MANAGEMENT OF ENDOCRINE DISEASE

Bone disorders associated with acromegaly: mechanisms and treatment

Gherardo Mazziotti1,2, Andrea G A Lania1,2 and Ernesto Canalis3

1Department of Biomedical Sciences, Humanitas University, 2Endocrine, Diabetes and Andrology Unit, Humanitas Clinical and Research Center, IRCCS, Rozzano, Milan, Italy, and 3Departments of Orthopaedic Surgery and Medicine, The UConn Musculoskeletal Institute, UConn Health, Farmington, Connecticut, USA

Abstract

Growth hormone (GH) and insulin-like growth factor-I (IGF-I) exert physiological actions on the skeleton throughout life, by stimulating longitudinal bone growth in children, the acquisition of bone mass during adolescence and the maintenance of skeletal architecture in adults. When GH and IGF-I are secreted in excess, bone remodeling is enhanced leading to deterioration of bone microstructure and impairment of bone strength. Indeed, acromegaly causes skeletal fragility, and vertebral fractures are reported in a remarkable number of subjects exposed to GH and IGF-I excess. The management of skeletal fragility in acromegaly is a challenge, since the awareness of this complication is low, the prediction of fracture risk is difficult to ascertain, the risk of fractures remains after the control of acromegaly and the effectiveness of bone-active drugs is unknown. This review is an update on bone disorders associated with acromegaly and provides a perspective of possible therapeutic approaches based on emerging pathophysiological and clinical information.

Introduction

Acromegaly is a chronic and disabling disease characterized by excessive secretion of growth hormone (GH) generally caused by a pituitary adenoma resulting in elevated circulating levels of GH and insulin-like growth factor (IGF-I) (1).

Under physiological conditions, GH and IGF-I are beneficial to skeletal health since they enhance longitudinal bone growth, as well as bone modeling and remodeling (2). Based on these physiological effects and the fact that subjects with acromegaly have characteristically enlarged bones, acromegaly has been overlooked as a risk factor for skeletal fragility and fractures (3, 4). Recently, this paradigm was revisited because of findings demonstrating that GH and IGF-I in

Invited Author’s profile

Gherardo Mazziotti, MD, PhD is an Associate Professor of Endocrinology at Humanitas University of Milan, Head of Metabolic Bone Diseases and Osteoporosis Section and bone specialist in the Pituitary Tumor Center of Excellence of Humanitas Research Center of Rozzano (MI), Italy. His main field of interest is the neuroendocrinology of bone and during the last 15 years, Dr Mazziotti has made several contributions to the understanding of the role of pituitary hormones, particularly growth hormone in bone metabolism.
excess may cause abnormalities in trabecular and cortical bone architecture leading to decreased bone strength and increased risk of vertebral fractures (VFs) (5).

The management of skeletal fragility in acromegaly is challenging since VFs are not predicted by changes in bone mineral density (BMD) (6), the fracture risk persists in subjects following the successful treatment of the disease (7, 8) and the efficacy and safety of bone-active drugs in acromegaly are unknown (5).

This review is an update on bone disorders associated with acromegaly and provides a perspective of possible therapeutic approaches based on emerging pathophysiological and clinical information.

Physiology of the GH-IGF-I axis in the skeleton

During the first two decades of life, GH and IGF-I play a central role in endochondral bone formation by stimulating chondrocyte proliferation and differentiation. These effects on the epiphyseal plate are paralleled by the actions of GH and IGF-I on bone modeling (Fig. 1), a process whereby bones are shaped or reshaped by the independent and uncoupled action of osteoblasts and osteoclasts. Bone modeling occurs either during skeletal development or after growth and throughout life (9, 10). GH and IGF-I also stimulate bone remodeling, a process of coupled bone resorption and formation, necessary to maintain calcium homeostasis and to remove potentially micro-damaged bone throughout life.

Bone remodeling is carried out in microscopic basic multicellular units (BMUs) by the activity of osteoclasts and osteoblasts (11, 12). Osteoclasts are multinucleated cells arising from mononuclear precursors of the hematopoietic lineage and are responsible for bone resorption, a process that takes 3–5 weeks. Thereafter, the resorbed surface attracts osteoblasts that fill the BMU with new matrix, in a process that takes 3–5 months. Osteoblasts derive from mesenchymal cells that reside in the bone marrow and they can differentiate further into lining cells or into osteocytes or can die by apoptosis (13, 14, 15). Osteocytes have cytoplasmic processes that connect them among themselves or to other cells in the bone environment to form a communicating network that plays a role in maintaining the material properties and structural strength of bone (16). Osteocytes are responsible for skeletal responses to mechanical load and are a significant source of receptor activator of NF kappa B ligand (RANKL) (17).

