.5 g/kg body weight) and GHRH (1 μg/kg body weight as an i.v. bolus at 0 min; GHRH-29, Gerref, Serono). Blood samples for basal hormone measurements and stimulation tests were carried out at 0800 h, after an overnight fast. GH measurements were carried out in a single run for each patient; serum GH assay (RIAs, Nichols Institute Diagnostics, San Clemente, CA, USA) had a sensitivity of 0.15 μg/l; sensitivity of IGF-I assay (RIAs, Nichols Institute Diagnostics, San Clemente, CA, USA) was 0.3 μg/l. Inter- and intra-assay coefficients of variation were: 2.9–4.5 and 2.4–4% for GH and 7.6–15.5 and 10.1–15.7% for IGF-I respectively. Bone-specific alkaline phosphatase (B-ALP) was measured by specific IRMA (Tandem-R Ostase, Beckman Coulter, San Diego, CA, USA); inter- and intra-assay coefficients of variation were: 3.7–6.7 and 7–8.1% respectively; osteocalcin (OC) by IRMA (Osteo-RIACT, Cis Bio International, Yvette Cedex, France); inter- and intra-assay coefficients of variation were: 1.2–2.8 and 3.6–5.2% respectively; serum cross-laps (S-CTX) by ELISA (Osteometer Bio Tech, Herlev, Denmark); inter- and intra-assay coefficients of variation were: 5.1–5.4 and 6.5–8.1% respectively.

Normal values in our laboratory were as follows: serum ionized calcium, 1.13–1.30 mmol/l; serum PTH, 10–65 pg/ml; serum IGF-I, 182–780 μg/l; 16–24 yr, 90–492 μg/l, 25–50 yr, 71–290 μg/l, > 50 yr, B-ALP 2–28 μg/l, OC 6.8–34 μg/l, S-CTX < 4520 pm/l.

In our laboratory, the lower value of peak serum GH after GHRH + Arg test in a group of normal subjects comparable for sex and age was 16.5 μg/l as previously reported (13, 14).

BMD was evaluated by dual energy X-ray absorptiometry (Hologic 4500 Elite, Hologic Inc., Waltham, MA, USA). BMD was measured in gram per centimeter square and expressed also as T-score. According to World Health Organization (WHO, 1994), definition regarding postmenopausal women, T-score values < −2.5 were considered osteoporotic, between −1 and −2.5 osteopenic and T-score > −1 normal.

### Statistical analysis

Data were reported as mean ± s.n.; differences for quantitative variables of patients were evaluated using ANOVA for repeated measures; differences for qualitative variables were measured by unpaired tests.

### Results

Based on GH response to GHRH + Arg stimulation test, PHP patients were subdivided into two groups (Table 1): 34 patients had a blunted GH response (mean 8.8 ± 4.2 μg/l, range 1.1–16.5 μg/l) indicating the presence of concomitant GHD (PHP-GHD); the remaining 16 patients had a normal GH response (mean 28.7 ± 11.8 μg/l, range 17.9–55.7 μg/l, P<0.0001 vs PHP with GHD) suggestive of normal GH secretion (PHP-no GHD). Mean GH values after GHRH + Arg in controls were significantly higher than those in PHP-GHD (P<0.0001), but not different from PHP-no GHD (Table 1). No difference was found between the two groups for age, age at menopause, BMI, serum ionized calcium, PTH and IGF-I concentrations.

