Low Bone Mass Is an Infrequent Feature of the Adult Growth Hormone Deficiency Syndrome in Middle-Age Adults and the Elderly

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Low bone mass is considered a characteristic feature of adult GH deficiency (GHD). Although low bone mass is universally observed in cohorts of GHD adults of young age, the situation is less clear with regard to cohorts of GHD middle-age adults or the elderly. We have examined the relationship between bone mineral density (BMD) and age in 125 severely GHD adults using dual-energy x-ray absorptiometry. This relationship was further examined with a calculated measure of volumetric BMD, bone mineral apparent density (BMAD).

A significant positive correlation was observed between age and BMD (Z scores) at the lumbar spine (r = 0.39, P < 0.0001), femoral neck (r = 0.47, P < 0.0001), total hip (r = 0.47, P < 0.0001), and ultradistal (r = 0.46, P < 0.0001) and distal radius (r = 0.52, P < 0.0001). Young adults were observed to have reduced bone mass, whereas elderly GHD patients had normal Z scores. After division of the cohort into age ranges (<30, 30–45, 45–60, and >60 yr), BMD Z scores at all five skeletal sites increased significantly across the age groups from youngest to oldest (P < 0.001). When BMD was assessed using absolute values (g/cm²), in contrast to the decline in BMD observed with aging in a normal population, BMD at the total hip and ultradistal and distal radius increased across the age strata of GHD adults (P = 0.0003, P = 0.004, and P = 0.002, respectively), and a trend toward an increase in lumbar spine and femoral neck BMD was also observed. No significant change in BMAD was observed across the four age groups. The percentage of patients observed to have BMD Z scores of less than −2.0 at the lumbar spine was 30, 11, 11, and 14% in the four age groups, respectively. At the femoral neck, the corresponding percentages were 36, 6, 7, and 0%, respectively.

In summary, we have shown that the effect of severe GHD on BMD is dependent on age. Low bone mass was observed in the young patients; however, patients over the age of 60 yr demonstrated a mean BMD Z score above that of the reference population and significantly greater BMD (g/cm²) when compared with young GHD adults. Few patients were observed to have BMD Z scores below −2.0 except patients aged less than 30 yr, which, in part, was explained by their shorter stature. Thus, significantly reduced bone mass is not a frequent observation in adults with GHD. (J Clin Endocrinol Metab 89: 1124–1130, 2004)
Subjects and Methods

Patients

This was a retrospective study including 125 hypopituitary adults with documented severe GHD; 61 patients were female, the mean age of the population was 37.7 ± 15.6 yr (range, 17–84 yr), and the body mass index was 27.9 ± 6.0 kg/m². Patients with a previous diagnosis of acromegaly or Cushings disease were excluded from the study. Patients who received spinal irradiation as a therapeutic intervention (n = 29) were excluded from the cohort when the lumbar spine BMD data were analyzed but were included in the analysis of the other measured skeletal sites. Severe GHD was defined by a peak GH response to a stimulation test of less than 3 µg/liter (12). The GH stimulation test of preference was the insulin tolerance test (n = 20); patients were drawn from the endocrine clinic of the Christie Hospital. Of GHD was reestablished during adulthood in all CO patients. All underwent two tests of GH reserve (13). The diagnosis of GHD was contraindicated or a second test was required to confirm GHD. One such method assumes that the vertebral heights of GHD patients differ from those of the mean (17, 18). This is calculated as bone mineral content/area, where area is the mean of the vertebral heights.

