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Review Article

Hylonome

The effects of growth hormone on cortical and cancellous bone

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Abstract

Growth hormone (GH) has profound effects on linear bone growth, bone metabolism and bone mass. The GH receptor is found on the cell surface of osteoblasts and osteoclasts, but not on mature osteocytes. *In vitro*, GH stimulates proliferation, differentiation and extracellular matrix production in osteoblast-like cell lines. GH also stimulates recruitment and bone resorption activity in osteoclast-like cells. GH promotes autocrine/paracrine insulin-like growth factor 1 (IGF-I) production and endocrine (liver-derived) IGF-I production. Some of the GH-induced effects on bone cells can be blocked by IGF-I antibodies, while others cannot. In animal experiments, GH administration increases bone formation and resorption, and enhances cortical bone mass and mechanical strength. When GH induces linear growth, increased cancellous bone volume is seen, but an unaffected cancellous bone volume is found in the absence of linear growth. Patients with acromegaly have increased bone formation and resorption markers. Bone mass results are conflicting because many acromegalics have hypogonadism, but in acromegalics without hypogonadism, increased bone mineral density (BMD) is seen in predominantly cortical bone, and normal BMD in predominantly cancellous bone. Adult patients with growth hormone deficiency have decreased bone mineral content and BMD. GH therapy rapidly increases bone formation and resorption markers. During the first 6-12 months of therapy, declined or unchanged BMD is found in the femoral neck and lumbar spine. All GH trials with a duration of two years or more show enhanced femoral neck and lumbar spine BMD. In osteoporotic patients, GH treatment quickly increases markers for bone formation and resorption. During the first year of treatment, unchanged or decreased BMD values are found, whereas longer treatment periods report enhanced or unchanged BMD values. However, existing trials comprising relatively few patients and limited treatment periods do not allow final conclusions to be drawn regarding the effects of GH on osteoporosis during long-term treatment.

Keywords: Growth Hormone, Bone Formation, Bone Resorption, Bone Mass, Mechanical Strength

Growth hormone (GH)

GH is a single chain 22 kDa protein, which is produced and stored in the somatotroph cells within the anterior pituitary gland. GH is secreted in pulses, and regulated by the hypothalamic peptides, GH releasing hormone (promotes secretion), and somatostatin (impedes secretion). Increased levels of circulating insulin-like growth factor 1 (IGF-I) also impede GH secretion[1]. Pulsatile administration of GH to GH-deficient rats has proved to be more potent than continuous infusion with respect to promoting growth and increasing circulating IGF-I levels[2,3]. However, in humans with growth hormone deficiency (GHD), the potency of pulsatile administration is less conspicuous[4].

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GH induces anabolic effects on several tissues including muscles and bones[5,6]. GH is important in the regulation of longitudinal bone growth, and patients with GHD are characterized by short stature and delayed bone maturation[6]. GH stimulates the production of liver-derived IGF-I, and systemic administration of GH was previously thought to stimulate linear growth by increasing liver secretion of IGF-I, which then induced growth in an endocrine manner[7]. However, it was later demonstrated that many cells, including osteoblasts and chondrocytes, produced IGF-I locally, and injections with GH directly into the growth plate were shown to induce local linear growth and local expression of IGF-I in a dose-dependent manner[8,9]. These experiments showed that GH had a direct stimulatory effect on the cells in the growth plate, but they did not exclude the fact that linear growth could be influenced by circulating levels of IGF-I. Using the Crelox P system, postnatal growth in liver-specific IGF-I gene-deleted animals was recently investigated, and although total serum IGF-I in these animals was only approximately 20% of the