### Table 1 Clinical and biochemical features of PHP and control postmenopausal women.

<table>
<thead>
<tr>
<th>PHP</th>
<th>GHD</th>
<th>No GHD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (No.)</td>
<td>34</td>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62.3 ± 8.4</td>
<td>62.3 ± 9.9</td>
<td>63 ± 8.7</td>
</tr>
<tr>
<td>Age of menopause (yr)</td>
<td>50.8 ± 2.4</td>
<td>51.4 ± 2.2</td>
<td>51.1 ± 3.2</td>
</tr>
<tr>
<td>BMI</td>
<td>25.9 ± 1.8</td>
<td>26.3 ± 1.7</td>
<td>26.1 ± 1.5</td>
</tr>
<tr>
<td>Ca++ (nmol/l)</td>
<td>1.51 ± 0.13</td>
<td>1.48 ± 0.10</td>
<td>1.24 ± 0.4**</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>188.1 ± 124.9</td>
<td>136.9 ± 59.3</td>
<td>48.3 ± 15.6**</td>
</tr>
<tr>
<td>T-score</td>
<td>−2.4 ± 1.6</td>
<td>−2.0 ± 1.0</td>
<td>−1.0 ± 0.4**</td>
</tr>
<tr>
<td>B-ALP (μg/l)</td>
<td>28.5 ± 23</td>
<td>19.2 ± 19</td>
<td>16.8 ± 8.3**</td>
</tr>
<tr>
<td>OC (μg/l)</td>
<td>36.6 ± 27.3</td>
<td>35.6 ± 24</td>
<td>18.7 ± 10.5**</td>
</tr>
<tr>
<td>S-CTX pM/l</td>
<td>5580.7 ± 4073</td>
<td>8808.4 ± 7751</td>
<td>3502 ± 1120**</td>
</tr>
<tr>
<td>Peak GH (ng/ml)</td>
<td>8.8 ± 4.2**</td>
<td>28.7 ± 11.8</td>
<td>32.6 ± 7.8*</td>
</tr>
<tr>
<td>IGF-I (ng/ml)</td>
<td>134.7 ± 60.8</td>
<td>126.0 ± 41.7</td>
<td>170.8 ± 78.3</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± s.n. Normal values: Ca+++ 1.13–1.30 mmol/l, PTH 10–65 pg/ml, B-ALP 2–28 μg/l, OC 6.8–34 μg/l, S-CTX < 4520 pm/l, IGF-I age > 50 yr 71–290 μg/l. *Mean peak GH values after GHRH + Arg stimulation. †P<0.05 GHD vs no GHD patients. **P<0.05 controls vs GHD patients. ***P<0.05 controls vs both GHD and no GHD patients.
Mean T-score was not statistically different between the two groups of PHP patients (-2.4 ± 1.2 in PHP-GHD vs -2.05 ± 1.01 in PHP-no GHD); however, osteoporosis (T-score < -2.5) and osteopenia (T-score > -2.5 and < -1) were found in 73 and 18% of PHP-GHD respectively, in 37 and 44% of PHP-no GHD respectively, and in 3 and 27% of controls respectively (Figs 1 and 2). The prevalence of osteoporosis in PHP-GHD was significantly higher than in PHP-no GHD patients (P<0.02) and controls (Table 2, P<0.02). The cumulative prevalence of bone mass reduction (osteoporosis + osteopenia) was 91% in PHP-GHD, 81% in PHP-no GHD (P=NS) vs 30% in controls (P=0.02). T-score was correlated with serum PTH levels (P=0.02) and not with ionized calcium, age, age at menopause, BMI, GH peak and IGF-I. Mean BMD was not statistically different between the two groups of PHP patients (0.77±0.14 g/cm² in PHP-GHD vs 0.82±0.14 in PHP-no GHD) and was correlated only with serum PTH (P=0.05).

T-score was correlated with markers of bone remodelling only in GHD patients (Fig. 3). Serum concentrations of markers of bone remodelling were increased in 42% (B-ALP), 54% (OC), and 67% (S-CTX) of PHP patients. However, as illustrated in Table 1, while mean values of each parameter in PHP-GHD and PHP-no GHD were significantly higher than in controls, no significant differences between the two groups of PHP patients were observed.

Discussion

The results of the present study demonstrate that PHP patients with concomitant GH deficiency (PHP-GHD) have a higher prevalence of osteoporosis than PHP patients without GHD patients (PHP-no GHD). The latter, in turn, have a higher prevalence of osteoporosis than controls. On the other hand, the prevalence of osteopenia is higher in PHP-no GHD than in PHP-GHD; thus, cumulating the two different degrees of bone mass reduction (osteoporosis and osteopenia), differences between the two groups attenuate, although changes are clearly more severe in PHP patients in whom the increase in PTH secretion is accompanied by an impairment in GH secretion.

Bone remodelling is regulated by a balance between bone resorption and bone formation (15). When the former prevails, osteoporosis develops, as in PHP. The adverse effects of PHP on bone are of special concern in postmenopausal women (15). As a matter of fact, osteoporosis has recently become the major factor in the process of prescribing therapy in asymptomatic PHP and the BMD threshold for recommending surgery has been increased (15).