Study protocol

A survey of the notes of patients under regular follow-up in the endocrine clinic of the Christie Hospital was undertaken to identify patients with biochemically defined severe GHD who had additionally undergone a measurement of BMD that postdated the diagnosis of severe GHD. None of the patients was receiving GH replacement therapy at the time of the study or had received it during adult life. In those patients who had previously received GH replacement during childhood (n = 35 of 44) to optimize final height, GH was stopped when linear growth ceased. In these 35 patients, the mean interval between discontinuation of GH therapy and BMD measurement was 6.7 ± 4.1 yr. Additional anterior pituitary hormone deficits had been adequately replaced for at least 6 months before BMD measurement in all patients. In patients meeting the above inclusion criteria, background data at the time of the BMD estimation were drawn from the database of the department of Clinical Radiology, Imaging Science, and Biomedical Engineering, University of Manchester, and the Christie Hospital medical records. Ethical approval for this study was granted by the South Manchester Local Research Ethics Committee, and all patients provided written informed consent.

Bone densitometry

BMD measurements were made between 1996 and 2001. Measurements included DXA of femoral neck, total hip, and lumbar spine (posteroanterior projection, L1–4) and single-energy x-ray absorptiometry (SXA) of the forearm (distal and ultradistal sites). These measures are of integral (cortical and trabecular) bone, with the various sites containing different proportions of cortical and trabecular bone (14); the cortical to trabecular ratios were as follows: lumbar spine, 50:50; femoral neck, 60:40; distal radius, 87:13; and ultradistal radius, 65:35. For DXA of the lumbar spine, total hip, and femoral neck, scanning was performed using a Hologic QDR-4500 Acclaim fan-beam scanner (Hologic, Inc., Bedford, MA) using software version V8.26f3. Forearm scans were performed in the nondominant forearm by SXA using an Osteometer DTX-100 scanner (Osteometer A/S, Roedovre, Denmark).

Experienced staff, who used standardized procedures recommended by the scanner manufacturers, performed all studies. Calibration and quality assurance testing of scanners were performed daily. The short-term in vivo precisions (coefficient of variation %) in our unit for the Hologic QDR-4500 were as follows: lumbar spine, 1.09%; femoral neck, 3.29%; and total hip, 1.26%. Precisions for the SXA measurements were as follows: distal radius, 1%; and ultradistal radius, 2.5%.

BMD was measured in g/cm², and the results are expressed as Z scores (the number of sds that the patient’s result differs from the mean BMD of appropriate sex- and age-matched reference data). The reference data provided by the relevant scanner manufacturer were used. For femoral neck, total hip, and total hip Z scores on the Hologic scanner, the National Health and Nutrition Examination Survey (NHANES III, 1988–1991) reference database was used (15, 16). Because DXA provides an areal density (g/cm²), results are size dependent. To take this into account, methods have been suggested to calculate a pseudovolumetric density. One such method assumes that the vertebrae are cubes and calculates bone mineral apparent density (BMAD) (17, 18). This is calculated as bone mineral content/area, where area is the mean of the vertebral heights.

Statistics

The data are presented as mean ± sds. Correlations were sought using Pearson’s test. The data were normally distributed, and therefore, comparisons between groups were performed using the Student’s t test. One-way ANOVA was used to examine differences across the groups, and the χ² test was used to examine differences in frequency of occurrence of events between groups. Multivariate analysis was performed using a forward stepwise multiple linear regression model. A P < 0.05 was accepted as significant.

Results

Overall cohort

Mean BMD Z scores at the lumbar spine, femoral neck, total hip, and ultradistal and distal radius for the cohort overall were −0.52 ± 1.40 (n = 96), −0.75 ± 1.46 (n = 118), −0.613 ± 1.33 (n = 112), −0.56 ± 1.37 (n = 114), and −1.06 ± 1.33 (n = 115), respectively. BMD values (g/cm²) at the five sites studied were positively correlated within individuals; the correlation coefficients ranged between 0.55 and 0.90 (P < 0.0001 for all correlations). Similar correlation coefficients were obtained when BMD was expressed as a Z score.

