The Impact of Congenital, Severe, Untreated Growth Hormone (GH) Deficiency on Bone Size and Density in Young Adults: Insights from Genetic GH-Releasing Hormone Receptor Deficiency

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GH and IGF-I have well recognized effects on bone elongation during development, but their importance for bone mineralization and structure during the growth phase are less well understood. Because children with GH deficiency are generally treated with GH, little detailed information exists in humans about the effects of long-term GH deficiency on bone development. The recently described syndrome of genetic GHRH-receptor deficiency in Pakistan (dwarfism of Sindh) affords a unique opportunity to examine the question of GH deficiency on bone development because the affected patients have congenital, severe, isolated GH deficiency, which had never been treated because of societal reasons. We performed dual energy x-ray absorptiometry scans in four adult males (age, 23–30 yr) to address the question of bone mineralization. Areal bone mineral density (BMD) was low (mean Z scores: −3.3, −2.1, −3.7, and −1.7) in the lumbar spine, femoral neck, forearm, and total skeleton, respectively. This low areal BMD is in part caused by the small bone size in these dwarfed patients. When corrected for size, volumetric BMD (bone mineral apparent density) was normal to near normal (mean Z scores: −1.2, +0.8, and +0.8 for lumbar spine, femoral neck and total skeleton, respectively). We conclude that GH/IGF-I deficiency has relatively little impact on bone mineralization during the bone accretion phase. This is in marked contrast to their effect on bone elongation and overall bone size. (J Clin Endocrinol Metab 88: 2614–2618, 2003)
Chicagore and were admitted to the Northwestern University General Clinical Research Center. DEXA was performed on a QDR-4500A scanner (Hologic, Inc., Bedford, MA).

**Results**

Table 1 summarizes the lumbar spine BMD results for the four patients. All had significantly decreased areal BMD. This finding is at least in part a function of the small bone dimensions. To correct for this limitation, we calculated volumetric BMD (BMAD) as a more accurate index of true bone density. Interestingly, volumetric BMD was much less diminished than areal BMD. Indeed, only one patient (no. 1) had a volumetric BMD outside the normal range. In three of four patients, the lumbar areal BMD values were higher than the average values for height-matched boys (Table 2). (No correction for bone size is necessary for this comparison since bone size in the two groups is similar.)

Table 2 shows the BMD findings for the total body. Here again, areal BMD was low, but volumetric BMD was within the normal range in 3, and actually high in one patient. To

**Data acquisition and reduction**

Bone mineral content (BMC) and areal BMD were measured for the lumbar spine (L1–L4), nondominant femoral neck, nondominant forearm, and total body, using standardized Hologic software. Areal BMDs were compared with normative values from the United States Caucasian Hologic reference database (Hologic software version 90/25/91), and age- and sex-appropriate Z scores were derived. T scores are identical to Z scores in these patients because of their age.

Because of the small size of the patients and their bones, areal BMD values underestimate true BMD. Therefore, volumetric BMD (bone mineral apparent density, BMAD) was calculated as described by Katzman et al. (16), using the following formula:

\[
\text{BMAD} = \frac{\text{BMC}}{\text{area}^{3/2}}
\]

To calculate Z scores for volumetric BMD, data were compared with the normative United States Hologic reference database where appropriate data were available (i.e. for the lumbar spine). For the other measurements (femoral neck, radius, and total skeleton), bone area measurements, and hence volumetric BMD data, are not available in the United States Hologic database. Therefore, we used a reference database for body composition of normal Russian Caucasians (n = 821; age 10–92 yr), collected by A.V.B. and V.S.O. as part of the Russian Space Agency Research Program (Bouillon, R., et al., manuscript in preparation). In all cases, Z scores were based on comparison with age- and sex-appropriate reference data.

Because of the small size of the patients, lumbar BMD values were also compared with those of height-matched boys (height-equivalent ages are between 7.4 and 9.5 yr), being cognizant of the inherent differences between a prepubertal bone and a postpubertal bone. (Normative values for pediatric BMDs are available in the Hologic database only for the lumbar spine.)

Percentage body fat, measured by DEXA under exclusion of the head (brain fat), was used as an index of nutritional status (17, 18).

Statistical analysis was performed by t test. Values are expressed as mean ± sd.

