GH and Bone—Experimental and Clinical Studies

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IT is well known that growth hormone (GH) is important in the regulation of longitudinal bone growth [1, 2]. Its role in the regulation of adult bone remodeling and bone metabolism is less well understood, but has attained considerable interest recently [1]. These studies demonstrate that GH exerts potent effects on bone remodeling, both in animals and in man. In the present review different mechanisms for the effect of GH on bone growth and remodeling will be discussed.

In vitro effects of GH on Osteoblasts and Osteoclasts

Effects of GH on osteoblasts

Osteoblasts express GH-receptors (GHR) [3, 4]. It has been reported that IGF I and II decrease the number of GHR [5] and, conversely, that IGFBPs increase the numbers and activity of GH receptors in cultured bone cells, suggesting a feedback mechanism in the GH/IGF axis at the local tissue level. Hypothetically, the local production of IGF and IGFBP might modify the effect of GH on bone growth and remodeling at local bone forming units [5, 6].

GH stimulates proliferation and differentiated functions of rodent, as well as human osteoblasts [3, 7, 8]. Several studies at our laboratory have indicated that cartilage stem cells are important target cells for the stimulatory effects of GH on longitudinal bone growth [9–11]. The target cells for the growth promoting effect of GH in bone have yet not been identified, but bone marrow derived precursors of human bone cells are responsive to GH [12], suggesting that GH directly interacts with bone progenitor cells. It has been suggested that at least some of the GH effects on osteoblasts are mediated by local stimulation of IGF production. IGFs are expressed in osteoblasts and exert anabolic effects on these cells [13, 14]. GH induces IGF-I expression in rodent osteoblasts, but so far there are no convincing data demonstrating a stimulatory effect of GH on IGF-I production in human osteoblasts [7, 15–17].

Several recent studies suggest that IGF binding proteins (IGFBPs) modify the IGF activity in bone tissue, a modulatory effect having been demonstrated for IGFBP 3, 4 and 5 [18]. GH increases the IGFBP-3 production in rat osteoblasts [19, 20] but no such effect of GH has been demonstrated on IGFBP-3 expression in human cells [7, 17, 21]. In rat, as well as human osteoblasts, it was found that GH decreases IGFBP-4, as determined by ligand blotting [21, 22]. In contrast, GH induced a twofold increase in IGFBP-5 mRNA in rat osteoblasts [20]. In conclusion, it seems evident that GH plays a regulatory role in the expression of IGFBPs in bone tissue. The precise physiological function of this regulation is...
still unclear.

**Effects of GH on Osteoclasts**

GH may also influence bone growth and remodeling by stimulating the recruitment and activity of osteoclasts. GH increases the number of osteoclasts in metaphyseal bone of the proximal tibia of hypophysectomized rats [23]. In a recent study by Nishiyama et al, on mouse stromal cells and hemopoetic blast cells, it was found that GH stimulates osteoclastic bone resorption through both direct and indirect actions on osteoclasts [24]. In another study [25], on mouse marrow cultures, GH inhibited osteoclast formation by means of an IGF-I independent mechanism. Available data therefore suggest that GH regulates osteoclast formation but that differences in culture conditions might influence the effects.

**Effects of GH on Bone Metabolism in Animals**

**Effects of GH in Rats**

Hypophysectomy of rats with subsequent replacement therapy with thyroxine and glucocorticoid is followed by a rapid and pronounced decrease in the amount of bone. This effect is reversed by GH treatment [23, 26]. GH administration increases cortical bone mass in old rats via a stimulation of subperiosteal bone formation without influencing the endosteal bone surface [27]. The increase in bone mass was accompanied with a concomitant increase in mechanical strength of the whole bone, corresponding to the increased bone mass [27]. Of special interest is the fact that GH increases cortical bone mass by inducing subperiosteal bone formation without increasing cancellous bone mass.

**Effects of GH transgenic mice**

The effect of GH on bone growth and remodeling has also been studied in transgenic mice. In most studies, the metallothionein promoter (MT) fused to the GH gene has been used, resulting in very high serum levels of GH [28–31]. The femora of MT-GH transgenic mice exhibited increased bone growth, bone mineral content (BMC), and mechanical strength [31]. The increase in mechanical strength was due to increased cortical width [1]. By studying bone formation in two different GH-transgenic lines with a bone specific GH-expression, resulting in high local concentrations of GH without affecting the serum concentrations of GH, it was found that GH exerted strong stimulatory effects [32, 33]. This finding clearly indicates that the dual effector theory of GH action also applies to bone tissue [34].

**Effects of GH on Bone Metabolism in Humans**

**Growth hormone deficiency (GHD)**

Several studies have shown a low bone mass in adults with childhood onset GHD [1]. Similar results have been observed in patients with multiple pituitary deficiencies, receiving conventional replacement therapy with corticosteroids, gonadal steroids and thyroxine, and isolated GHD, suggesting that the lack of GH is the most important factor explaining the observed low bone mass in childhood onset GHD [35, 36]. At present, there are no studies showing that GH replacement during childhood results in normalization of bone mineral density (BMD) when peak bone mass is reached, suggesting that GH is also important for the additional increase in bone mass that occurs after the completion of linear growth. As a result, it has been proposed that GH treatment should be continued until the attainment of peak bone mass [37].

An increase in the prevalence of decreased BMD has also been found in several recent studies of patients with adult onset GHD [38–44]. In a study by Rosén et al [41], of 95 patients (55 males and 40 women) with adult onset GHD with a mean age of 54 years, BMC was assessed in the third lumbar vertebra by dual-photon absorptiometry. BMC was found to be reduced in all males and in females with untreated, as well as treated gonadal deficiency. Interestingly, BMC was reduced in patients under 55 years of age but was normal in patients over 55 years of age, suggesting that GH-deficiency in patients under 55 years of age should receive special clinical attention.