A significant correlation was observed between age and BMD Z scores at all five sites (lumbar spine, r = 0.39, P < 0.0001; femoral neck, r = 0.47, P < 0.0001; total hip, r = 0.47, P < 0.0001; ultradistal radius, r = 0.46, P < 0.0001; and distal radius, r = 0.52, P < 0.0001; Fig. 1, A–E). The relationship described by the correlations showed less deficit in BMD Z scores in GHD adults of greater age. At the lumbar spine, the relationship was described by the following equation: y = 0.036x − 2.01, where x is the patient’s age and y is the mean Z score for GHD patients of that age. The use of a second order curve to describe the relationship between age and BMD Z score at each of the five sites did not improve the respective correlation coefficients. The age beyond which GHD had no appreciable effect on BMD Z score (i.e. y = 0) was 56 yr at the lumbar spine, 55 yr at the femoral neck, 54 yr at the total hip, 51 yr at the ultradistal radius, and 61 yr at the distal radius.

Stratification by age (Table 2)

The cohort was arbitrarily divided into age ranges (<30, 30–45, 45–60, and >60 yr). Across the age groups, from lowest to highest age, there was a significant increase in height (P = 0.02), weight (P < 0.0001), and body mass index (P = 0.0006). Additionally, the proportion of patients with isolated GHD decreased from 50 to 0% (P = 0.002). The estimated duration of GHD was not significantly different between the four age strata (P = 0.38).

A significant increase in BMD Z scores was observed with progression across the age strata from the youngest to the oldest (ANOVA: lumbar spine, P = 0.0007; femoral neck, P = 0.0001; total hip, P < 0.0001; ultradistal radius, P < 0.0001; and distal radius, P < 0.0001). When assessed by absolute
Fig. 1. The relationship between BMD and age in 125 adults with severe GHD at the lumbar spine (A), femoral neck (B), total hip (C), ultradistal radius (D), and distal radius (E). BMD is represented in age-related SD scores (Z scores).
BMD values (g/cm²), no significant change occurred across the age groups in lumbar spine (P = 0.14) or femoral neck (P = 0.21) BMD, or in BMAD (P = 0.90), a measure that attempts to compensate for differences in the volume of the vertebral bodies as a consequence of height. There was, however, a significant increase in BMD (g/cm²) at the total hip (P = 0.003), ultradistal radius (P = 0.004), and distal radius (P = 0.002), with progression across the age groups and the highest BMD being observed in the older patients (Table 2).

The percentages of patients in the age ranges of less than 30, 30–45, 45–60, and more than 60 yr who were observed to have BMD Z scores of less than −2.0 at the lumbar spine were 30, 11, 11, and 14%, respectively. At the femoral neck, 36, 6, 7, and 0% of patients, respectively, had a Z score of less than −2.0. Similar decreases in the percentage of patients with Z scores below the normal range with increasing age were observed at the total hip and ultradistal and distal radius (Table 2).

**Gender**

After subdividing the cohort by gender the relationship between age and BMD Z score remained significant at all five sites studied in both the female and male subgroups (r = 0.28–0.64). Mean BMD Z score in females vs. males at the lumbar spine (−0.51 ± 1.36 vs. −0.59 ± 1.52, P = 0.79), femoral neck (−0.91 ± 1.23 vs. −0.60 ± 1.64, P = 0.25), total hip (−0.70 ± 1.07 vs. −0.53 ± 1.55, P = 0.44), ultradistal radius (−0.49 ± 1.46 vs. −0.63 ± 1.29, P = 0.61), and distal radius (−0.93 ± 1.24 vs. −1.19 ± 1.40, P = 0.28) were not significantly different.

**Timing of onset of GHD**

Mean BMD Z scores for AO patients were significantly higher compared with the mean BMD Z scores of the CO patients at all five sites (lumbar spine, −0.28 ± 1.39 vs. −1.18 ± 1.26, P = 0.006; femoral neck, −0.35 ± 1.35 vs. −1.59 ± 1.33, P < 0.0001; total hip, −0.23 ± 1.26 vs. −1.45 ± 1.10, P < 0.0001; ultradistal radius, −0.15 ± 1.22 vs. −1.38 ± 1.30, P < 0.0001; and distal radius, −0.66 ± 1.14 vs. −1.88 ± 1.32, P < 0.0001). However, the AO cohort patients were significantly older than the CO cohort (44.3 ± 14.9 vs. 25.7 ± 7.5 yr, P < 0.0001).

