Abstract Growth hormone (GH) is fundamental for the maintenance of bone mass and metabolism both during childhood and in adulthood. This effect is due to a complex interaction between circulating GH and IGF-I produced peripherally. In vitro data and experimental animal models have clarified many of the regulatory mechanisms underlying the characteristic skeletal changes occurring in acromegaly. This review focuses on the effects of GH excess on bone metabolism and mass in acromegalic patients and, in particular, on the influence of factors such as hypogonadism, gender, age and therapy on bone metabolism and arthropathy.

Key words Acromegaly • Growth hormone • IGF-I • Bone

Introduction

Longitudinal bone growth during childhood is due to growth hormone (GH)-dependent stimulation of precursor cells in epiphyseal cartilage, while maintenance of adult bone mass results from GH-driven bone modelling processes [1, 2]. These effects are the consequence of complex interactions between systemic GH, insulin-like growth factor (IGF) I and II, IGF binding proteins (BPs) and locally produced IGF-I and IGFBPs (Figs. 1, 2).

IGF-I and IGF-II interact with two specific receptors: the type 1 receptor, through which mitogenic and functional effects are activated; and the type 2 receptor, which probably inhibits IGF activity by competing with type 1 receptor binding. IGF-I and IGF-II also cross-react with the insulin receptor. IGF-I production is mainly stimulated by the action of GH in liver, although it takes place in all peripheral tissues, where IGF-II and the IGFBPs are also synthesized [3]. GH also stimulates production of IGFBP3 and ALS, other components of the high molecular weight IGF ternary complex, in the liver [3].

Some IGFBPs, in particular types 3 and 5, not only inhibit IGF action by competing with the membrane receptor but also may potentiate IGF action, probably because they bind to the cell membrane or to the extracellular matrix and protect IGF from being degraded by proteases [4]. IGFBP proteases are produced ubiquitously and can act in an autocrine or paracrine way on the IGF system [5].

Lastly, IGF activity (particularly IGF-II) also depends on binding to vitronectin in the extracellular matrix, which potentiates IGF action [6], and to the integrin receptor which influences intracellular signalling of the type 1 receptor [7, 8].

Regarding bone, a direct effect of GH and IGF-I on osteoblasts was demonstrated by the finding of functional GH and IGF-I receptors in human and rat osteoblast cul-
tures [9, 10]. GH and IGF-I regulate osteoblast proliferation, with GH exerting a prominent IGF-I-independent effect on differentiation, and IGF-I acting mainly on differentiated osteoblasts. Canalis et al. [11] first reported that osteoblasts produce IGF-I and that IGF-I has a mitogenic action on bone cells. Osteoblasts also synthesize IGF-II, and the balance between IGF-I and IGF-II production depends on the different bone districts. Further insight into the role of systemic IGF-I in the development and maintenance of adult bone mass has recently been acquired by the use of global and liver IGF-I knockout mice: in the former a reduction in bone size and an increase in trabecular bone volume was observed [12], due to increased connective tissue; the latter knockout mice have reduced cortical bone mineral density with no changes in trabecular bone. Moreover, IGF-I overexpression increases bone mineral density and trabecular bone volume [13], while GH overexpression initially leads to increased bone formation and subsequently to increased bone resorption [14].

Local inhibitors of IGF synthesis are transforming growth factor β (TGF-β) and cortisol [15, 16], while parathyroid hormone (PTH) exerts a stimulatory effect [17, 18]. IGFs also regulate production of collagen and matrix apposition [19]. In addition, GH, IGF-I and IGFBPs may all modulate osteoclast function and thus bone resorption [20]. Lastly, IGFBP-2 to -5 have also been demonstrated to be present in bone. In particular, IGFBP-4 has an inhibiting effect on IGF action, while IGFBP-5 has a potentiating effect, both in vitro and in vivo, probably by binding to sites independent of the type 1 IGF receptor [21].

Bone metabolism and density in acromegaly

In acromegaly (Fig. 3), changes in skeletal structure and metabolism are due to the chronic GH and IGF-I overproduction. Biochemical markers of bone remodelling are...
increased, and correlate well with circulating GH and IGF-I levels [9, 10]. In particular, urinary excretion of hydroxyproline and creatinine is increased in the vast majority of acromegalic patients and correlates with plasma IGF-I levels; however, a more specific indicator of bone collagen turnover, urinary type I collagen cross-linked N-telopeptide, correlates with serum GH [22]. Moreover, most markers rapidly decrease during effective treatment [23–26]. It is of particular interest to note that the controlled selective blockade of the GH receptor by the antagonist pegvisomant in acromegaly resulted in decreased measures of both bone formation and resorption. In fact, in a 12-week placebo-controlled trial, administration of pegvisomant was associated with a significant reduction in bone turnover markers osteocalcin, serum procollagen I carboxy-terminal propeptide and N-telopeptide [24]. The use of this experimental model is of particular interest because it rules out possible interfering actions on bone of other drugs used in the treatment of acromegaly, such as somatostatin analogs.