The question whether a reduced bone mass in GHD-patients results in an increased fracture rate
has received limited attention. Nevertheless, it has been reported that the frequency of osteoporotic vertebral fractures is increased in hypopituitary patients [38] and recently Rosén et al [45], demonstrated that the fracture rate in patients with adult-onset GHD was greater than that in healthy controls. These results suggest that the reduced bone mass in GHD-patients is relevant from a clinical point of view.

**Treatment of GHD patients with GH**

Trials involving adults with childhood onset GHD have yielded conflicting results regarding the effect of GH on bone mass. Several short-term, placebo-controlled [46-48] and short-term open trials [49-52] have failed to show any increase in BMD or BMC during GH treatment. In fact, in some of these studies [47-49] a slight decrease in BMD or BMC after 3-6 months of treatment was observed, but after a more prolonged treatment periods (12-30 months) several studies have disclosed more encouraging results [48, 53-55]. Short-term trials [44, 56-59], 6-18 months in adults with adult onset GHD, have failed to show any increase in BMC or BMD. In contrast, in the longest placebo-controlled trial reported so far (18 months), Baum et al [60], reported a significant increase in BMD in lumbar spine and

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**Fig. 1.** BMD (BMC/area) in response to 2 yr of GH treatment in two subgroups of patients with adult-onset GH deficiency. One group comprises 13 patients with a baseline z-score of less than −1 SD (broken line), and the second group are 31 patients with a baseline z-score of −1 SD or more (solid line). Values are given as means ±SEM. P values denote the difference between the percent changes from baseline in the two groups of patients, determing by two-way ANOVA. (Reproduced with permission from Johannsson et al [61])

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*— z score ≥ −1, --z-- z score ≤ −1*
femoral neck of 5.1 and 2.4%, respectively. Since bone absorptiometry only detects the mineralized component of the bone, the reduction in BMD observed after short periods of GH treatment is best explained by increased remodeling activity, with an increased in remodeling space and an increase in the proportion of new unmineralized bone.

Johannsson et al [61], recently demonstrated that 2 years of GH treatment in 24 men and 20 women with adult-onset GHD induced a sustained increase in overall bone remodeling activity and a net gain in BMD in several weight-bearing skeletal locations. A significant increase in BMD first became apparent after 18 months, which may explain why previous trials of shorter duration were unable to demonstrate an increase in BMD. Interestingly, patients with a z-score of less than -1 SD demonstrated the most pronounced increase in BMD in response to GH (Fig. 1).

Effects of GH on bone metabolism and bone mass in patients with normal GH secretion

Several studies have demonstrated that GH increases markers for bone resorption as well as bone formation in subjects with normal GH secretion [62]. The responsiveness of osteoporotic patients to GH is similar to that of healthy subjects in this respect [63]. As in laboratory animals [27], GH seems to stimulate the formation of periostal bone, as determined by bone histomorphometry [64], but larger clinical studies with this method or computer tomography are needed to confirm the site of GH action on bone tissue.

The present clinical methods of treatment for osteoporosis rely almost exclusively on agents aimed at reducing bone resorption. In contrast, GH has a stimulatory effect on bone formation, as well as bone resorption, and the gain in BMC/BMD that was observed after several months of GH treatment in adult GHD, occurred after the first remodeling cycle [61]. There are as yet no treatment trials with GH of adequate duration (>18 months) in patients with postmenopausal osteoporosis. In a two year study of postmenopausal women, the addition of GH to continuous, combined or sequential calcitonin treatment had no additional effects on total body calcium [65]. Holloway et al, have recently presented a study in which postmenopausal women were given a cyclic GH treatment for 7 days every 56th day. This cyclic treatment was repeated 12 times and resulted in a minor but statistically significant increase in BMD of the lumbar spine and of the hip (1–2%) [66]. In summary, the potential beneficial effect of GH in patients with osteoporosis is still unclear. Long term studies (more than 2 years) are needed to find out whether GH treatment ultimately increases bone mass.

![Fig. 2. The "Biphasic model" of GH action in bone remodeling. According to this model; GH results in increased bone resorption with a concomitant bone loss followed by a later increase in formation. From the moment when bone formation is stimulated more than bone resorption (transition point), bone mass is increased, but a net gain of bone mass of GH may take some time as the initial decrease in bone mass first must be replaced (reproduced with permission from Ohlsson et al [1]).](image-url)
Summary and Conclusions

GH increases bone formation both via a direct interaction with GH receptors on osteoblasts and via locally produced IGF-I (autocrine/paracrine action). GH deficiency results in decreased bone mass in both man and laboratory animals and treatment of GHD patients with GH for several months results in increased bone mass. GH treatment also increases bone mass and the total mechanical strength of bones in rats with normal GH secretion. Because of the short duration of GH-treatment in man with normal GH secretion, the effect on bone mass is still inconclusive. The action of GH on bone metabolism in GHD adults is twofold: It stimulates both bone resorption and bone formation. A “Biphasic model” of GH action in bone remodeling has recently been proposed [1] (Fig. 2). According to this model the net effect of GH first results in a loss of bone mass, followed by a net increase in bone mass. The transition point occurs when bone formation proceeds at a higher rate than bone resorption. Taking all clinical studies of GH-treatment of GHD adults into account, it appears that the “transition point” occurs after approximately six months and that a net increase in bone mass usually is seen after 12-18 months of GH treatment. It should be emphasized that the “Biphasic model” of GH action in bone remodeling is proposed based on findings in GHD adults, and it remains to be clarified whether or not it is valid for subjects with normal GH secretion.

References