**Multivariate analysis**

Multivariate analysis was performed using BMD Z score as the dependent variable and at BMD, height, weight, timing of onset of GHD, gender, and the number of pituitary hormone deficits as the independent variables. Weight explained 16% (r² = 0.16, P = 0.0012) and age at BMD explained 8% (r² = 0.08, P = 0.0018) of the variability in BMD Z score at the lumbar spine in adults with severe GHD. At the spine, none of the additional variables achieved significance. At the femoral neck, 49% of the variance in BMD Z score was explained by a combination of weight (r² = 0.42, P < 0.0001) and age at the time of BMD measurement (increment in r² = 0.07, P = 0.0003). Forty-six percent of the variance in total hip BMD Z scores was accounted for by weight (r² = 0.40, P < 0.0001) and age at BMD measurement (increment in r² = 0.06, P = 0.0006). At the ultradistal and distal radius, age (r² = 0.21, P = 0.001; and r² = 0.27, P < 0.0001, respectively) and timing of onset (increment in r² = 0.04, P = 0.014; and increment in r² = 0.03, P = 0.01, respectively) explained 25% and 30% of the variation in BMD Z scores, respectively.

**Discussion**

In a large cohort of hypopituitary adults derived from a single center, we have demonstrated that the effect of severe GHD on BMD at the lumbar spine, femoral neck, and distal and ultradistal radius is dependent on age. The importance of age in defining the relative BMD of patients with severe GHD. In adults with severe GHD, height, weight, timing of onset of GHD, gender, and pituitary hormone deficits are major determinants of BMD at the lumbar spine, femoral neck, and distal and ultradistal radius. The use of a calculated pseudovolumetric measure of BMD derived from the bone mineral content and vertebral area, BMAD, was not significantly different across the age strata, which suggested that the relatively high prevalence of patients with BMD Z scores of less than −2.0 in the youngest age group may, in part, be related to their shorter height. The importance of age in defining the relative BMD of patients with severe GHD may explain the contradictory findings of previous studies examining BMD in GHD patients during middle and old age. The mean age of the patients investigated for the effect of GHD on BMD in the study by Janssen et al. (10) was 47 yr. From our study, using the regression line for age and lumbar spine BMD Z score, one may predict that, for an age of 47 yr, the mean Z score for lumbar spine BMD would be in the region of −0.35. In the study by Holmes et al. (9), the mean age of the patients was younger, at 42.4 yr. From the regression line, it would be expected that the mean lumbar spine BMD Z score would lie in the region of −0.5 sn score (SDS). The cohorts studied by
TABLE 2. Demographics, BMD (g/cm², Z score), and percentage of patients with BMD Z scores of less than 2.0 after division of patients according to age

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Age</th>
<th>&lt;30 yr</th>
<th>30–45 yr</th>
<th>45–60 yr</th>
<th>&gt;60 yr</th>
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<tbody>
<tr>
<td>n</td>
<td></td>
<td>52</td>
<td>32</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td></td>
<td>23.3 ± 4.2</td>
<td>36.9 ± 4.2</td>
<td>51.5 ± 3.8</td>
<td>66.8 ± 5.9</td>
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<tr>
<td>Height (cm)</td>
<td></td>
<td>161.3 ± 12.7</td>
<td>164.2 ± 11.1</td>
<td>166.4 ± 7.8</td>
<td>170.8 ± 8.5</td>
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<tr>
<td>Weight (kg)</td>
<td></td>
<td>67.3 ± 19.0</td>
<td>77.6 ± 17.1</td>
<td>81.4 ± 15.5</td>
<td>91.1 ± 19.7</td>
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<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>25.8 ± 6.3</td>
<td>28.6 ± 4.9</td>
<td>29.4 ± 5.4</td>
<td>31.2 ± 6.3</td>
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<td>CO/AO (%)</td>
<td></td>
<td>36/16</td>
<td>7/25</td>
<td>1/26</td>
<td>0/14</td>
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<tr>
<td>IGHD (%)</td>
<td></td>
<td>50</td>
<td>41</td>
<td>22</td>
<td>0</td>
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<tr>
<td>Duration GHD (yr)</td>
<td>9.8 ± 6.5</td>
<td>13.2 ± 9.4</td>
<td>9.7 ± 8.8</td>
<td>8.8 ± 7.2</td>
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BMD (g/cm²)