The increase in bone mass typically involves cortical bone, while for trabecular bone data are not unequivocal. Earlier studies reported a high prevalence of osteoporosis in acromegalic patients, despite low fracture rates. In fact, vertebral bone density is normal or slightly reduced in these patients, while limbs generally have increased density [22, 27–30]. Vestergaard and Mosekilde [31] observed that, in a large cohort of newly diagnosed acromegalic patients who underwent surgery, the fracture rate was significantly lower before surgery as compared with controls, as a consequence of the anabolic effects of GH on bone [31]. Normal or increased bone mineral density (BMD) at the femoral neck and lumbar spine was recently observed [32] in patients in remission after treatment for acromegaly. Similar results were obtained in patients in remission for 5 years or longer. No relationship between BMD and disease severity or duration was found before treatment. Thus, the anabolic effect of GH on trabecular and cortical bone appears to persist after remission of acromegaly. On the other hand, other studies failed to observe significant differences in BMD between acromegalic patients and controls [27, 33]. This discrepancy could be due to differences in skeletal sites examined, diagnostic equipment used, and grouping of patients regardless of gender and gonadal status.

Gonadal status may influence the effects of GH and IGF-I excess on bone [34]. Femoral BMD is increased only in acromegalic patients with active disease, regardless of gonadal status, and vertebral BMD only in eugonadal patients, regardless of disease activity. Furthermore, these effects are gender-independent. The same authors [35] reported that bone density forearm is normal, while bone density in the femur increases independently of the gonadal status; moreover an increased bone mass can be documented in the spine, but not in the femur or in the forearm in eugonadal patients, while hypogonadal patients have values of trabecular bone mass at both sites similar to those in the matched controls. Other authors reported increased BMD in eugonadal acromegalic patients, at both femoral and lumbar spine levels [36]. Overall, GH and IGF-I excesses increase the cortical bone density, regardless of age and gonadal function, while hypogonadism seems to counteract the anabolic effect of GH on the trabecular bone of young and middle-aged patients [37]. The implications of these finding are that eugonadal acromegalic patients are not at risk of decreased lumbar spine and femoral neck BMD. However, if these patients develop hypogonadism, they may be at risk of reduced lumbar spine BMD and osteoporosis [36]. Thus, it may be advisable to screen for hypogonadism and to start hormone replacement therapy as soon as it is diagnosed.

**Acromegalic arthropathy**

Acromegalic patients often complain of symptoms due to acromegalic arthropathy, a condition characterized by osteoarthrosis, reduced articular space and calcification of ligamentous insertions and joint capsules (Fig. 4) [1, 38, 39]. GH and IGF-I excesses are responsible for replication of articular chondrocytes and increased matrix synthesis [1]. As a result, there is thickening of the cartilage, widening of the joint space, alteration of normal joint geometry and hypermobility. Moreover, GH and IGF-I stimulate
growth of periarticular structures and cause sinovial hypertrophy, which in turn exacerbates the abnormal mechanical loading of the joint. Effective treatment of acromegalic disease at this stage can stop arthropathy progression and even reverse manifestations, but when degenerative changes have progressed and fissures of the cartilage surface have appeared, alterations may become permanent [38, 40].

Therefore, joint thickness may also be increased in patients cured by surgery compared to controls [38]. At this stage there are in fact calcifications and osteophyte formation, cartilaginous fissures extend to the subchondral bone, articular cartilage becomes ulcerated while bones show accelerated turnover, eburnation and subchondral cyst formation [1]. Eventually, thinning of the articular cartilage and narrowing of the joint space become predominant features of arthropathy, resembling those of osteoarthritis. Radiological signs can be detected early in the course of the disease and usually precede other clinical manifestations. Ultrasonography is a valuable tool in the evaluation of periarticular soft tissue structures such as joint capsules and tendons. By this technique, increased thickness of both weight-bearing (knees) and non-weight-bearing (shoulder and wrist) joints can be shown in patients with active acromegaly compared to controls [41].