**TABLE 1.** Lumbar spine bone mineralization (L1–L4) and height

<table>
<thead>
<tr>
<th>Patient</th>
<th>Areal BMD g/cm²</th>
<th>Z scorea</th>
<th>% normalb</th>
<th>Volumetric BMD g/cm³</th>
<th>Z scoreb</th>
<th>% normalb</th>
<th>Height cm</th>
<th>Z scoreb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.564</td>
<td>−4.8</td>
<td>52</td>
<td>0.100</td>
<td>−1.9</td>
<td>84</td>
<td>−3.62</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>0.820</td>
<td>−2.5</td>
<td>75</td>
<td>0.139</td>
<td>1.62</td>
<td>113</td>
<td>−0.01</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>0.703</td>
<td>−3.5</td>
<td>64</td>
<td>0.117</td>
<td>−0.61</td>
<td>95</td>
<td>−1.16</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>0.845</td>
<td>−2.2</td>
<td>77</td>
<td>0.142</td>
<td>1.88</td>
<td>115</td>
<td>0.09</td>
<td>101</td>
</tr>
<tr>
<td>Mean</td>
<td>0.733</td>
<td>−3.25</td>
<td>67</td>
<td>0.125</td>
<td>0.25</td>
<td>102</td>
<td>−1.18</td>
<td>89</td>
</tr>
<tr>
<td>SD</td>
<td>0.128</td>
<td>1.17</td>
<td>11.5</td>
<td>0.020</td>
<td>1.8</td>
<td>15</td>
<td>1.73</td>
<td>13</td>
</tr>
</tbody>
</table>

As reference group, both the United States Caucasian (Hologic) and the Russian Caucasian normal age-matched adults were used to calculate the Z score.

a Versus American (Hologic) database.
b Versus Russian Caucasian database.

**TABLE 2.** Comparison between areal BMD (L1–L4) in GHRH-R-deficient adults and height/size-matched normal boys

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Areal BMD g/cm²</th>
<th>Normal boys matched for height [Age (yr)]</th>
<th>Areal BMDa g/cm²</th>
<th>Z scoreb (patients vs. normal boys)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>0.564</td>
<td>8.75</td>
<td>0.645</td>
<td>−1.01</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>0.820</td>
<td>9.5</td>
<td>0.665</td>
<td>+1.94</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>0.703</td>
<td>9.5</td>
<td>0.665</td>
<td>+0.48</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>0.845</td>
<td>7.4</td>
<td>0.620</td>
<td>+2.96</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+1.09</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.73</td>
</tr>
</tbody>
</table>

a Data obtained from Hologic.
To calculate volumetric BMD Z scores, only the Russian Caucasian normal adults were used as reference group because bone area and, hence, volumetric BMD data are not available for the United States Caucasians.

**TABLE 4. Forearm bone mineralization**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Areal BMD (g/cm²)</th>
<th>Z score</th>
<th>% normal</th>
<th>Volumetric BMD (g/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.615</td>
<td>-3.68</td>
<td>75</td>
<td>0.160</td>
</tr>
<tr>
<td>2</td>
<td>0.632</td>
<td>-3.4</td>
<td>77</td>
<td>0.151</td>
</tr>
<tr>
<td>3</td>
<td>0.615</td>
<td>-3.7</td>
<td>74</td>
<td>0.169</td>
</tr>
<tr>
<td>4</td>
<td>0.615</td>
<td>-3.68</td>
<td>75</td>
<td>0.160</td>
</tr>
<tr>
<td>Mean</td>
<td>0.615</td>
<td>-3.68</td>
<td>75</td>
<td>0.160</td>
</tr>
<tr>
<td>SD</td>
<td>0.031</td>
<td>0.53</td>
<td>4</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Volumetric Z scores cannot be calculated because of lack of bone area data from a suitable normal control population.

**Discussion**

The present study demonstrates that volumetric BMD is relatively normal in young adult males with congenital, severe, untreated GHD. This somewhat unexpected result suggests that GH and IGF-I, although crucially important for bone elongation and accretion, are less important for bone mineralization. The patients included in this study had severe GHD due to genetic deficiency of the GHRH-R, which is necessary for somatotrope development, GH synthesis, and GH secretion (see Ref. 21 for review). As a result of their null mutation in the GHRH-R gene, it can be safely assumed that they had never secreted significant amounts of GH, and their severe dwarfism attests to that fact. Because of the environment they grew up in, they had never received exogenous GH or other endocrine therapy, thus presenting a particularly pure paradigm of GHD. Nutrition appears to have been adequate, as judged by several criteria, including nutritional histories, evaluation of food supply in their environment, clinical assessment, and measurement of body fat mass by DEXA. The patients were at or near their peak bone mass in the third decade of life, when peak bone mass is attained in both normal and GH-deficient subjects (22–26). It appears from this unique experiment of nature that bone mineralization or volumetric BMD in young adult men is relatively independent of GH and IGF-I. Direct measurement of volumetric bone density is possible by quantitative computed tomography (CT) of the lumbar spine and peripheral quantitative CT of the forearm (27). These techniques were not readily available for our patients. However, calculated volumetric density closely reflects true density (28, 29) and is widely used to estimate volumetric density in populations or patient groups that differ in height or bone size (30–32).

Cortical bone width and mass were not measured separately from trabecular bone. However, since bone size and total body calcium are markedly decreased and since both parameters are reflecting cortical rather than trabecular bone, it can be assumed that cortical bone mass must be markedly decreased in these patients without affecting the true density of the existing cortical bone.

