Neuroendocrinology of Bone Metabolism

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Abstract

Neuroendocrinology of bone is a new area of research based on the evidence that pituitary hormones may directly modulate bone remodeling and metabolism. As a matter of fact, skeletal fragility associated with high risk of fractures is a common complication of pituitary diseases characterized by either hypo- or hyperfunction of the pituitary gland. This chapter deals with physiological, pathophysiological, clinical, and therapeutic aspects concerning the effects of pituitary hormones on skeletal health.

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Introduction

Pituitary hormones are involved in the regulation of skeletal physiology, and bone loss commonly occurs in pituitary disorders (Mazziotti et al. 2015a). The traditional paradigm is that pituitary-derived hormones exert their biological effects on bone by peripheral mediators produced by target glands under their stimulation. However, over the recent years, there has been a growing evidence to suggest that pituitary hormones may bypass traditional endocrine organs to exert remarkable direct effects on the skeleton. This chapter will deal with physiological, pathophysiological, clinical, and therapeutic aspects of direct and indirect effects of pituitary hormones on skeletal health.

Pituitary Hormones and Bone: Physiological and Pathophysiological Aspects

The skeleton is an extremely dynamic tissue with a continuous remodeling process guided by bone-forming osteoblasts and bone-resorbing osteoclasts (Canalis et al. 2007a). The balance between bone resorption and bone formation is crucial to guarantee skeletal homeostasis, whereas osteoporosis develops when bone resorption exceeds bone formation (Mazziotti et al. 2012). Pituitary diseases may affect bone remodeling either by increasing bone resorption or inducing impairment in bone formation (Mazziotti et al. 2015a).

Growth hormone (GH)-insulin-like growth factor-1 (IGF-I) axis has an important role in the regulation of bone growth and bone metabolism during lifespan (Giustina et al. 2008). GH stimulates the proliferation of cells of the osteoblastic lineage and affects the fate of mesenchymal precursors favoring osteoblastogenesis and chondrogenesis and opposing adipogenesis (Giustina et al. 2008). Specifically, GH downregulates the expression of fetal antigen-1, which is the soluble form of delta-like 1 or Pref-1, and as a consequence may regulate adipogenesis (Abdallah et al. 2007). GH also stimulates the expression of bone morphogenetic proteins, which are important for the differentiation of osteoblasts and for bone formation (Kassem et al. 1993). In addition to its effects on the differentiation of osteoblasts, GH stimulates, either directly or indirectly through IGF-1, the differentiated function of mature osteoblast (Giustina et al. 2008). GH also stimulates the carboxylation of osteocalcin, which is a marker of osteoblastic function (Hubina et al. 2004). Most of the effects of GH on mature osteoblasts are mediated by systemic IGF-I (Digirolamo et al. 2007). Interestingly, when synthesized by peripheral tissues, IGF-I expression is controlled by diverse hormones (prevalently GH) and by other growth factors (Giustina and Veldhuis 1998). In osteoblasts, synthesis of IGF-I is induced by

parathyroid hormone (PTH), thyroid hormones, and estrogens, whereas the effects of GH seem to be modest (Giustina et al. 2008). In addition to the effects on osteoblastogenesis and bone formation, GH and IGF-I modulate bone resorption by regulating synthesis of osteoprotegerin and receptor activator of nuclear factor-B ligand (RANKL) by osteoblasts (Giustina et al. 2008). In fact, GH was shown to stimulate production of osteoprotegerin and its accumulation in the bone matrix, whereas IGF-I induces RANKL synthesis and, as a consequence, osteoclastogenesis (Rubin et al. 2002; Ueland et al. 2002; Mrak et al. 2007). Besides the direct effects on bone remodeling, GH and IGF-I regulate calcium and phosphate metabolism (Kamenický et al. 2014). Specifically, GH and IGF-I were shown to stimulate the conversion of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D by the calcium-dependent activation of renal 1-alpha-hydroxylase, increasing the resorption of calcium and phosphate in the intestine and kidney (Kamenický et al. 2014).

Gonadotropin-gonadal sex steroids axis plays a key role in maintaining bone health throughout life, and secondary hypogonadism is an important factor involved in the pathogenesis of skeletal fragility of patients with pituitary diseases (Riggs et al. 2002). Over the recent years, there has been evidence that follicle-stimulating hormone (FSH) may have direct pro-resorptive effects on mature osteoclasts and low FSH values were suggested to attenuate the negative effects of hypogonadism on the skeleton in experimental models of osteoporosis (Sun et al. 2006; Iqbal et al. 2012). In humans, the possible involvement of FSH in the pathogenesis of osteoporosis was suggested by the observation that amenorrheic women with higher FSH levels had greater bone loss than those with lower values in face of near-equal estrogen levels (Devleta et al. 2004). Moreover, in perimenopausal women increases in bone resorption markers and decrease in bone mineral density (BMD) were better correlated with serum FSH than estrogen levels (Zaidi 2007). However, clinical models of gonadotropin-releasing hormone agonist therapy and in vitro fertilization procedure failed to demonstrate a clinically significant effect of FSH on bone remodeling (Drake et al. 2010; Omodei et al. 2013). Therefore, possible consequences of low FSH values on the skeleton in patients with pituitary diseases have to be considered currently only as a working hypothesis.