In vitro effects of GH and IGF-I on bone formation and resorption

The GH receptor is expressed by chondrocytes and osteoblasts (18, 19, 20, 21) and its expression is under the control of IGF-I (22) and of IGF-binding proteins (IGFBPs) (23, 24). GH stimulates osteoblastogenesis directly or indirectly (25, 26, 27). For example, GH suppresses the expression of fetal antigen 1, the soluble form of delta-like-1, known to suppress fat and bone mass (27). GH also stimulates the expression of bone morphogenetic proteins, which along with Wnt play a role in enhancing osteoblastogenesis (28, 29, 30). GH stimulates the carboxylation of osteocalcin, which is a marker of osteoblastic function (31).

Although GH may have direct effects on cells of the osteoblast lineage, most of the effects in osteoblasts and bone formation are mediated by the systemic form of IGF-I, synthesized in the liver under GH control (32).
It is important to note that the synthesis of IGF-I in osteoblasts is not enhanced by GH and is under the control of parathyroid hormone (PTH) (33, 34). IGF-I has modest effects on osteoblast differentiation and enhances the function of mature osteoblasts (35). IGF-I upregulates type I collagen transcription and decreases the synthesis of matrix metalloproteinase 13, a collagen-degrading protease (36), ensuring the maintenance of appropriate levels of bone matrix and bone mass. IGF-1 stimulates the expression of RANKL and, as a consequence, osteoclastogenesis (37). The IGF-I receptor is present in preosteoclasts and mature osteoclasts (38, 39), and IGF-I enhances the formation of osteoclast-like cells in cultures of bone marrow macrophages (40).

The effects of IGF-I on bone are modulated by IGFBP-2 and -4. IGFBP-2 stimulates osteoblastogenesis (41, 42), whereas IGFBP-4 inhibits the differentiation of progenitor cells and the functions of osteoblasts and osteoclasts (43, 44). The latter effects may be counteracted by a concomitant increase of IGF-I bioavailability induced by IGFBP-4.

**In vivo effects of GH and IGF-I on bone formation and resorption**

Pre-clinical studies have indicated that systemic IGF-I is necessary to maintain cortical bone structure, whereas skeletal IGF-I appears to play a more significant role in the maintenance of cancellous bone (2). Mice carrying mutations in the GH-releasing hormone receptor (lit/lit mouse) or the GH receptor exhibit reduced cortical bone, but normal trabecular bone and this may be accounted for by the GH-independent local production of IGF-I (2, 45, 46). Similarly, mice carrying a liver-specific Igf1 deletion display a modest skeletal phenotype, characterized by a decrease in cortical volume, secondary to a reduction in periosteal bone formation (47). In contrast, the conditional deletion of the IGFI receptor (Igf1r) in murine osteoblasts causes a decrease in bone formation and trabecular bone volume (48).

Consistent with the *in vitro/ex vivo* studies reporting direct stimulatory effects of IGFBP-2 on osteoblastogenesis (41, 42), Igfbp2-null mice have low osteocalcin levels, abnormalities in trabecular bone structure and reduction in mineralizing surface/bone surface (49). These effects are observed in male but not in female mice, possibly reflecting the protective effects of persistently high circulating IGF-I concentrations in female mice (50). Interestingly, recombinant IGFBP-2 stimulates bone formation and protects against the bone loss observed following ovariectomy and skeletal unloading in rats (51). The effects of IGFBP-4 on the skeleton *in vivo* were evaluated in mice following the inactivation (43) or the overexpression of *Igfbp4*, as well as the administration of recombinant IGFBP-4 (52). Igfbp4-null male mice have increased trabecular bone, whereas female Igfbp4-null mice have a decrease in trabecular bone volume. The reasons of these sex-related findings are unclear (43).

**Effects of GH and IGF-I on calcium-phosphate metabolism**

GH and IGF-I regulate calcium and phosphate metabolism (55). These effects are mainly mediated by the activation of vitamin D by GH and IGF-I. GH stimulates calcitriol production in experimental animals (56) and men (57), an effect mediated by the stimulation of 1α-hydroxylase in the proximal renal tubule by IGF-1 (58). The activation of vitamin D leads to a positive calcium balance secondary to an increase in intestinal calcium absorption (59) and renal calcium reabsorption in the distal tubule (60).