values of the corresponding wild type littermates, no differences in gains in body weight and femoral linear growth were found between the groups[10,11]. This indicates that the circulating level of IGF-I has little if any effect on growth. However, in this Crelox P model, an increase in serum GH is observed, and this might compensate for a possible decrease in linear growth induced by a decline in circulating levels of IGF-I. In serum, most of the IGF-I is bound to the IGF-binding proteins (IGFBPs), and only a minor fraction circulates as free IGF-I. Although serum IGF-I is decreased fivefold in the Crelox P animals, the concentration of free serum IGF-I does not differ between the gene-deleted animals and their wild type littermates[12]. It is very difficult in clinical trials and animal experiments to discriminate between effects caused by GH-induced local production of IGF-I, and effects caused by GH-induced increases in circulating levels of IGF-I. Furthermore, GH has been shown to induce effects that seem to be independent of IGF-I (for recent extensive review see[7]).

In the present review, we will focus on the effect of GH on bone cells *in vitro*, changes in bone metabolism and bone mass of animals subjected to GH administration, human diseases with increased and decreased GH secretion, and finally, clinical trials in which GH has been given to osteoporotic patients.

Effects of GH on osteoblasts and osteoclasts *in vitro*

Osteoblasts

GH has been shown to stimulate the proliferation and differentiation of a number of osteoblastic cell lines[13-17]. GH also stimulates the production of type I procollagen, osteocalcin and alkaline phosphatase in osteoblastic cells[14,16-18].

IGFs are expressed in osteoblastic cells and they exert stimulatory effects on cell proliferation and the production of extracellular matrix molecules[14,15,18]. The proliferative activity induced by GH can be prevented by adding IGF-I antiserum to the system[14]. As GH stimulates IGF-I production in rodent osteoblastic cells, this strongly suggests that IGF-I is a mediator for GH[16]. In human osteoblastic cells, however, the role of IGF-I as a mediator is unclear because most investigations have not been able to show increased IGF-I production or IGF-I mRNA expression when GH is added to the system[17-19].

IGFBPs are expressed in osteoblastic cells and IGFBP-3, -4, and -5 have been shown to influence IGF activity[20,21]. In rodent osteoblasts, GH enhances the production of IGFBP-3 and -5[15,20,22]. However, these effects cannot be demonstrated in human osteoblasts[17,19,23]. On the contrary, GH decreases the production of IGFBP-4 in both rodent and human osteoblastic cells[23,24]. Both IGFBP-3 and -5 seem to increase the stimulatory effect of IGF-I on the osteoblastic cells, whereas IGFBP-4 decreases the effect of IGF-I on these cells[15,23,24].

The GH receptor (GHR) is a member of the cytokine receptor superfamily. GH has two binding sites for the GHR, and when GH forms a receptor dimer complex, the JAK2/STAT cascade is activated[7]. The GHR is located on osteoblastic cells, and both GH and IGF-I down-regulate the number of GHRs[13,25]. IGFBP-3 and -5 up-regulate the number and the activity of the GHRs[15,20,22,25,26].

Different pathways seem to occur for GH and IGF-I, and the two hormones do not activate identical genes in osteoblasts[27]. Both GH and IGF-I have been shown to increase the expression of BMP-2 and -4 mRNA in human dental pulp fibroblasts[28]. However, IGF-I antibodies suppressed the effect of IGF-I, but not the effect of GH.

Osteoclasts

GH stimulates both the recruitment and the activity of the osteoclasts. Nishiyama et al. added GH to unfractionated bone cells and showed a dose-dependent osteoclast-like cell formation[29]. GH also stimulated osteoclast-like cell formation when added to spleen-derived hemopoietic blast cells (in the absence of stromal cells). Furthermore, the authors showed that GH stimulated bone resorption within a cellular system containing both osteoclasts and stromal cells, whereas GH did not stimulate bone resorption when added to isolated osteoclasts. In another study, Guicheux et al. added either GH or IGF-I to unfractionated bone cells and found that both substances increased the formation of osteoclast-like cells and stimulated the resorption activity of the osteoclasts[30]. By adding antiserum to IGF-I at the start of culturing, the stimulatory effects of both GH and IGF-I on osteoclastic resorption activity were suppressed[30,31]. GH and IGF-I also stimulated both cathepsin and metalloproteinase activities in unfractionated bone cells, and the effects of both GH and IGF-I could be blocked by IGF-I antiserum[32]. In addition, the experiment showed that GH did not induce proteinase activity when added to purified osteoclasts. The IGFBPs also influenced the osteoclast recruitment and activity.