Hypogonadism is traditionally considered the main mechanism causing skeletal fragility in patients with prolactinomas (Klibanski et al. 1988). However, there is also evidence that prolactin (PRL) may have sex hormone-independent effects on bone remodeling. In fact, PRL receptor was demonstrated in osteoblasts, and PRL was shown to decrease in vitro osteoblast proliferation with a secondary impairment of bone formation and mineralization (Seriwatanachai et al. 2009; Coss et al. 2000). Moreover, PRL induced increase in RANKL/osteoprotegerin expression in osteoblasts leading to an increase in bone resorption (Seriwatanachai et al. 2008a, b). The direct effects of PRL on skeletal remodeling may play a role in determining bone loss in postmenopausal women and eugonadal males with hyperprolactinemia (Mazziotti et al. 2011a, b).

Thyrotropin (TSH)-thyroid axis is important for the control of longitudinal growth, since thyroid hormones have physiological stimulatory effects on bone remodeling and bone mineralization (Gogakos et al. 2010). However, when thyroid hormones increase, bone remodeling is excessively stimulated with consequent bone

loss and decrease in skeletal strength (Vestergaard and Mosekilde 2003). The effects of thyroid hormones on bone may be modulated at different levels by TSH and GH (Mazziotti et al. 2015a). The peripheral deiodination and activation of thyroxine is stimulated by GH (Martins et al. 2007), and this effect may explain why hypopituitary patients treated for GHD are predis posed to the negative effects of thyroid hormone overtreatment (Mazziotti et al. 2014). Over the recent years, there has been convincing evidence that TSH may have direct inhibitory effect on bone resorption. In animal models, the lack of TSH signal was shown to increase bone resorption leading to osteoporosis regardless of the effects of thyroid hormones (Abe et al. 2003). Also in humans, TSH was clearly shown to exert direct effects on bone remodeling with inhibition of bone resorption (Mazziotti et al. 2005), and TSH levels in the low-normal range were found to be associated with high risk of vertebral fractures in postmenopausal women with osteopenia or osteoporosis (Mazziotti et al. 2010a). Based on this assumption, one could argue that low TSH values may favor skeletal fragility in patients with hypopituitarism, although the evidence to support such a hypothesis is still lacking.

Skeletal fragility is a frequent and well-known complication of glucocorticoid excess, as it occurs in patients with corticotropin (ACTH)-secreting adenomas (i.e., Cushing disease) (Mazziotti et al. 2016a) as well as in those treated with exogenous corticosteroids (Mazziotti et al. 2010b). ACTH has been shown to stimulate bone formation (Isales et al. 2010), but the potential skeletal effects of relatively high ACTH values in patients with Cushing disease are still unknown. The central pathophysiological mechanism of bone loss during long-term use of glucocorticoids is reduced bone formation, due to actions that affects osteoblast differentiation and function (Mazziotti et al. 2006a). However, during the first phase, a significant increase in bone resorption (ultimately leading to the observed early increase of risk of fractures) may occur (Mazziotti et al. 2006a). Besides the direct effects on bone cells, glucocorticoids may also have indirect effects mediated by derangements in neuroendocrine signals in the pituitary gland. Glucocorticoids modulate GH by various and competing effects on the hypothalamus and pituitary gland, with final effects depending on hormone concentrations and time of exposure (Mazziotti and Giustina 2013a). Exposure to chronic glucocorticoid excess, even if mild as in "subclinical hypercortisolism," during treatment with inhaled corticosteroids and overtreatment of hypoadrenalism, causes the increase in hypothalamic somatostatin tone with consequent impairment of GH secretion which may play a pathophysiological role in glucocorticoid-induced osteoporosis contributing to the development of a more severe impairment of bone quality with increased risk of fractures (Mazziotti et al. 2016b). As a matter of fact, both exposure to glucocorticoid excess and GHD are associated with a "low-turnover osteoporosis." Interestingly, there is a cross talking between glucocorticoids and GH-IGF-I axis, since the latter may modulate the activation of corticosteroids at peripheral tissues (Giavoli et al. 2004). In fact, GH stimulates the peripheral inactivation of cortisol in cortisone; this effect explains why patients with untreated GHD are particularly predisposed to negative effects of glucocorticoid excess on bone (Mazziotti et al. 2010c). Glucocorticoids may have also neuroendocrine effects on sex hormone production. Specifically,

glucocorticoids inhibit the release of gonadotropins with consequent secondary hypogonadism which may contribute to increased risk of fractures by impairment of skeletal remodeling and muscle function (Canalis et al. 2007b).

Oxytocin and vasopressin were shown to exert direct effects on bone via specific receptors on osteoblasts and osteoclasts (Tamma et al. 2009, 2013). Both osteoblasts and osteoclasts express oxytocin receptors, whose stimulation enhances bone mass. Consistent with this, mice deficient in oxytocin or its receptor display profoundly impaired bone formation with consequent low-bone-turnover osteoporosis (Tamma et al. 2009). In contrast, bone resorption remains unaffected in oxytocin deficiency because, even while oxytocin stimulates the genesis of osteoclasts, it inhibits their resorptive function (Tamma et al. 2009). Vasopressin was instead shown to have a double effect on bone remodeling, with stimulating effects on bone resorption and inhibitory effects on bone formation (Tamma et al. 2013). However, the role of oxytocin and vasopressin in skeletal fragility of patients with pituitary diseases is still unknown.

Skeletal Fragility in Pituitary Diseases: Clinical and Therapeutic Aspects

Measurement of biochemical markers of bone turnover may be useful in the clinical management of skeletal fragility in patients with pituitary diseases. Markers of bone formation are direct or indirect products of active osteoblasts expressed during various phases of their development and reflect different aspects of osteoblast function. