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Impact of the growth hormone replacement on bone status in growth hormone deficient adults☆

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ABSTRACT

Introduction: Growth hormone deficiency (GHD) is associated with reduced bone mineral density (BMD). GH replacement has positive effect on BMD but the magnitude of this effect and its mechanism are debated.
Objectives: The objectives of this study was first, to assess the effect of GH replacement on BMD, and second, to evaluate the effect of GH treatment on bone turnover and microarchitecture and to assess the factors influencing the effect of the therapy on BMD.
Patients and Methods: Adult GHD (AO-GHD) and childhood onset GHD (CO-GHD) patients treated with GH using IGF-I normalization GH replacement regimen were prospectively followed during 2 years. Lumbar spine (L1–L4) and total femur BMD by Hologic discovery, in the subset of patients also bone turnover markers; osteocalcin and carboxy-terminal collagen crosslinks (CTx) were assessed at baseline and at months 3, 6, 12 and 24, respectively. The trabecular bone score (TBS) derived from lumbar spine DXA by the iNsight® software was assessed in a subset of study population at baseline and months 12 and 24.
Results: In total, 147 GHD patients (age 35.1 years, 84 males/63 females, 43 of childhood onset GHD/104 AO-GHD) were included. BMD of lumbar spine and femur increased significantly during the treatment (14% and 7% increase at 2 years, respectively; $p < 0.0001$).
Bone markers increased during the first 12 months of treatment with subsequent decrease of CTx. At month 24, significant increase in TBS was observed (4%, $p = 0.02$).
BMD increase was significantly higher in males (15% increase in males vs. 10% in females, $p = 0.037$) and childhood onset GHD (CO-GHD) patients (13% increase in CO-GHD, $p = 0.004$).
Conclusion: GH supplementation leads to an increase of BMD with corresponding changes in bone turnover markers and changes in microarchitecture as assessed by trabecular bone score. Positive effect of GH on bone status is more pronounced in males and CO-GHD adults.

1. Introduction

Growth hormone (GH) increases linear bone growth through complex hormonal reactions, mainly mediated by insulin like growth factor-1 (IGF-1) that is produced mostly by hepatocytes under influence of GH and stimulates differentiation of epiphyseal prechondrocytes. On the molecular level, GH acts via receptor activator of nuclear factor-kappaB (RANK), its ligand (RANK-L) and osteoprotegerin system [1], by stimulating the production of osteoprotegerin and its accumulation in bone matrix. The anabolic effect of GH on bone has been demonstrated both *in vitro* and *in vivo* [2]. IGF-I and GH play a key role in the linear bone growth after birth [3] and regulation of bone remodeling during the entire lifespan [4,5]. These anabolic effects of GH are important to maintain the peak bone mass (PBM) and to achieve the trabecular bone microarchitecture during late adolescence and early adulthood. This PBM is defined as the maximal bone mass after growth completion and its decreased value seems to be related to higher occurrence of fractures in elderly patients [6].

Both forms of GHD, childhood onset (CO-GHD) as well as adult-onset GHD (AO-GHD) are associated with reduced bone mineral density (BMD) and higher risk of osteoporotic fractures. While in patients with CO-GHD the low bone mineral density (BMD) might be explained by the reduced PBM, the pathophysiological mechanism of osteopenia related to AO-GHD is not fully understood [7]. It has been shown that

☆ Summary: In this study, we have evaluated the impact of adult growth hormone deficiency treatment on bone status. After 2 years of growth hormone treatment, a significant increase in bone mineral density was observed and proved by osteoformation predominance in the second year of treatment. In a subset of study patients trabecular bone score raised during treatment.

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bone remodeling markers are decreased in patients with AO-GHD compared to control healthy group and this defect is rapidly restored after GH replacement [8]. After 3 months of treatment, the predominance of bone resorption was observed followed by osteoformation after 6 months, suggesting that the effect of GH on bone remodeling is biphasic [9]. Short-term studies consistently show little or no effect of GH replacement on BMD [10,11] and increase of BMD is observed only in studies with the minimum duration of follow-up of 12 to 24 months [12–27]. In general, an initial decrease of BMD is noted after 6 to 12 months of treatment. Possible explanation of this phenomenon is increased bone space after amplified activation of bone turnover, which in turn results in decreased bone density [27-33]. It is well known that hypopituitary patients after GH treatment improve their well-being and physical activity [10,24,34]. These indirect effects of GH treatment are helpful in maintaining bone mass.

Most data gathered thus far on the effect of GH replacement on bone status comprise the measurement of quantitative changes of bone mass and the studies assessing the bone quality are scarce. Some studies have relied primarily on two-dimensional measures of density, which are affected by bone size [35]. When size corrections or volumetric density measurements are used, most studies suggest that a GH deficiency results in normal or near-normal BMD [36-38]. Study with transiliac bone biopsies revealed no histomorphometric differences between the trabecular bone of GH-deficient men and controls [39] and GH treatment in this population showed no changes in trabecular structure [40,41]. On the other hand, in the rat models of GHD trabecular microarchitecture was significantly compromised with a smaller number of thinner trabeculae and a reduced connectivity density [42]. In a study of Kristensen et al. [43], early (prepubertal) and late (postpubertal) GH treatments of GH-deficient rats lead to recovery of bone macroarchitecture and early treatment resulted in a significant improvement of bone microarchitecture. Thus, animal studies have suggested that GH has effect specifically on the bone quality. Although few small size human studies failed to demonstrate this effect, their limited methodological quality does not allow firm conclusions on this subject.