GH has profound effects on linear bone growth, bone metabolism and bone mass (10). GH plays a crucial role in the maintenance of bone mass in adults by regulating bone remodelling through a complex interaction of circulating GH, IGF-I, IGF binding protein (IGFBP) factors and locally produced IGF and IGFBP acting in an autocrine and paracrine way (16). In vitro GH stimulates osteoclastic bone resorption through direct and indirect actions on osteoclast differentiation and through indirect activation of mature osteoclasts, possibly via local IGF-I/II production from osteoblasts (17). Unfortunately, at present locally produced IGF-I cannot be evaluated and therefore we think it is not possible to differentiate in vivo GH and IGF-I actions.

Adult patients with GHD have decreased bone mineral content and BMD, the severity of which is related to the timing, age of onset and severity of GHD (12, 18). An increased prevalence of osteoporosis has been found in several studies of patients with adult-onset GHD (18). Patients with isolated GHD had similar

Table 2 The patients GHD present a significantly higher incidence of osteoporosis.

<table>
<thead>
<tr>
<th>GHD</th>
<th>No GHD</th>
<th>Total</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with osteoporosis</td>
<td>25</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>Patients without osteoporosis</td>
<td>9</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>16</td>
<td>50</td>
</tr>
</tbody>
</table>

Figure 1 Prevalence of osteoporosis (■), osteopenia (□) and normal bone density (▲) in patients with hyperparathyroidism with associated GH deficiency (GHD), without GHD (no GHD), and in controls. For significance of differences, see text.

Figure 2 T-score values in patients with hyperparathyroidism with associated GH deficiency (GHD) and without GHD (no GHD).
In this section, the prevalence of fractures to those with multiple pituitary hormone deficiencies (12, 18) is discussed. GH replacement therapy can improve BMD in these patients (19).

As we previously reported, PHP is a condition often associated with functional GHD (5); the latter can be reverted by surgically removing parathyroid adenoma(s) responsible for PHP (7). Hypercalcemia rather than the increase in serum PTH seems to account for the development of GHD, as shown by our recent studies in two families with FHH (8). The results of the present study suggest that the combination of PHP and GHD in postmenopausal women seems to have an additive effect in bone remodelling, even if a direct effect of GHD status on T-score and/or BMD could not be demonstrated. It is difficult to speculate on the possible mechanisms involved in the process in vivo. The use of bone turnover markers is controversial (20–22). In fact, while in postmenopausal women, there is a correlation between bone turnover markers and BMD (23), in the same patients B-ALP and short-term changes in collagen cross-links during therapy are important predictive factors in bone mass recovery (23). OC as a marker of bone formation and deoxypiridinoline, bone resorption, are increased in the majority of PHP patients, denoting a high rate of bone turnover with persistent coupling between formation and resorption (1, 2). On the other hand, no conclusive data are available on the effects of GHD on bone remodelling in adults. Serum levels of OC, reflecting osteoblast activity and bone formation have been found to be decreased, increased or unchanged.

Figure 3 Correlation between T-score values and serum concentrations of markers of bone remodelling in patients with hyperparathyroidism with associated GH deficiency (GHD) (A) or without GHD (B).
(10, 11). Most studies have shown that there is no difference in resorption markers between controls and adult GHD patients (12).

In our PHP of patients, in many instances serum levels of all markers were increased, in keeping with the literature (1–3). Moreover, no difference was found between GHD and no GHD patients; however, a significant correlation was demonstrated between T-score and each of the biochemical markers only in the subgroup of GHD patients. It seems, therefore, that lack of GH could be an important factor in influencing the degree of bone mass loss.

In conclusion, an impairment of GH secretion, frequently concomitant with PHP and due to hypercalcaemia, could be involved as a pathogenic factor in the abnormalities of bone metabolism accompanying PHP. The more severe degree of bone mass reduction observed in the presence of GHD should represent an additional indication for a definitive resolution of PHP by surgery, avoiding further delay or postponing.

Acknowledgements

This work was partially supported by Grants from the University of Pisa (Fondi di Ateneo) and M.I.U.R., Rome to Ennio Martino, from the University of Pisa and from Ministry of Education, University and Research (M.I.U.R., Rome) to Maurizio Gasperi, and from the University of Insubria at Varese to Luigi Bartalena.

References

21 Stepan J. Clinical utility of bone markers in the evaluation and follow-up of osteoporotic patients: Why are the markers poorly accepted by clinicians? Journal of Endocrinological Investigation 2003 6 458–463.