GH has phosphate-retaining actions in the kidney (55). The anti-phosphaturic effect of GH is due to an increase in the maximal tubular phosphate reabsorption rate and is independent of the actions of PTH (61). GH and IGF-I may influence circadian PTH secretion and pulsatility, but the physiological and pathophysiological implications of these effects remain unclear (62).

**Acromegaly: epidemiology and clinical aspects**

Acromegaly is a chronic disease with an estimated prevalence of 30–60 cases/100,000 and an incidence of approximately 3–4 cases/100,000 inhabitants (63). The sex ratio is close to 1 and the mean age at the time of diagnosis ranges between 40 and 50 years of age (64, 65).
Bone disorders in untreated acromegaly

Effects of GH excess on bone formation and resorption

In acromegaly, bone turnover is enhanced with a greater increase in bone resorption than in bone formation (6). The predominant effects of GH excess on bone resorption were reported in several studies evaluating biochemical markers of bone turnover (69, 70, 71). The increased bone turnover is directly related to the levels of circulating GH and IGF-I (40). The increased bone remodeling is likely due to the actions of IGF-I on the induction of RANKL leading to enhanced osteoclastogenesis (40, 72, 73). Analyzing gene expression in sphenoid bone tissue samples of subjects with acromegaly, Belaya et al. suggested that GH excess may induce mesenchymal stem cell commitment toward cartilage or adipocytes instead of toward mature osteoblasts (74). It was hypothesized that the cartilage growth induced by GH excess may influence osteoblast and osteoclast function directly in a way similar to the one occurring during normal endochondral ossification (74). One may speculate that acromegalic osteopathy and arthropathy share common pathophysiological mechanisms (Fig. 1), as proposed in individuals with concomitant osteoarthritis and osteoporosis (75, 76).

Effects of GH excess on bone histomorphometry and architecture

The increase in bone turnover in acromegaly may lead to bone loss and abnormalities in bone structure. Transgenic mouse models overexpressing GH under the control of a metallothionein 1 transcriptional regulatory element exhibit markedly increased bone resorption and impaired trabecular and cortical bone architecture and mechanical competence (77, 78). Abnormalities in bone structure also are found in subjects with acromegaly. Indeed, seminal human studies using histomorphometric analysis revealed an increase in trabecular and cortical bone mass and high activity of osteoclasts and osteoblasts at the tissue level (79). However, recent work using microarchitectural and histomorphometric analysis has allowed a better understanding of the trabecular and cortical bone structural changes in acromegaly (80). Dalle Carbonare et al. recently described reduced trabecular bone volume, trabecular thickness and increased trabecular separation demonstrating decreased cancellous bone; cortical thickness was increased, but the cortical bone was porous in subjects with acromegaly and VFs compared to subjects without acromegaly (81). These results were consistent with previous data reporting abnormal bone architecture and altered biomechanical competence in subjects with active acromegaly (82). Using the less invasive high-resolution-peripheral quantitative computerized tomography (HR-pQCT), Madeira et al. reported decreased trabecular density, trabecular bone volume/tissue volume and trabecular number in the distal tibia and radius of subjects with acromegaly. These structural alterations closely correlated with the gonadal function of the subjects studied (83). However, subsequent work demonstrated abnormalities in trabecular bone microstructure and strength in active acromegalic patients seven when gonadal function was normal (84, 85, 86). In addition to these changes in cancellous bone, the cortical bone compartment is affected, and GH excess is associated with increased cortical porosity/pore volume (81, 84, 87) and decreased cortical density (85).