Thus, trabecular bone microarchitecture might play a role in increased fracture rate of GHD patients. Trabecular bone score (TBS) is a novel non-invasive modality designed to assess the trabecular microarchitecture parameters derived from DXA images. Currently, no studies are available on the effect of GH replacement on TBS. TBS has been evaluated in secondary osteoporosis and showed better sensitivity than conventional assessment of BMD. A study with glucocorticoid-induced osteoporosis showed significant difference in TBS between the active 1 year prednisone (5–15 mg/day) treatment group and the controls in contrast to BMD that showed no difference [44]. In another study with rheumatoid arthritis patients, TBS identified additional eight cases (5%) with high fracture risk that would not have been detected by conventional BMD assessment [45]. Large retrospective study with more than 29,000 postmenopausal women showed [46] that TBS independently predicts fractures in a subpopulation of patients with diabetes. Thus, TBS seems to provide additional information on the bone quality through specific assessment of the microarchicture, which can be of value in analyzing the mechanism of GH replacement-induced increase in BMD.

Taken altogether, the studies performed so far demonstrated that GHD is related to reduced bone mineral density and that the long-term replacement therapy can successfully revert this condition. However, the studies analyzing bone formation and the qualitative changes in bone microarchitecture are scarce and the effect of GH on bone status is not fully understood.

Therefore, the aim of this prospective study with GHD patients undergoing replacement therapy was to primarily assess the long-term changes in BMD. In addition, in a subset of patients we analyzed the temporal changes in bone turnover markers and the effect of GH replacement on bone microarchitecture.

The primary objective of this study was to assess the effects of recombinant human GH (rhGH) on bone mineral density status after 12 and 24 months of treatment, respectively.

Secondary objectives were, first, to assess the changes of bone remodeling status; second, to perform gender and type of GHD onset-stratified analysis of bone response; and third, to evaluate the GH replacement-induced changes of lumbar spine TBS.

2. Patients and methods

2.1. Patients

From May 2005 until October 2011, a prospective study was performed in three national referral centers specified at the treatment of GHD. The regional medical ethical committees in each center gave approval for the study. Diagnosis of GHD was confirmed by stimulation testing using insulin tolerance test with hypoglycemia (ITT) according to the current guidelines of Endocrine Society [46] which uses the cut-off value of stimulated GH in ITT of 3 μg/L. The inclusion criteria were as follows:

1. Adults with GH deficiency diagnosed according to the current guidelines of the Endocrine Society regardless of gender, onset and etiology
2. Stable replacement for other pituitary deficiencies, if present
3. No present or history of treatment for osteoporosis with any antiresorptive drug
4. Levels of 25-OH-D3 and calcium in reference range, or adequate supplementation with corresponding preparation

In further analysis, patients were stratified according to the gender, onset of the disease (AO-GHD or CO-GHD) and etiology of hypopituitarism defined as postoperative, congenital, idiopathic, postradiative, posttraumatic and inflammatory. All patients had MRI of pituitary gland performed in the time of GHD diagnosis.

2.2. Growth hormone supplementation and other treatment

All patients have received recombinant human growth hormone (rhGH) in IGF-I-normalizing GH replacement regimen, subcutaneously, once a day. The average dose was 0.35 mg/day. Patients were treated for other pituitary deficiencies and the effectiveness of this treatment was monitored regularly by measurement of target hormone levels. Patients with antiresorptive treatment were not included in the study. A standard dose (800 IU/day) of 25-OH-D3 and oral calcium (1000 mg per day) has been administered to patients with vitamin D deficiency. The levels of calcium and vitamin D were checked semi-annually.

2.3. Outcome measures

Basic anthropometric measurements of body length, body weight, waist circumference and body mass index (BMI) were assessed at baseline and at month 24 of the treatment with rhGH.

IGF-I levels were assessed at baseline and at months 6, 12 and 24 of the treatment from 2005 until 2008 by IMMULITE® 2000 (interassay variability CV 2.4%–4.7%) and from 2008 by IMMULITE® 2500 (interassay variability CV 2.4%–4.7 %), a solid phase, enzyme labeled chemiluminiscent immunometric assay.

The levels of osteocalcin (OC) and carboxy-terminal collagen crosslinks (CTx) at months 3, 6, 12 and 24, respectively. OC was assessed as N-MID osteocalcin by electrochemiluminescence assay (ECLIA) on the Elecsys analyzer with interassay variability CV of 1.1%–1.8%. CTx (β-CrossLaps/serum) was assessed by ECLIA as well on the same analzer with interassay variability CV of 1.8%–3.2%.

In all patients, serum levels of calcium and 25-OH-D3 were measured at baseline, and at months 12 and 24 of the treatment. Calcium was assessed by photometric analysis with *O*-cresolphthalein-