<table>
<thead>
<tr>
<th>BMD (g/cm²)</th>
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<th>30–45 yr</th>
<th>45–60 yr</th>
<th>&gt;60 yr</th>
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</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>0.924 ± 0.12</td>
<td>0.975 ± 0.13</td>
<td>0.989 ± 0.15</td>
<td>1.027 ± 0.19</td>
</tr>
<tr>
<td>BMAD</td>
<td>0.245 ± 0.02</td>
<td>0.248 ± 0.03</td>
<td>0.251 ± 0.03</td>
<td>0.250 ± 0.04</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.759 ± 0.12</td>
<td>0.798 ± 0.14</td>
<td>0.792 ± 0.16</td>
<td>0.842 ± 0.14</td>
</tr>
<tr>
<td>Total hip</td>
<td>0.847 ± 0.14</td>
<td>0.903 ± 0.14</td>
<td>0.93 ± 0.18</td>
<td>1.00 ± 0.17</td>
</tr>
<tr>
<td>Ultra distal radius</td>
<td>0.364 ± 0.07</td>
<td>0.373 ± 0.08</td>
<td>0.410 ± 0.09</td>
<td>0.445 ± 0.09</td>
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<tr>
<td>Distal radius</td>
<td>0.439 ± 0.07</td>
<td>0.459 ± 0.08</td>
<td>0.488 ± 0.07</td>
<td>0.521 ± 0.07</td>
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BMD (Z score)

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<th>45–60 yr</th>
<th>&gt;60 yr</th>
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</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>−1.25 ± 1.03</td>
<td>−0.70 ± 1.11</td>
<td>−0.07 ± 1.44</td>
<td>0.37 ± 1.77</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>−1.55 ± 1.20</td>
<td>−0.72 ± 1.19</td>
<td>−0.13 ± 1.50</td>
<td>0.57 ± 1.21</td>
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<tr>
<td>Total hip</td>
<td>−1.34 ± 1.09</td>
<td>−0.64 ± 1.02</td>
<td>−0.01 ± 1.40</td>
<td>0.58 ± 1.28</td>
</tr>
<tr>
<td>Ultra distal radius</td>
<td>−1.14 ± 1.10</td>
<td>−0.72 ± 1.14</td>
<td>0.18 ± 1.48</td>
<td>0.42 ± 1.47</td>
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<tr>
<td>Distal radius</td>
<td>−1.74 ± 1.19</td>
<td>−1.12 ± 0.99</td>
<td>−0.45 ± 1.28</td>
<td>0.19 ± 1.15</td>
</tr>
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</table>

Z score < −2.0 (%)

<table>
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<th>Z score &lt; −2.0 (%)</th>
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<th>30–45 yr</th>
<th>45–60 yr</th>
<th>&gt;60 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>30</td>
<td>11</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>36</td>
<td>6</td>
<td>7</td>
<td>0*</td>
</tr>
<tr>
<td>Total hip</td>
<td>20</td>
<td>9</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Ultradistal radius</td>
<td>20</td>
<td>13</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Distal radius</td>
<td>38</td>
<td>13</td>
<td>4</td>
<td>0*</td>
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</table>

BMI, Body mass index; IGHD, isolated GHD.

a P < 0.05; b P < 0.0001; c P < 0.001; d P < 0.01 for trend across age groups (ANOVA).

