Is increase in bone mineral content caused by increase in skeletal muscle mass/strength in adult patients with GH-treated GH deficiency? A systematic literature analysis

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Abstract

Objective: Adult patients with GH deficiency (GHD) are characterized by a reduced muscle mass, but also reduced bone mineral density (BMD) and content (BMC), which have been ascribed to GHD per se. The aim of this study was to investigate if changes in BMD/BMC in adult GHD patients could be due to a muscle modulating effect, and if treatment with GH would primarily increase muscle mass and strength with a secondary increase in BMD/BMC, thus supporting the present physiological concept that mass and strength of bones are mainly determined by dynamic loads from the skeletal muscles.

Method: We performed a systematic literature analysis, including 51 clinical trials published between 1996 and 2008, which had studied the development in muscle mass, muscle strength, BMD, and/or BMC in GH-treated adult GHD patients.

Results: GH therapy had an anabolic effect on skeletal muscle. The largest increase in muscle mass occurred during the first 12 months of therapy. Most trials measuring BMD/BMC reported significant increases from baseline values. The significant increases in BMD/BMC occurred after 12–18 months of treatment, i.e. usually later than the increases in muscle parameters. Only seven trials studied both muscle and bone variables concomitantly. No trials studied the relationship between the changes in muscle and bone measurements.

Conclusion: Although in vitro studies have shown that GH has a direct effect on bone remodeling, present physiological concepts and the results of clinical trials from 1996 to 2008 suggest that the anabolic changes in muscle mass and strength may also contribute to changes in BMD/BMC in GH-treated adult GHD patients.

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Introduction

GH deficiency (GHD) leads to changes in body composition. Fat mass is increased and is accompanied by an atherogenic lipid profile (1–6). GHD patients have smaller hearts and lower cardiac outputs than the healthy population (2–4) and the cardiovascular mortality rate is increased in GHD patients (1, 2). Functional limitations, fatigue, reduced physical activity, and reduced quality of life have been reported (1–4, 6, 7).

GH has a well-known anabolic effect on, for example, skeletal muscles, and patients with GHD are characterized by a reduced muscle mass, but also reduced bone mineral density (BMD) and bone mineral content (BMC), which have been ascribed to GHD per se (1–7). Correspondingly, the increase in bone and muscle mass by GH therapy has in most publications been seen as separate GH influences on bones and muscles respectively.

A review of the literature showed that the present knowledge about the interaction between skeletal muscles and bones in adult patients with GHD is rather limited. The aim of this study was therefore to investigate if changes in BMD/BMC in adult patients with GHD could be due to a muscle modulating effect, and if treatment with GH would primarily increase muscle mass and strength with a secondary increase in BMD and BMC, thus supporting the present physiological concept that mass and strength of bones are mainly determined by dynamic loads from the skeletal muscles (8–10).

Materials and methods

This analysis of the literature included 51 clinical trials that were selected from the PubMed online database, based on the following criteria. All articles were published during the period 1996–2008, and were required to explicitly mention at least one of the search terms: muscle mass, muscle strength, BMD, and/or BMC in connection with GHD and GH. The PubMed search was limited to ‘all adult’ patients.

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All selected trials studied the development in at least one of the aforementioned parameters during GH substitution therapy in adult patients with GHD.

Our analysis first focused on the effect of GH therapy on muscle mass and muscle strength, the latter including isometric, isokinetic, and peak handgrip strength.

The effect of GH therapy on BMD/BMC was analyzed with emphasis on hip, femoral neck, lumbar spine, radius, and total body measurements, separately.

We further analyzed the results of seven of the 51 clinical trials, which reported measurements of both muscle and bone parameters.

Results

Effect of GHD and GH replacement on muscles

Nineteen clinical trials (11–29) reported measurements of muscle mass or muscle strength. The results of these trials are summarized in Tables 1 and 2.

Table 1 Clinical trials published during the period 1996–2008, which have described the development in muscle mass or muscle strength in GH-treated adult patients with GH deficiency.