Effects of GH excess on fracture risk

The structural abnormalities in cancellous bone of subjects with acromegaly explain the increased incidence of VFs but do not seem to be a cause of fragility fractures in long bones (3, 4, 66). The fragility of the peripheral skeleton is mainly related to the properties of cortical bone, which is affected in a distinct manner by GH, possibly
because bone remodeling is less active in cortical than in trabecular bone. Moreover, GH hypersecretion induces periosteal bone formation with a consequent increase in cortical bone mass, which may in part counteract the potential negative effects of high bone remodeling that lead to a porous cortical bone. Interestingly, the moment of inertia of the femoral bone is high in an experimental model of acromegaly (88). GH excess causes vertebral fragility, which is related to focal areas of erosion creating stress risers on trabeculae. These effects are closely related to high bone remodeling, an activity that takes place mainly in cancellous bone. Applying a radiological and morphometric approach (89) (Fig. 2), Bonadonna et al. described for the first time an increase in the prevalence of VFs in post-menopausal women with acromegaly (90). In addition, cross-sectional studies confirmed this finding consistently and demonstrated an increased incidence of VFs in pre-menopausal women and male subjects with acromegaly (91, 92, 93, 94, 95). The overall median prevalence of VFs in acromegaly is about 40%, a fracture risk which is three- to eight-fold greater compared to control subjects (6). Interestingly, the prevalence of VFs is slightly greater in men than in women (5). A recent study provided suggestive evidence that VFs are a consequence of the skeletal exposure to GH and IGF-I excess, since the risk of fractures was correlated with the duration of active disease (7). Moreover, a higher incidence of fractures was found in individuals harboring an exon-3 deficient GH receptor that has increased affinity for GH (96).

VFs are not a simple radiological finding but they should be considered a marker of skeletal fragility, since an association between fractures and abnormalities in bone microstructure was found following the analysis of bone samples from individuals with acromegaly by histomorphometry, tridimensional dual-energy X-ray absorptiometry (DXA) of the proximal femur and peripheral HR-QCT of the bone structure at the distal radius (81, 85, 87).

Noteworthy, VFs develop more frequently in the thoracic spine and they are often anterior wedge fractures (91), possibly contributing to the kyphosis of subjects with acromegaly (97). The fact that more than 50% of individuals with fractures have either multiple or severe VFs (95), may predispose subjects with fractures to have back pain, impaired quality of life and a possible worse outcome of cardiopulmonary complications in acromegaly (98, 99).

Effects of GH excess on calcium and phosphate metabolism

Active acromegaly is associated with mild hyperphosphatemia and a tendency toward hypercalcemia and hypercalciuria (55, 72), closely related to increased calcitriol-stimulated phosphate and calcium absorption in the gut and to the direct antiphosphaturic action of IGF-I (55). Hypercalciuria may be considered, at least in part, a marker of skeletal fragility reflecting the increased bone turnover induced by GH excess (55).

Notwithstanding the stimulatory effects of GH and IGF-I on vitamin D activation by the kidney (55), hypovitaminosis D is found in patients with acromegaly consistently (100, 101). There is evidence suggesting lower peripheral bioavailability of vitamin D in acromegaly because of an increase in serum levels of vitamin D-binding protein (102, 103). GH excess influences PTH pulsatility with prolongation of pulse duration and increase in pulse mass (104); however, the skeletal implications of these effects are unclear.

Bone disorders in treated acromegaly

The therapeutic goals in acromegaly are the normalization of the hormonal excess, the removal of the tumor and the control of the clinical manifestations of the
disease. Altogether, these lead to a decrease in mortality. Transsphenoidal surgery is considered the first line of treatment, especially in subjects harboring fully resectable tumors or those with neurological complications, such as visual impairment (67).

Medical treatment is based upon the administration of either long-acting somatostatin analogs (SSAs) or GH receptor antagonists (GRAs). These are usually prescribed in patients with persistent disease after surgery or in selected cases as a first line of treatment (67). First-generation (i.e. octreotide LAR and lanreotide autogel) and second-generation (pasireotide) SSAs are effective in controlling GH secretion and tumor size, whereas the GRA pegvisomant normalizes IGF-I levels without any significant effect on tumor mass (105). Stereotactic radiosurgery may be used as adjuvant or alternative therapy in subjects with inoperable or residual disease or in those who are not surgical candidates (67).

**Effects of acromegaly therapy on bone turnover, bone structure and calcium-phosphate metabolism**

Cross-sectional and prospective studies have demonstrated a decrease in serum levels of biochemical markers of bone turnover following the biochemical control of acromegaly (5). However, it is unclear whether the decrease in bone turnover is accompanied by an improvement in bone structure, and a reduction in fracture risk. Recent studies hypothesized that osteoblastogenesis may be impaired in subjects with controlled acromegaly, but the studies do not offer a direct proof that osteoblast number or function is altered in these individuals (74, 106, 107). Dalle Carbonare et al. reported decreased osteoblast number and function and reduced osteocyte number in bone samples from patients with controlled acromegaly compared to those with active disease, but the impact of these histomorphometric findings on fracture risk was uncertain since all subjects included in the study had VFs (81). Further findings to support the concept that skeletal fragility persists notwithstanding biochemical control of acromegaly are the impairment of trabecular microstructure as assessed by DXA measurement of trabecular bone score (TBS) (108) and altered tissue-level properties of cortical bone as measured by impact microindentation in individuals with treated acromegaly (109). These may be the result of permanent or irreversible alterations in bone structure or persistently increased bone remodeling.