Recently, it has been shown that IGFBP-5 stimulates osteoclast formation and osteoclastic bone resorption activity in unfractionated bone cells[31]. IGFBP-5 also stimulated osteoclast-like cell formation when added to spleen-derived hemopoietic blast cells. IGF-I antibodies could neither block the GH-induced nor the IGFBP-5-induced recruitment of new osteoclasts originating from primitive hemopoietic blast cells[29,31], and this strongly suggests that the formation of new osteoclasts from primitive blast cells does not include IGF-I mediation. GH has not been able to stimulate pure osteoclast-like cells *in vitro*, and it is therefore of interest to know whether these cultured cells express mRNA for the GHR. However, we are not acquainted with such investigations. In tissue sections from femoral epiphyses and mandibular alveolar bone, GH receptors have been shown on active osteoclasts[33,34].

In conclusion, GH appears to increase recruitment and activity of both osteoblasts and osteoclasts. IGF-I seems to mediate some, but not all, of the GH-induced effects.

The effects of GH in animals

In bone tissue, GHRs have been shown on active osteoblasts and osteoclasts but not on mature osteocytes[33,34]. GH treatment

of animals increases biochemical markers of bone formation and resorption[35,36]. Since GH increases bone metabolism *in vivo*, animal models are useful when evaluating the GH-induced changes in bone mass and bone mechanical strength.

Rats

Systemic GH administration increases bone mass in both normal and ovariectomized (OVX) rats[37-41]. Fluorochrome labeling has shown that GH induces periosteal bone deposition at the diaphysial bone surfaces of long bones without influencing the endocortical surfaces of these bones (Fig. 1)[38,41]. The same findings have been shown using quantitative computer tomography (pQCT)[42]. Polarization microscopy shows that the new collagen fibers in the bone are organized in a similar way to the adjacent primordial bone. The new bone can be depicted by fluorochrome labeling, but the borderline between the new and the older bone can often be seen using light microscopy (Fig. 1). An increase in cortical bone mass is observed, corresponding to an increase in mechanical strength[37-41]. When correcting the mechanical data for the dimensions of the bone, the same mechanical quality of the osseous tissue is found in normal and GH-treated rats. Resistance to bending and torsion increases when the osseous tissue is located far from the neutral axis (the center of the medullary cavity). Because GH induces new bone periosteally, the new bone is located as far as possible from the neutral axis, and this explains the ability of GH to induce substantial enhancement of the bending strength in the diaphyses.

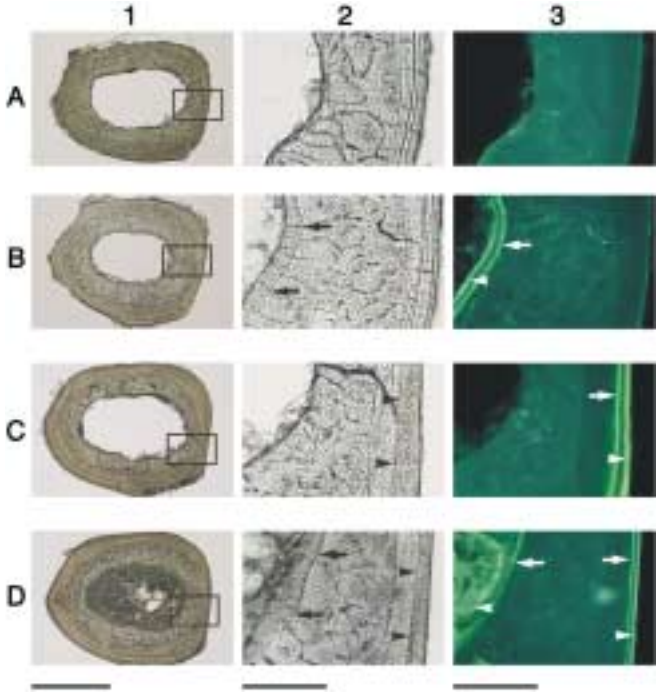

Figure 1. Cross-sections of the femoral diaphysis from ovariectomized rats injected with parathyroid hormone (PTH) and/or growth hormone (GH) for 56 days. Row A: vehicle-injected rat; row B: PTH-injected rat; row C: GH-injected rat; row D: PTH plus GH-injected rat. Using light microscopy, the unstained appearance of the whole diaphysis is shown in column 1, and the area inside the frame is shown in column 2. In column 2, the periosteal surface at the start of treatment is indicated by black arrowheads, and the endocortical surface at the start of treatment by black arrows. The animals were labeled with calcein at day 28 and with tetracycline at day 49 of treatment. Using epifluorescence microscopy, the area inside the frame is shown in column 3. The calcein labeling is indicated by white arrows and the tetracycline labeling by white arrowheads. Dimensions are given by bars (column 1: 2 mm; columns 2 and 3: 0.5 mm). (Reproduced from Andreassen TT and Oxlund H: J Bone Miner Res 2000; 15:2266-2275 with permission of the American Society for Bone and Mineral Research).

When measuring the bone mineral density (BMD) of the diaphyses by Archimedes' principle, (bone mineral content per volume), identical densities are found in GH-treated and normal two-year-old rats[38]. In one-year-old rats, GH treatment has been shown to induce a slight increase in diaphysial BMD when measured either by Archimedes' principle or by pQCT (bone mineral content per volume)[42]. When measuring BMD using dual-energy X-ray absorptiometry (DXA), (bone mineral content per area), an increased BMD is found in the GH-treated animals. GH administration normally increases BMD when measured by DXA but not when measured by Archimedes' principle or pQCT. This is due to the different normalization methods (area versus volume). Area does not increase to the same extent as volume when periosteal bone formation takes place all around the tubular-shaped diaphyseal bone. In one experiment, we found that the GH-induced periosteal bone deposition increased diaphysial bone volume by approximately 20%, whereas the external diameter (being the only dimension to increase when calculating the DXA area) increased by only approximately 6%. In young growing rats, however, GH has been shown to decrease diaphysial BMD measured by volume, whereas diaphysial BMD measured by area was unchanged[43]. These findings are in agreement with a decreased mineralisation of the newly formed bone, and high doses of GH given to very young rats have been shown to induce substantial amounts of new less mineralized bone[44].

The cortical shell of the vertebral body responds differently. GH induces periosteal bone formation at the surface toward the abdominal cavity (Fig. 2)[39]. At the periosteal surface toward the vertebral canal, GH does not induce new bone deposition, but bone deposition takes place at the endocortical surface[39]. GH enhances the strength of the vertebral body in both normal and OVX rats, and when the data are corrected for bone mass per cross-sectional area, the same mechanical qualities are found in GH-treated and normal animals. In the rat vertebral body, 2/3-3/4 of the bone originates from the cortical shell and the mechanical strength can therefore be attributed primarily to the cortical bone[39].

Fluorochrome labeling on withdrawal from GH treatment persists completely six weeks later, both at the periosteal diaphysial surface and at the endocortical surface of the vertebral body[38]. This shows that the new bone is preserved after the end of treatment, contrary to what is observed in intermittent parathyroid hormone-treated animals (PTH), where new bone is quickly resorbed at the endocortical surface of the vertebral

body after withdrawal from treatment[45]. GH treatment has been shown to induce resorption cavities inside the cortical shell in the vertebral body (Fig. 2). However, such resorption cavities have never been found in diaphysial bones.

Cancellous bone volume, mineralizing surface, and trabecular thickness increase when the GH administration induces growth from the growth plate[46]. However, in old rats with no linear growth, treatment with GH does not influence cancellous bone volume or trabecular thickness[39]. In rats, remodeling takes place in the cancellous bone of the vertebral body, but at present, it is not known whether GH influences the length of the time period needed for completion of a remodeling cycle.

Glucocorticoid (GC) administration has been shown to decrease linear growth, bone formation, bone mass, bone strength, and muscle mass[46,47]. In an attempt to counteract these effects, growing rats have been given GC in combination with GH. When using GC with protracted effect, only insignificant effects of GH have been found[47]. However, in combination with GC without protracted effect, GH has been shown to counteract the GC-induced decline in linear growth and cortical bone formation[46]. At the vertebral body cancellous bone surfaces, GC alone has substantially decreased mineralizing surfaces, and this effect is not counteracted by combined treatment with GC and GH.

Intermittent PTH treatment increases rat bone mass and mechanical strength by inducing endocortical and cancellous bone deposition, whereas the periosteal bone deposition is modest (Fig. 1)[41,45]. Combined treatment with GH and PTH increases bone formation substantially, both in the vertebral body and in the femoral diaphysis[41,48]. Interestingly, the combined treatment results in a more pronounced formation of new bone at the endocortical surface than that induced by PTH alone, although GH alone does not influence the endocortical surface (Fig. 1)[41]. The relationship between GH, IGF-I, and PTH could be of interest for the results of combined GH plus PTH treatment. The dose of GH used in the experiments almost doubles serum levels of IGF-I, and GH is also able to increase local IGF-I production in rat osteoblast-like cells. Using osteoblast-like cells, the mitogenic effects of IGF-I and PTH are shown to be potentiated when the two substances are given in combination[49]. Potentiated cancellous bone formation is seen when IGF-I and PTH are given in combination to rats[49].

Two different rat models are used when investigating GHD, hypophysectomized rats, and dwarf rats (DW) with normal pituitary functions except GH. Hypophysectomy (HX) induces a decrease in the vertebral body and metaphysial cancellous bone volume, trabecular number, trabecular thickness, and bone formation[50,51]. Tetracycline labeling prior to HX shows that bone resorption is augmented after HX, although both the bone surface area covered with osteoclasts as well as the number of osteoclasts are decreased[52,53]. Circulating osteocalcin declines, and the amounts of osteocalcin, type I procollagen, and IGF-I mRNA are decreased in the osteoblasts[54,55]. In DW rats, cancellous bone volume, BMD, and circulating alkaline phosphatase are decreased, compared with both normal and food-restricted rats that have growth retardation identical to the DW rats[56]. When GH is given to GH-deficient rats, an increase is seen in bone formation, bone mass, and circulating levels of osteocalcin and alkaline phosphatase[54-56]. The models show that GHD reduces bone formation and bone mass, and that GH administration counteracts these effects.

Very recently, a GH-deficient transgenic rat model has been described. The bone mass is decreased, the osseous

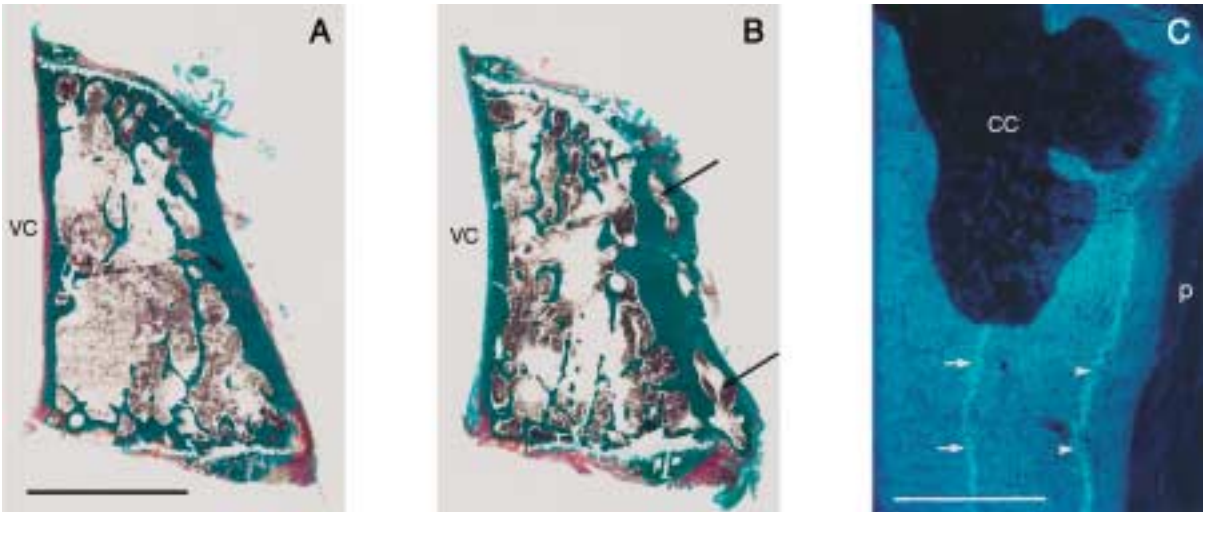

Figure 2. Photomicrographs of longitudinal sections of the vertebral bodies of L-6 from a vehicle-injected rat (A) and a growth hormone 80-day rat (B). The cranial cavity and the caudal cavity of the anterior wall found in the growth hormone 80-day rat are indicated by black arrows. C shows the bottom of the cranial cavity of the anterior wall in a growth hormone 80-day rat using epifluorescence. The tetracycline lines from labeling days 41 (white arrows) and 69 (white arrowheads) are shown. The cavity has developed during growth hormone injection as the tetracycline labeling line from day 41 is found to be partly degraded and replaced by the cavity. The labeling line from day 69 is still intact inside the bone wall. Dimensions are given by bars (A-B: 3 mm; C: 0.4 mm). vc = vertebral canal, p = periosteal surface, cc = cranial cavity. (Reproduced from Andreassen TT et al.: J Bone Miner Res 1996; 11:1094-1102 with permission of the American Society for Bone and Mineral Research).

tissue is undermineralized, and a corresponding decrease is found in the mechanical strength of the bones[57].

Mice

GH-overexpressing mice have been created. When the metallothionin promoter is fused to the GH gene, a very high serum level of GH is found, and a substantial increase in bone growth is seen in these animals[58]. Femoral dimensions, cortical thickness, and BMC are increased, whereas femoral BMD remains unchanged when calculated as BMC per volume[59]. Mechanical strength of the femoral diaphysis is also enhanced. The modelling of the femoral diaphysis with age is different in these animals, as the ellipsoid shape of the diaphysis has changed compared with normal animals[59]. Ovariectomy of GH-transgenic mice impairs development of bone mass. In order to increase bone mass, this model therefore requires sex hormones[60]. Based on these observations, we compared our data from GH-treated normal and OVX rats, and found no difference in GH-induced bone formation rate between the groups. In an experiment using OVX rats, separate and combined treatment with estrogens and GH were administered and the same anabolic responses on bone mass were observed, both when GH was given alone and in combination with estrogens[37].

By fusing an osteocalcin promoter or a beta-globin regulatory-element to the GH gene, local expression of GH occurs in bone osteoblasts and bone marrow erythroid tissue[61,62]. The systemic effects of GH are limited in these models. Bone mass and bone strength increase in both models, but when the mechanical data are corrected for dimensions, decreased mechanical quality of the osseous tissue is seen.

Recently, a mouse model has been created with defects in the GHR[63]. This model has disproportional growth and decreased cortical bone cross-sectional area. It also has decreased cortical bone BMC and BMD, even when the BMD is calculated as bone mass per volume. The results correspond with very recent data showing bone undermineralization in GH-deficient transgenic rats[57].