<table>
<thead>
<tr>
<th>References</th>
<th>Number of patients (end)</th>
<th>Sex (M/F)</th>
<th>Age (range/years)</th>
<th>Study design</th>
<th>Duration of treatment/ months</th>
<th>Muscle mass</th>
<th>Muscle strength</th>
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<tr>
<td>Jørgensen et al. (13)</td>
<td>29</td>
<td>19/10</td>
<td>45.5 (20–61)</td>
<td>R, DB, PC</td>
<td>12</td>
<td>Isometric: +</td>
<td></td>
</tr>
<tr>
<td>Baum et al. (12)</td>
<td>32</td>
<td>32/0</td>
<td>51 (24–62)</td>
<td>R, PC</td>
<td>18</td>
<td>Isokinetic: NS</td>
<td></td>
</tr>
<tr>
<td>Wallymahmed et al. (27)</td>
<td>30</td>
<td>10/20</td>
<td>33.5</td>
<td>R, DB, PC/O</td>
<td>12 (36)</td>
<td>Isometric: +</td>
<td></td>
</tr>
<tr>
<td>Johannsson et al. (25)</td>
<td>56</td>
<td>35/21</td>
<td>45 (19–74)</td>
<td>O</td>
<td>24</td>
<td>Isokinetic: +</td>
<td>Isokinetic: + a</td>
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<td></td>
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<td></td>
<td>Peak grip: NS</td>
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<td></td>
<td></td>
<td>Isokinetic: + b</td>
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<tr>
<td>Bell et al. (14)</td>
<td>51</td>
<td>27/24</td>
<td>21–60</td>
<td>R, DB, PC/O</td>
<td>12</td>
<td>Isometric: +</td>
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<td>Rodriguez-Arnao et al. (18)</td>
<td>35</td>
<td>18/17</td>
<td>39.8 (21.1–59.9)</td>
<td>R, PC</td>
<td>12</td>
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<td></td>
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<td>Janssen et al. (16)</td>
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<td>28/0</td>
<td>48.7 (22–70)</td>
<td>O</td>
<td>12</td>
<td>Isokinetic: +</td>
<td></td>
</tr>
<tr>
<td>ter Maaten et al. (17)</td>
<td>38</td>
<td>38/0</td>
<td>28 (20–35)</td>
<td>O</td>
<td>55 (39–69)</td>
<td>+ c</td>
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<tr>
<td>Gibney et al. (15)</td>
<td>21</td>
<td>??</td>
<td>28 (21–48)</td>
<td>R, DB, PC/O</td>
<td>120</td>
<td>+ c</td>
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<td>15/13</td>
<td>41 (18–68)</td>
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<td>20.2 (16–26)</td>
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<td>24</td>
<td>NS c</td>
<td>+ c</td>
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<tr>
<td>Koranyi et al. (21)</td>
<td>42</td>
<td>28/14</td>
<td>31.2 (17.1–61.0)</td>
<td>O</td>
<td>60</td>
<td>Isometric: +</td>
<td>Isokinetic: +</td>
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<td>Peak grip: NS</td>
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<tr>
<td>Bex et al. (20)</td>
<td>100</td>
<td>59/41</td>
<td>50 (25–65)</td>
<td>R/O</td>
<td>24</td>
<td>Isometric: +</td>
<td>Isokinetic: NS a</td>
</tr>
<tr>
<td>Svensson et al. (11)</td>
<td>109</td>
<td>61/48</td>
<td>50 (22–74)</td>
<td>O</td>
<td>60</td>
<td>Isometric: +</td>
<td></td>
</tr>
<tr>
<td>Boguszewski et al. (24)</td>
<td>18</td>
<td>11/7</td>
<td>41.5 (21–58)</td>
<td>O</td>
<td>12</td>
<td>Peak grip: +</td>
<td></td>
</tr>
<tr>
<td>Götherström et al. (23)</td>
<td>26</td>
<td>12/14</td>
<td>65 (61–74)</td>
<td>O</td>
<td>60</td>
<td>Peak grip: NS</td>
<td>Isometric: + g</td>
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<tr>
<td>Hoffmann et al. (22)</td>
<td>166 (123)</td>
<td>67/64</td>
<td>18–70</td>
<td>R, DB, PC</td>
<td>12</td>
<td>Isokinetic: NS</td>
<td></td>
</tr>
<tr>
<td>Götherström et al. (28)</td>
<td>109</td>
<td>61/48</td>
<td>50 (22–74)</td>
<td>O</td>
<td>120</td>
<td>Isometric: +</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Peak grip: NS</td>
</tr>
<tr>
<td>Norman et al. (29)</td>
<td>20</td>
<td>2/18</td>
<td>55.6</td>
<td>O</td>
<td>24</td>
<td>Isometric: +</td>
<td>Isokinetic: NS h</td>
</tr>
</tbody>
</table>