The biochemical control of acromegaly is usually accompanied by a significant and rapid decrease in serum calcium and phosphorus with the normalization of hypercalciuria and secondary increase in serum PTH (72, 110, 111). The decrease in serum phosphate after the biochemical control of acromegaly was not related to changes in serum fibroblast growth factor-23 (112), a phosphaturic factor that promotes renal phosphate excretion and inhibits renal synthesis of dihydroxyvitamin D₃ (113). The impact of the alterations in calcium and phosphate metabolism on skeletal function is unknown.

**Effects of acromegaly therapy on fracture risk**

The persistent abnormalities in bone structure explain why fracture risk persists in some patients with cured acromegaly (7, 8), particularly, when hypogonadism is present (7, 114), diabetes mellitus coexists (115) or when pre-existing (i.e., prevalent) VFs are identified (7, 8). The latter finding is consistent with the concept that VFs are a marker of skeletal fragility in acromegaly (116, 117). Based on the hypothesis that the drugs used in acromegaly may have direct effects on peripheral targets independent of the biochemical control of the disease (118, 119, 120), some studies investigated the possible effects of SSAs and pegvisomant on fracture risk in acromegaly (114, 121). However, the results of these studies were inconclusive since the design did not allow to discriminate the skeletal effects of the drugs from those on the activity of the underlying disease.

**Proposed approach to subjects with acromegaly-induced skeletal fragility**

**Diagnosis of osteopathy in acromegaly**

In clinical practice, measurement of BMD at the lumbar spine, total hip and femoral neck by DXA is the mainstay for the diagnosis of osteoporosis and prediction of fracture risk (122). Unfortunately, this approach has not been validated in acromegaly, where abnormalities of bone microarchitecture associated with GH hypersecretion are not captured by BMD. Degenerative joint alterations, characterized by osteophyte formation and facet-joint hypertrophy may lead to an overestimation of BMD measured at the lumbar spine (5). Moreover, BMD could be influenced by the bone enlargement caused by GH excess (123). Because of these reasons, a limited number of subjects exposed to GH excess have decreased BMD,
and bone density is not a reliable predictor of fracture risk in acromegaly (6). Subjects with acromegaly may develop VFs even in the presence of normal BMD (90, 91, 95).

Volumetric BMD measured by QCT is used to determine the bone density of the trabecular compartment independent from the cortical bone and is not influenced by changes in the size of bones. Volumetric BMD was reported to be decreased in acromegaly (124, 125), but the value of this finding in predicting VF risk is unknown, in part due to a lack of specific and standardized cut-offs for identifying individuals with osteoporosis. A more accurate evaluation of bone microstructural alterations associated with GH hypersecretion and VFs may be provided by HR-QCT (83, 87), but the high cost and increased radiation dose limit their use in clinical practice. However, there are more feasible diagnostic techniques that may assist the clinician in the identification of acromegalics with skeletal fragility and predisposed to VFs. A non-invasive bone structure assessment using DXA images termed 3D-SHAPER was developed to analyze the cortical bone layer independent of the trabecular macrostructure at the proximal femur (126) and lumbar vertebrae (127). This approach demonstrated a decrease in cortical volumetric BMD at the proximal femur in acromegalic subjects with VFs compared to those without fractures (85). Another simple and feasible approach to assess bone structure using DXA images is the measurement of TBS, a gray-level textural metric that can be extracted from the 2D lumbar spine DXA image. TBS captures the mean rate of pixel gray-level variations in the DXA image. A high TBS value reflects better trabecular bone structure, whereas a low TBS value indicates impaired structure that is prone to fractures (128). Low TBS values are found in subjects with acromegaly and VFs (85). Based on this knowledge, non-invasive 3D-SHAPER and TBS assessments could be valuable in the assessment and management of individuals with acromegalic osteopathy.