The most frequently affected joints are hands, knees and hips, as well as cervical and lumbar spine, although any joint can be involved. When disease duration is long, severe degenerative changes may occur at several levels. Severe arthropathy may be present in up to 40% of patients, while most patients (75%) present with mild manifestations (Table 1).

Typical features of acromegaly are prognathism and widening of the interdental spaces. These changes lead to dental malocclusion and temporomandibular joint syndrome in about one-third of cases. Recently, a rat model of acromegaly (acrogiantism) was developed to investigate the time course of mandibular enlargement by continuous subcutaneous human recombinant IGF-I infusion [42]: after discontinuation of IGF-I administration, the mandibula did not continue to grow but did not return to control size either, at variance with the maxilla and femur. These data suggest that mandibular occlusal treatment should be taken into consideration in acromegalic patients only after serum IGF-I levels have normalized and bone growth has ceased.

**Neurological complications associated with bone alterations**

Typical feature of acromegaly is also symptomatic carpal tunnel syndrome, which affects 20%–60% of patients [1, 43]. Prevalence may be even higher if subclinical conditions detected by nerve conduction studies are considered [44]. Hand MRI may reveal increased nerve size and signal intensity in patients with symptoms of neuropathy compared with asymptomatic ones [45]. The major pathogenetic factor for median neuropathy in acromegaly seems to be increased edema of the median nerve, but an increase in connective tissue, demyelination of Schwann cells, an increase in extracellular fluid of the carpal bones and bony or synovial overgrowth of carpal bones can be involved as well [37]. It is interesting to note that while presence and severity of carpal tunnel syndrome do not seem to correlate with GH and IGF-I levels, nor with duration of disease, nerve swelling decreases after successful treatment of acromegalic disease, suggesting that control of hormone levels is essential for regression of nerve abnormalities [43, 44].

**Respiratory complications**

Respiratory disorders of acromegaly are frequent and complex in their origin and development. Certainly, structural changes in the upper and lower airways induced by the hypertrophic action of GH, a decrease in pulmonary elasticity with a concomitant increase in lung volume due

| Reference        | Year | Mild arthropathy | Severe arthropathy |
|------------------|------|------------------|--------------------|
| Detenbeck et al. [50] | 1973 | 62%              | 16%                |
| Bluestone et al. [51] | 1971 | 62%              | 38%                |
| Dons et al. [52]  | 1988 | 76%              | ND                 |
| Podgorsky et al. [53] | 1988 | 74% (peripheral) | 28%<sup>a</sup>    |
|                  |      | 45% (vertebral)  |                    |
| Barkan [39]      | 1997 | ND               | 30%                |

*ND, not determined; <sup>a</sup> 22% in men, 35% in women*
to alveoli overgrowth, and hyperstimulation of the respiratory center mediated by the somatostatinergic tone and triggered by an altered sensitivity threshold to carbon dioxide are the major factors involved in the pathogenesis of sleep apnea, the prominent type of breathing disorder of acromegaly [1]. However, anatomical changes affecting craniofacial bones and soft tissues, respiratory muscles and cartilage, lung volume, rib cage geometry and activity of the respiratory muscles are also involved.

Acromegalic patients develop a barrel chest due to kyphosis caused by changes in vertebral bodies and by elongation and diversion of the ribs. In particular vertebral bodies increase in size due to periostal bone apposition, while the intervertebral discs become thicker in the cervical and lumbar spine, and thinner in the thoracic region [46, 47]. The epiphyses of the costochondral junctions fail to close and may cause prominence of the costochondral junction [48]. These anatomical changes impair chest mechanics and markedly alter the inspiratory muscle activation. Furthermore, acromegaly is associated with muscle weakness and wasting due to alterations of type I and type II muscle fibers, small cell infiltration, thickening of the capillary basement membrane and segmental fiber degeneration, all which may contribute to the impairment of physiological breathing [49].

Conclusions

In conclusion, effects of GH on linear bone growth, bone metabolism and bone mass are relevant. In vitro, GH stimulates proliferation, differentiation and extracellular matrix production in osteoblast-like cell lines, as well as recruitment and bone resorption activity in osteoclast-like cells. Acromegaly results in increased bone turnover and appendicular cortical bone mass, while vertebral bone mass is largely unaffected. However, evaluation of the effects of GH is frequently obscured by concomitant hypogonadism. Arthropathy affects most acromegalic patients and is a leading cause of morbidity and functional disability. Only the early stages are seemingly reversible by effective treatment of the acromegalic disease, while nothing can be done to stop the vicious cycle of articular changes in long-term disease.

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