M/F, male/female; R, randomized; DB, double-blinded; PC, placebo-controlled; O, open; /O, initial design followed by open phase; GH, GH-treated group; NT, untreated group; CO, childhood-onset GHD; AO, adult-onset GHD; +, significant increase; −, significant decrease; NS, insignificant change. Changes are relative to baseline values. The trials are presented chronologically and are identified by the first author’s name.

aNot for knee flexion.
bSignificant for knee extension in the treated group in males and for flexion of the arm in the treated group in females. All other changes were insignificant.
cChanges in muscle cross-sectional area interpreted as changes in muscle mass.
dNo significant changes in muscle strength (average of 3 muscle groups) in GH group. Significant decrease in muscle strength in the untreated group.
eSignificant for females in the GH-treated group. Changes in all other groups were insignificant.
fStrength modality not specified.
gOnly significant for knee flexion, significant for knee extension.
hOnly significant for patients with previous acromegaly. Not significant for patients with previous non-functioning pituitary tumor.
Muscle mass was measured in four trials, three of which reported significant increases from baseline values (15–17). One trial found no significant changes (19).

Significant increases in muscle strength compared to baseline were reported in 10 out of 12 trials, measuring isometric muscle strength (11, 13, 14, 18, 21, 23, 25, 27–29).

Significant increases compared to baseline were reported in half or less than half of the trials measuring isokinetic muscle strength (16, 21, 25, 28) and peak handgrip strength (11, 20, 21, 28) respectively. The rest of these trials reported insignificant changes (12, 16, 19–26, 28, 29). No trials reported significant reductions in muscle mass or muscle strength.

Five trials only included patients with adult-onset GHD. Three of these trials reported significant increases in muscle mass or strength compared to baseline (13, 20, 23), while three trials reported insignificant changes (12, 22, 23). Two trials only included patients with childhood-onset GHD. One trial found significant increases in muscle mass compared to baseline (17) while one found insignificant changes (19).

One trial found a better effect of GH therapy in patients with childhood onset than adult-onset GHD (21).

Three trials included only male patients. Two of these trials found significant increases in muscle mass compared to baseline (16, 17). One trial reported significant increases in isokinetic muscle strength (16), while one trial reported insignificant changes (12). One trial reported insignificant changes in isometric muscle strength compared with baseline (17).

Trials comparing results for male and female patients have found similar changes in muscle strength following GH therapy (11, 14, 20, 23, 28). One trial found a larger treatment effect on peak handgrip strength in female patients (20). Four trials found lower muscle strength in females than in males (11, 20, 24, 28).

Three placebo controlled trials found no significant differences in isometric muscle strength between the GH and the placebo groups (13, 14, 18).

A 10 year follow-up trial found significant changes in muscle strength in the GH-treated group compared with baseline and significant decreases in muscle strength in the untreated group (15), while Götherström et al. found significantly increased isometric and isokinetic muscle strength after 10 years of GH therapy (28).

Ter Maaten et al. reported that the increase in muscle area, corresponding to the muscle mass, was maximal during the first 12 months of GH therapy. The increase in muscle mass became significant relative to baseline after 12 months of treatment (17). A 12-month trial also found significant increases in muscle mass (16).

In a formerly placebo-treated group, muscle mass increased significantly after 12 months of GH therapy (19).

Intrinsic muscle strength, defined as the strength/muscle mass ratio, was not significantly changed in GHD patients compared with a control group. No significant changes in intrinsic muscle strength occurred during GH therapy (16).