Monkeys

Experiments with GH administration to rodents nearly all include linear growth resulting in modelling drifts. No Haversian osteons are present in rats and mice, which makes the evaluation of GH-induced changes in cortical bone remodeling impossible. In adult monkeys, however, the growth plates are closed and remodeling takes place in both cortical and cancellous bone. In one experiment, GH was given for 10 months to monkeys with hypogonadism, which partly prevented a decline in spinal BMD[64]. However, GH was not able to change serum levels of osteocalcin. Cancellous bone metabolism was studied in a 7-week experiment in which monkeys were given GH, IGF-I, and GH plus IGF-I[65]. No changes in bone volume were seen in any of the groups. GH alone and GH plus IGF-I increased the bone formation rate, due mainly to an increase in mineral apposition rate. GH plus IGF-I also increased the surfaces covered with osteoclasts, and factorial analysis showed that this was predominantly due to GH. Osteocalcin gene expression was enhanced in both groups given GH. The histomorphometric findings are consistent with an increased bone turnover induced by GH.

In conclusion, GH administration increases bone turnover in animal models. In the rat model, GH enhances cortical bone mass and thereby increases the strength of the bone. Cancellous bone volume is increased when GH administration induces linear growth. However, when no linear growth occurs, cancellous bone volume seems rather unaffected.

The effects of GH in humans

GH has a major effect on circulating levels of IGF-I and IGFBP3, and it has been proposed that the GH-IGF-I axis influences adult bone mass[66]. A positive correlation between circulating IGF-I and total BMC and BMD has been found in healthy adults and in patients with osteoporosis[67-69]. In osteoporotics, both decreased circulating IGF-I levels, and levels within the normal range have been reported[70,71]. Independent of BMD, however, decreased serum IGF-I levels have been found to be strongly associated with an increased risk of osteoporotic fractures[69].

Acromegaly

Biochemical markers for bone formation and bone resorption are increased in patients with active acromegaly, and successful treatment normalizes the markers[72-74]. GH administration to healthy adults also augments formation and resorption markers, and the responses occur within the first weeks of administration[75]. Iliac crest bone biopsies from acromegalic patients show increased width of both the outer and inner cortical lamellae, and increased bone formation at both the periosteal and endocortical surfaces[76]. Increased bone volume, and increased mineralizing surface and resorption surface are found in the cancellous bone from these biopsies. The above cortical bone histomorphometric results are in agreement with bone data from long-term GH-treated dogs showing augmented femoral and tibial cortical bone mass as well as increased bone deposition at both the periosteal and endocortical surfaces[77]. The dog experiment, however, did not include cancellous bone measurements.

Bone mass has been measured in acromegalics and the results are conflicting, probably because many of these patients may have secondary hypogonadism due to the pituitary adenoma[73,78]. The results of a longitudinal study using DXA on eugonadal acromegalic patients showed an unambiguous increase in BMD of the cortical bone from the distal radius, whereas no differences in BMD of cancellous bone from the lumbar vertebrae were seen[79]. Normal BMD values of the lumbar vertebrae were found in eugonadal acromegalics with increased serum osteocalcin, urinary hydroxyproline and pyridinoline[72].

In conclusion, eugonadal acromegalics have increased bone formation and resorption. Cortical bone mass seems to be increased, whereas cancellous bone mass seems to be largely unaffected.

Growth hormone deficiency (GHD)

Patients with GHD have decreased BMC and BMD, and a corresponding increased fracture frequency has been found[80-82]. When adult GH-deficient patients are treated with GH, a number of trials have shown decreased lumbar spine and femoral neck BMD and BMC during the first 6-12 months of GH therapy, although the results are not fully unambiguous[83-86]. When the GH treatment was continued for two years or more, all trials found increased lumbar spine and femoral neck BMD and BMC levels compared with initial values[87-91]. Serum and urinary biochemical bone markers showed enhancement of bone formation and resorption during the GH treatment[83,85-89]. The biochemical markers increased rapidly when the treatment started and the initial decline in BMD and BMC can be explained by an expansion of the remodeling space in the bones.