The high incidence of fractures related to GH hypersecretion (6), untreated hypogonadism (7), diabetes mellitus (115) and pre-existing VFs (7, 8) are all compelling reasons for a direct evaluation for the presence of VFs by a morphometric approach in all subjects with acromegaly at the time of diagnosis and during their follow-up (i.e., every 18 months) depending on the risk profile at baseline. Quantitative morphometry is performed on spinal X-ray images (129), although a quantitative approach may also be applied to images of the spine acquired either by DXA (130) or by chest X-rays (99, 131). VFs are identified by describing the shape and heights of vertebral bodies. According to a quantitative morphometric approach, VFs are defined as mild, moderate and severe based on a height ratio decrease of 20–25%, 25–40% and over 40%, respectively (89). Noteworthy, the diagnosis of mild VFs in acromegaly may be challenging particularly when they involve the upper thoracic vertebrae, due to the presence of osteophytes and deformities of vertebral bodies caused by arthropathy (Fig. 2). Arthropathy is one of the most prevalent and invalidating complications of acromegaly, affecting both weight- and non-weight-bearing joints (132).

**Treatment of osteopathy in acromegaly**

No studies have been performed on the effectiveness and safety of bone-active drugs in acromegaly; therefore, no specific guidelines have been developed. The treatment of acromegalic osteopathy cannot be evidence based. However, some recommendations based on the experience of one of the co-authors (GM) and results of recent clinical studies can be considered.

The fundamental question is who may benefit from a treatment with bone-active drugs? The early identification of individuals with VFs may offer guidance on the subsequent therapeutic approach. Based on the results of a few longitudinal studies on VFs (7, 8), anti-osteoporotic therapy may be considered in subjects with either multiple or moderate-severe pre-existing VFs, regardless of the state of the underlying acromegaly. In fact, progression of VFs has been observed in individuals with controlled/cured acromegaly with two or more prevalent VFs (8) and in those subjects with a higher spine deformity index (7), which is an composite measure of the grade of VFs calculated by summing the score of each individual fracture (133). The management of acromegalic subjects with single mild VFs is more uncertain, because of their lower predictive value and the potential pitfalls in the diagnosis of these fractures in the presence of arthropathy. In these cases, the analysis of bone structure by non-invasive diagnostic tools, such as TBS or 3D-SHAPER DXA may assist clinicians in the identification of vertebral deformities associated with skeletal fragility (85). This could serve as a guide for therapeutic decision making, particularly in males with coexistent risk factors for fractures, such as untreated hypogonadism (7) and diabetes mellitus (115). Bone-targeted therapy may also be considered in individuals without VFs but with persistently active acromegaly in an effort to prevent fractures secondary to the continued skeletal exposure to GH excess. Based on the results from longitudinal studies (7, 121), it may be reasonable to start...
anti-osteoporotic drugs in patients without prevalent fractures when acromegaly is persistently active despite multimodal therapy for one year or longer.

The choice of bone-active drugs to use in acromegaly is another challenge, since no studies have been performed to test their efficacy and safety in this clinical setting. Based on pathophysiological considerations, inhibitors of osteoclastogenesis and bone resorption, such as denosumab and bisphosphonates, may counteract the effects of GH and IGF-I excess on bone remodeling. Anabolic therapy with teriparatide or abaloparatide might not be effective, due to their stimulatory effects on bone remodeling and on the synthesis of IGF-I by the skeleton. However, when VFs progress despite the biochemical control of acromegaly and when bone remodeling is not enhanced (6, 72), anabolic therapy may be considered to restore the trabecular bone microstructure and prevent additional fractures.

Conclusions

Osteopathy is an emerging complication of acromegaly, characterized by increased bone turnover, profound abnormalities in trabecular bone structure and high risk of VFs. These skeletal abnormalities are usually accompanied by mild hyperphosphatemia and a tendency toward hypercalcemia and hypercalciuria. Treatment of acromegaly improves but does not restore skeletal architecture and the risk of VFs persists even in selected subjects with controlled/cured acromegaly. Clinical awareness of this complication of acromegaly is necessary due to the potential negative impact of VFs on quality of life and cardio-respiratory function as well as an increased risk of mortality. Studies are needed to identify the determinants of skeletal fragility in active and controlled acromegaly and to evaluate the effectiveness and safety of bone-active drugs in this clinical setting.

Declaration of interest

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