**Effect of GHD and GH replacement on bones**

Measurements of BMD and/or BMC (12, 17, 20–22, 24, 30–61) were reported by 38 clinical trials. The results are summarized in Table 3.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Number of trials</th>
<th>Significant increase</th>
<th>Insignificant change</th>
<th>Significant decrease</th>
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<tr>
<td>Muscle mass</td>
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<td>1</td>
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<tr>
<td>Isometric strength</td>
<td>12</td>
<td>10</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Isokinetic strength</td>
<td>8</td>
<td>4</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Peak handgrip strength</td>
<td>8</td>
<td>3</td>
<td>7</td>
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</table>

Table describes the number of clinical trials that have reported significant increases, insignificant changes and significant decreases respectively, in the different variables. All changes are relative to baseline values.

### Table 3

<table>
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<th>BMD</th>
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<td>Number of trials</td>
<td>Significant increase</td>
<td>Insignificant change</td>
<td>Significant decrease</td>
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<tr>
<td>Hip</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>26</td>
<td>16</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>34</td>
<td>28</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Radius</td>
<td>8</td>
<td>3</td>
<td>4</td>
<td>2</td>
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<tr>
<td>Total body</td>
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<td>4</td>
<td>9</td>
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<table>
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<tr>
<td></td>
<td>Number of trials</td>
<td>Significant increase</td>
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<td>Significant decrease</td>
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<td>Hip</td>
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<td>Femoral neck</td>
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<td>Lumbar spine</td>
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<td>Radius</td>
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<tr>
<td>Total body</td>
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<td>8</td>
<td>4</td>
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</table>

Table describes the number of clinical trials that have reported significant increases, insignificant changes and significant decreases respectively, in BMD and BMC in the different regions of measurement. All changes are relative to baseline values.
Significant increases in BMD compared to baseline were seen mainly in the lumbar spine (12, 17, 20, 21, 24, 30, 31, 33–38, 42–46, 50, 52–54, 56–61) and, to a lesser extent, in the femoral neck (12, 17, 21, 24, 31, 33–38, 54, 57–59, 61). The majority of trials measuring BMD (21, 30, 32, 35–37, 39, 41, 58) reported insignificant changes from baseline values. Two trials measuring BMD in the radius (20, 47) as well as two trials measuring total body BMD (47, 49) reported significant decreases compared to baseline. The decreases occurred after 24 months (20) and 12 months (47, 49) of GH therapy respectively.

Significant increases in BMC compared to baseline were seen mainly in the lumbar spine (20, 21, 30, 35, 40, 59) and total body measurements (17, 21, 30, 35, 40, 45, 58, 59) but also, to a lesser extent, in the femoral neck (35, 40, 59). The only trial measuring hip BMC reported an insignificant increase from baseline (30). One trial reported a significant decrease in radius BMC compared to baseline (47).

Measurements of BMD/BMC were reported by six placebo-controlled trials. The results seem rather inconclusive with a slight majority of trials, however, reporting insignificant differences between the GH and placebo groups (data not shown) (12, 39, 47, 49, 52, 60).

An initial decrease in BMD and/or BMC has generally been observed during the first 6–12 months of GH therapy (17, 33, 35, 43, 52, 54). This was followed by an increase in BMD and/or BMC, which became significant compared to baseline after 12–24 months of treatment (17, 33, 62).

Larger BMD increases have been documented in male patients than in female patients (62), and greater improvements and earlier changes in bone parameters have been reported in patients with childhood-onset GHD compared with patients with adult-onset GHD (21, 62).

**Effect of GHD and GH replacement on both muscles and bones**

Seven trials have reported measurements of both muscle and bone parameters. The results of these trials are summarized in Table 4.

In the trial that reported a significant increase in muscle mass, there were also significant increases in all the measured bone parameters (17).

Two trials reporting significant increases in muscle strength, also found significant increases in most, but not all, BMD and BMC values (18, 21, 37).

One trial reporting insignificant changes in muscle strength, also found insignificant changes in BMD values in the hip and lumbar spine (22).

Two trials found significant increases in lumbar spine BMD and femoral neck BMD values while reporting insignificant changes in muscle strength (12, 24).

In one trial, lumbar spine BMD and BMC increased significantly in males while peak handgrip strength did not increase.
not change significantly. The same trial reported a significant increase in peak handgrip strength in females while reporting insignificant changes or significant reductions in BMD/BMC (20).