Toogood et al. (11) and Fernholm et al. (19) had median ages of 66 and 68 yr, respectively, which we would predict to result in a mean lumbar spine BMD Z score of around +0.35 SDS. Given that the difference in BMD expected between the patient cohorts and the reference populations in all these studies was in the region of 0.4 SDS and the number of patients in each study was small, it is unlikely that these studies were sufficiently powered to reliably establish this mild degree of variation from normality. In agreement with the findings from our study, Rosen et al. (20) demonstrated reduced BMD in AO GHD patients of less than 55 yr of age; however, in the patients over age 55 yr, BMD was not significantly different from that of the control population.

Studies investigating BMD in adult GHD have consistently found low bone mass in CO GHD patients (21–24), but in AO GHD patients, studies have reported both low bone mass (9, 20, 25) and normal BMD (10, 11, 19). In this study, when analyzing the cohort overall, and in a previous study from our unit (26), we demonstrated that CO GHD adults have lower bone mass than AO GHD patients. The latter study (26), however, did not match the patient groups for age, a variable that we have now shown to impact significantly on the BMD Z scores of GHD adults.

One of the most important observations from this study is that, with the exception of patients aged less than 30 yr, the percentage of patients with BMD values (Z scores) below the normal range, which reflect significantly reduced bone mass requiring intervention, is small and decreases further with increasing age. The natural history of BMD over time in adult patients with untreated GHD is not known. Cross-sectional data from the normal population show peak bone mass to be reached around the age of 30 yr; thereafter, BMD (g/cm²) slowly decreases with increasing age. In contrast to observations in the normal population in our cross-sectional data from GHD adults, we have not observed a decrease in BMD with increasing age. In fact, BMD (g/cm²) at the total hip and femoral neck and in BMAD across the age groups is significantly increased. A trend toward an increase in BMAD was also observed, whereas volumetric measures of BMD in the normal population tend not to change with age. The absence of a statistically significant increase in BMD at the lumbar spine and femoral neck was also for BMD to increase. A trend toward an increase in BMAD was also observed, whereas volumetric measures of BMD in the normal population tend not to change with age. The absence of a statistically significant increase in BMD at the lumbar spine and femoral neck in BMAD across the age groups is unlikely to be explained by differences in pathophysiology between these sites and sites at which a significant increase in BMD was observed, but instead, it is probably a result of the statistical power of the study. One might speculate that the BMD of a young GHD adult may follow the regression line and lead to an improvement in the patient’s BMD (Z score, g/cm², and g/cm³) with time. A more likely explanation is that, with progression across the age strata, a higher proportion of patients had reached peak bone mass before they acquired GHD and that GH plays only a minor role in bone mineral maintenance.

BMD derived from DXA is an areal measure of BMD (g/cm²) and, as a consequence, is influenced by the greater anteroposterior depth of a bone that is related to increases in height (27). In our study, when the patients are stratified...
according to age, an increase in height and weight is observed across the age groups in the same direction as the increase in BMD. Height and weight were highly correlated. Inclusion of height and weight into the multivariate analysis confirms that weight is an important predictor of BMD at weight-bearing skeletal sites (lumbar spine and femur) but not at the radius. It must be noted, even with correction for height and weight in the multivariate analysis, that age remained a significant determinant of BMD at all five skeletal sites.