Our data are consistent with another, similar example of largely untreated GHD in Russia (33). In that case, a cohort of GH-deficient patients received either no GH treatment or was only sporadically treated. Although areal BMD was low, volumetric BMD was relatively normal. Additional support for the present conclusion can be found in the literature. DeBoer et al. (25) studied 70 young adult patients with childhood onset GHD (25 with isolated GHD) and found that volumetric BMD was more normal (mean lumbar Z score, −0.9) than areal BMD (mean lumbar Z score, −1.59). Of note, this volumetric BMD is within the normal range. Baroncelli et al. (30) examined the relationship between body/bone size and areal vs. volumetric BMD in children and concluded that volumetric BMD is unaffected by anthropometric parameters. However, they found that volumetric BMD was decreased in children with GHD.
although to a much lesser degree than areal BMD. Low areal BMD was reported in five Israeli adult patients with genetic GH insensitivity (Laron syndrome), but no corrections were made for body/bone size (34). Bachrach et al. (35) assessed BMD and histomorphometry in young adults with genetic GH insensitivity from Ecuador. These patients are functionally similar to ours in that they had complete absence of GH action due to GH receptor deficiency, with a similar degree of dwarfism and severe IGF-I deficiency (36). Whereas their areal BMD was reduced in the spine, femoral neck, and total body, corresponding volumetric BMD was normal or even increased (35). Histomorphometry of iliac crest biopsies demonstrated essentially normal cortical and trabecular bone, with the exception of poor trabecular connectivity (35). Another example is the single patient with genetic IGF-I deficiency, who had severely reduced areal BMD of the lumbar spine, but normal or near-normal volumetric BMD (37). This patient is unique because he has high GH levels and normal direct (i.e., non-IGF-I dependent) GH action. The aggregate of these observations confirms the importance of both GH and/or IGF-I for bone growth but raises questions about the importance of these hormones for normal bone mineralization. It also illustrates that conventional (areal) BMD can be misleading in underestimating bone mineral in cases where bone size is reduced. The large majority of studies do not address this issue.

Appropriate animal models are also helpful in illuminating our findings. The closest model for our patients is the little (lit/lit) mouse, which harbors a severely inactivating missense mutation in the GHRH-R and thus represents the murine homolog (38–40). Its dwarfed phenotype is very similar to the human phenotype, both physically and biochemically (21). One study using carcass analysis showed that the percentage of body mineral was lower in homozygous little mice than in their heterozygous littermates, but the difference was relatively small (41). Recent studies have shown that the little mouse has relatively normal volumetric bone density and trabecular structure, as measured by micro-CT, compared with heterozygous littermates (Rosen, C. J., personal communication). Detailed histomorphometric as well as DEXA and quantitative computerized tomography data are available in the GH receptor knockout (Laron) mouse (42). In that model, BMC, areal BMD, and bone dimensions are significantly reduced, but trabecular volumetric BMD and trabecular bone volume are not significantly different from normal (43, 44).

It is intriguing that these conditions of severe, congenital GHD, or GH resistance are associated with relatively normal bone mineralization, whereas milder, acquired forms of GHD appear to be associated with true osteopenia. In particular, adults with acquired GHD frequently exhibit decreased areal BMDs, and their normal bone size minimizes geometric artifacts such as the one encountered in this study. Therefore, reports of osteopenia based on areal BMD in adults are probably accurate but should and can be verified by direct measurements. Because of the complex effects of GH and IGF-I on bone growth, maturation, and components of bone turnover (1), the possibility, albeit unlikely, must be considered that mild GHD leads to greater bone loss than severe GHD. Another potential explanation for the apparent discrepancy between the present data and those in adult GHD may lie in the age of onset of GHD. Our patients were in their third decade, when peak bone mass is achieved. They were GH-deficient during a period in their life when bone accretion took place. Most adult patients with GHD are older and spend all or at least part of their GH-deficient time during a period of physiological bone loss. It is possible that GHD with an onset after peak bone mass is achieved results in accelerated bone loss, whereas an onset before that may not exhibit the same effect.

Our observations and hypothesis about the GH/IGF-I effects on volumetric bone density do not contradict observations on increased fracture risk in GHD patients. Indeed, it is possible that fractures, and particularly cortical bone-related fractures, are more dependent on bone size and mass than on volumetric density, especially in patients with either very short or tall stature.

In summary, we report that congenital, severe, untreated GHD results in relatively normal BMD in young (23–30 yr old) adult men affected by genetic GHRH-R deficiency. While bone size and hence areal BMD is substantially reduced, estimated volumetric BMD is near normal. Although GH and IGF-I are critical for bone growth and skeletal development, the present data raise questions about the role of these hormones in bone mineralization during the bone accretion phase of life.

Acknowledgments

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References