In two trials, the significant increases in muscle parameters occurred prior to the significant increases in bone parameters (17, 18, 37). In one trial, however, the increase in lumbar spine BMD was contemporary with the increase in muscle parameters (17). In most of the studies, muscle strength and bone variables were only measured at the same cross sectional time point at baseline and one time point after initiation of GH replacement, and not longitudinally with several measurements.

**Discussion**

This analysis confirmed that GH has an anabolic effect on skeletal muscle. It particularly seemed to increase muscle mass and isometric muscle strength when given in physiologically therapeutic doses to adult GHD patients. The effects on isokinetic muscle strength and peak handgrip strength were not as obvious. According to one trial, the increase in isometric muscle strength could be explained by the increase in muscle mass (16). This anabolic effect of GH on skeletal muscle is in accordance with biochemical studies showing that GH reduced the expression of myostatin in skeletal muscle in adult GHD patients (63). Other studies have also reported changes in muscular gene expression related to muscular hypertrophy following GH therapy (64, 65).

With a few exceptions, BMD and BMC either increased significantly or did not change significantly compared with baseline during GH treatment of GHD patients. However, the significant increases in BMD/BMC were not evenly distributed in different regions of the body. The most consistently significant increases in BMD occurred in the lumbar spine and, to a smaller extent, in the femoral neck while the significant increases in BMC were seen primarily in the lumbar spine and in the total body values, but also, to a smaller extent in the femoral neck. Thus, the significant increases in BMD/BMC seemed to occur primarily in the weight bearing regions of the axial skeleton.

BMD has been reported to reach a plateau level after 3 years of treatment (33). However, other trials have found progressive increases in BMD after 4 (46), 6 (45) and 10 years (31, 59) of treatment respectively. In one trial, BMD in the femoral neck decreased between 5 and 10 years of treatment following an initial increase (33). However, other trials have found progressive increases in BMD after 4 (46), 6 (45) and 10 years (31, 59) of treatment respectively. In one trial, BMD in the femoral neck decreased between 5 and 10 years of treatment following an initial increase (31).

The effects of GH therapy on BMD/BMC are also reflected by increased levels of biochemical markers of bone metabolism as well as altered expression of genes in bone, related to a stimulation of bone remodeling (18, 33, 34, 36, 38, 39, 41, 42, 46, 54, 59, 60, 62, 66–69).

Answering the question of whether changes in BMD/BMC are due to changes in the skeletal muscle mass or strength is difficult since no clinical trials have addressed a causal relationship between GH effects on skeletal muscle and bone in GHD patients.

Analyses of the trials listed in Table 4, comprising those trials measuring effects of GH on both muscle and bones, suggested that there could be a connection between increases in muscle mass and strength and changes in BMD/BMC in adult GHD patients treated with GH. This supports the present physiological concept that the mass and strength of bones are primarily determined by dynamic loads from the skeletal muscles (8–10).

One might expect that the muscular hypertrophy caused by GH would result in a generalized increase in BMD/BMC. However, even though GH and other cytokines influence muscular hypertrophy, physical activity is also of great importance. Therefore, it might be expected that the muscle groups, which are used the most, will benefit the most from GH treatment. The possible uneven distribution of muscular hypertrophy could lead to a corresponding distribution of bone remodeling.

A similar hypothesis has been proposed previously (40). It has also been proposed that the increased quality of life reported in GHD patients treated with GH could lead to more physical activity, thus stimulating an increase in muscle mass and strength (40).

Based on the temporal distribution of significant increases in muscle and bone parameters during GH treatment, it is possible that the early increase in muscle mass could contribute to the increase in BMD/BMC.

A biochemical study showed that GH treatment of adult GHD patients increased the expression of insulin-like growth factor-1 (IGF1) in muscle as well as the circulating blood levels. The same study reported an altered muscular expression of genes regulating protein metabolism after 2 weeks of GH therapy (64).

In healthy elderly men, GH administration increased the intramuscular level of mechano-growth factor and a subtype of IGF-I (IGF-IEa) after 12 weeks and 5 weeks of therapy respectively (65).