By calculating BMAD, we have mathematically corrected areal BMD (g/cm²) to provide a pseudovolumetric measure of BMD (g/cm³) (17, 18). No significant difference in BMAD was observed across the age groups. It can be assumed that the patients in the two oldest age strata were of normal height, having not been influenced by the presence of GHD during childhood growth. Additionally, these patients had normal BMD as exemplified by the normal mean BMD Z scores. BMAD in the youngest age strata was lower, although not significantly, than in the two oldest age groups. This latter observation may imply that much of the observed reduction in DXA areal BMD and the higher proportion of patients with subnormal BMD Z scores in the youngest patients may falsely result from their reduced stature. Thus, it is likely that fewer patients than those observed to have BMD Z scores of less than −2.0 truly have significantly reduced BMD. In agreement with this finding, BMAD has been reported to be normal in patients with severe GHD resulting from GH-receptor defects (Larson’s syndrome) despite reduced BMD Z scores (28).

GH is intricately involved in bone growth and turnover. This is supported by the finding of reduced serum and urinary markers of bone turnover in GHD adults (11, 29) and the increase in these markers after GH replacement therapy (30–33). Bone turnover is a coupled process that occurs continuously throughout life; bone resorption is followed in time by bone formation. With ageing, it has been proposed that, at the level of the remodeling unit, this process becomes increasingly inefficient. Thus, in the elderly, at the end of each remodeling cycle, small deficits in bone mass are accrued (34, 35), which lead to the observed age-related loss of bone mass. The effect of GHD on the skeleton would thus be dictated by the patient’s age. GHD during adolescence and young adult life, before attainment of peak bone mass and when bone mass is being accrued, would slow this acquisition and result in osteopenia. Whereas in the elderly in whom bone turnover is inefficient, a reduction in bone turnover as a consequence of GHD could reduce the rate of bone mineral loss, possibly resulting in a normal or increased BMD. Further support for this hypothesis comes from the finding of increased bone loss in elderly men and women (36–40) and increased frequency of hip fractures in elderly women (41) with bone resorption markers in the upper regions of the normal range. Changes in BMD in the elderly may relate to the rate of bone turnover; hormone deficiencies (i.e. GH) and replacements (i.e. estrogen) that reduce bone turnover and hence bone resorption tend to increase BMD.

BMD is a surrogate marker of fracture risk (5, 6). Our data suggest that young adults with GHD may be at increased fracture risk relative to age-matched healthy controls. In contrast, from the BMD measurements alone, we would predict elderly GHD adults not to be at an increased risk of fracture. This is, however, a simplistic view because reduced muscle mass has been shown to be a determinant of the risk of hip fracture and a number of studies report GHD adults to have reduced muscle mass (1, 30, 42, 43), although a difference has not been demonstrated between elderly GHD adults and age-matched normal volunteers (44, 45). Hypopituitary patients may additionally be at greater risk of falls due to poor vision, a consequence of previous optic chiasmal compression. Thus, the elderly with severe GHD may be at increased fracture risk despite normal BMD. Currently, however, insufficient information exists to determine whether or not long-term GH replacement normalizes the increased fracture risk of the hypopituitary adult; nonetheless, our data suggest that low bone mass is not a primary indication for GH replacement in a hypopituitary adult over the age of 30 yr. Indeed, the finding of a pathologically low bone mass in such a patient should stimulate consideration of alternative explanations other than GHD.

To summarize, we have demonstrated the effect of severe GHD on BMD at the lumbar spine, femoral neck, total hip, and distal and ultradistal radius to be dependent, in part, on age. Younger patients were observed to have reduced bone mass relative to the normal population. However, patients over the age of 60 yr demonstrated a mean BMD Z score above that of the reference population and significantly greater BMD (g/cm²) when compared with young GHD adults. Overall, few patients, except those aged less than 30 yr, had significantly reduced bone mass (i.e. a BMD Z scores of less than −2.0), and correction of BMD to provide a pseudovolumetric measure of bone density suggested that the reduced stature of the younger patients may explain, at least in part, this higher frequency of subnormal BMD Z scores. Thus, low bone mass is not a frequent observation in GHD adults. Despite normal BMD, an increase in fracture prevalence may still be observed in the elderly GHD population as a consequence of increased falls related to muscle weakness and visual field defects.

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