Only a few studies have examined the effect of GH on cortical bone formation. Histomorphometric measurements using iliac crest biopsies have shown that GH treatment for one year increases the cortical thickness[92]. Analyses of DXA pictures reveal that both femoral neck and lumbar spine bone areas increase after GH treatment for 33 and 45 months, respectively[90]. Histomorphometric analyses of cancellous bone have been performed after one year of GH treatment using iliac crest biopsies[92,93]. Neither of the experiments found changes in bone volume, but osteoid surface, mineralizing surface, and erosion surface were increased.

In conclusion, GH treatment of adult patients with GHD initially decreases lumbar spine and femoral neck BMD and BMC, probably by increasing the remodeling space. Treatment periods for two years or more, however, increase both lumbar spine and femoral neck BMD and BMC. At present, it is not known whether these increases are due to an increased amount of cortical bone or if changes in cancellous bone volume might affect the parameters as well. Biochemical resorption and formation markers are elevated during GH treatment.

Osteoporosis

GH administration to postmenopausal osteoporotic women and men with idiopathic osteoporosis increases the biochemical markers for bone resorption and formation within the first week of treatment[87,94]. Histological examinations of rib bone biopsies from severe osteoporotic men treated with GH for 8-15 months show periosteal bone formation and intracortical bone resorption[95]. In studies using different treatment schemes, GH was given in combination with either calcitonin or bisphosphonate. Postmenopausal osteoporotics were treated for up to two years with either GH alone or in combination with calcitonin[96-99]. Little effect was seen, but radial shaft BMC decreased during the treatment in two of the studies[96,98]. Postmenopausal osteoporotics were given GH for two years (daily injection for one week every three months), and this treatment decreased lumbar spine and femoral shaft BMD[100]. When the one-week GH administration was followed by a three-week calcitonin treatment period, no decrease in lumbar spine BMD was seen, whereas femoral shaft BMD was decreased. Serum osteocalcin and urinary pyridinoline increased both in the patients given GH alone and in the patients given GH followed by calcitonin. Combined GH and bisphosphonate therapy for six months did not influence the BMD of the lumbar spine, femoral neck, proximal radius, and distal radius in postmenopausal osteoporotics[101]. During the treatment, serum osteocalcin increased, whereas urinary free deoxypyridinoline remained unchanged.

Daily GH treatment of postmenopausal osteoporotics resulted in decreased femoral neck BMD, and unchanged lumbar spine BMD after one year of therapy[102]. After the second year of therapy, however, femoral neck BMD had returned to initial values and lumbar spine BMD was now increased. In a very recent trial, GH was given daily for three years to postmenopausal osteoporotics[103]. GH did not influence lumbar spine and femoral neck BMD and BMC during the treatment. However, one year after withdrawal from the GH therapy, lumbar spine and femoral neck BMC were increased.

Based on existing clinical trials, few anabolic effects were found during the first two years of GH therapy. Only one study includes a longer treatment period, and in this trial no anabolic effect was observed until after withdrawal from the therapy.

In summary, human trials are characterized by an increase in both bone formation and resorption when GH is administered. To what extent the resorption can be inhibited by combined treatment with GH and anti-resorptive agents like bisphosphonates remains to be thoroughly investigated. The animal experiments clearly show that periosteal bone deposition can be induced by GH treatment. From a mechanical point of view, periosteal bone formation is desirable because new osseous tissue at this location increases the strength of the bone to a maximum degree. At present, little information is available with respect to GH-induced periosteal bone formation in humans. The advances within the field of computer tomographic resolution techniques enable gaugements of periosteal bone deposition in humans. Hopefully, such measurements will be performed.

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