In comparison, biochemical markers of bone resorption, e.g. the carboxy-terminal telopeptide of type I collagen and urine pyridinol, are reported to increase significantly from baseline values after 3–6 months of GH therapy in GHD patients (18, 33, 36, 38, 39, 41, 42, 46, 60, 67). Markers of bone formation, e.g. bone-specific alkaline phosphatase, osteocalcin, and the epitope of C-terminal propeptide (PICP) have similarly been reported to increase significantly from baseline values after 3–24 months of GH therapy (18, 33, 34, 36, 38, 39, 41, 42, 46, 54, 59, 60, 66, 67).

Although not studied in detail, the temporal distribution of significant changes in gene expression and the levels of biochemical markers also points to the possibility that an early increase in muscle mass could contribute to the increase in BMD/BMC.
However, another explanation could be that GH/IGF1 stimulates bone remodeling which occurs as a biphasic process, dominated initially by bone resorption and only later by bone formation (62, 70, 71). This biphasic sequence might also explain the initial decrease in BMD/BMC reported in several clinical trials (62).

Because significant increases in BMD/BMC do not usually occur until 12–18 months of treatment, clinical trials with duration of 12 months or less cannot be expected to find significant increases in bone parameters. All but one trial with duration of 24 months or longer found significant increases in BMD/BMC in at least one region of measurement, while this was only the case in slightly more than half of the trials with duration of <24 months. This temporal distribution could also explain some of the insignificant results of the placebo-controlled trials.

It is possible that certain subgroups of patients respond better to GH therapy than others. Several trials showed that male patients respond better to GH treatment than females, especially in terms of BMD/BMC. Particularly, estrogen replacement seems to reduce the sensitivity to GH (16, 72). It is therefore important to analyze the results of GH therapy separately for males and females as well as for the total population. In the majority of the performed clinical trials on this subject, more males than females were included in the study populations.

It should also be addressed whether the patients have childhood-onset or adult-onset GHD, and whether or not the childhood-onset GHD patients had achieved a proper peak bone mass after childhood GH therapy or whether they had too long a lag period from childhood treatment to recommencement of GH replacement in adulthood.

In relation to BMD/BMC, it is also important to know the status of other hormonal axes, including the thyroid (73, 74), parathyroid (75), gonadal (76–78), and adrenocortical axis (79), all of which may also influence bone remodeling.

Several in vitro studies have shown that murine and rat osteoblasts express GH-receptors on their cell surface. This makes a direct effect of GH on bone tissue possible (80–82). In vitro studies of human osteoblast-like cells have shown that these cells express functioning GH-receptors as well (82, 83). There thus seems to be scientific evidence of a direct effect of GH and IGF1 on human bone tissue (62, 84).

Such a direct effect of GH on bone remodeling could explain why increases in BMD/BMC could be seen in spite of insignificant changes in muscle parameters in three of the trials listed in Table 4. However, another possibility could be a type 2 error, since most of the studies included very few patients, and a power calculation was not always given to justify the significance of the non-significant results. In the two papers with a power calculation, only one of the measured variables namely BMD, was included in the analysis (39, 60).

The clinical trials included in this analysis of the literature were published during the period 1996–2008. This period was specifically chosen, since during that period and today, the goal of GH replacement therapy has been to achieve normal levels of serum-IGF1. In the earlier trials from 1985 to 1996, the doses of GH for adults were determined by using childhood doses and extrapolating calculated doses according to the bodyweight of the adult patient. This regimen led to too high levels of serum-IGF1, equivalent to those seen in patients with acromegaly. It has been estimated that only clinical trials published since the mid-1990s have achieved physiological conditions during GH therapy (85).

Also, in many of the earlier trials, the sample sizes were relatively small compared to the sample sizes of most trials from the period 1996–2008. Thus, due to the statistical power there may have been a smaller risk of type 2 errors in the more recent clinical trials, although it has not been eliminated.

Conclusion

Although in vitro studies have shown that GH has a direct effect on bone remodeling, current physiological concepts, and the results of clinical trials from the period 1996–2008 suggest that the anabolic effect from GH on muscle mass and strength may also contribute to changes in BMC and BMD in GH treated adult GHD patients. The number of studies that can be used for such assessment is, however, extremely small, and none of the published studies have been designed to answer this question. Studies addressing this particular issue are, therefore, needed to clarify the relative contribution of mechanisms, in order to provide proper recommendations for this patient group in terms of, for example, additional physical training.

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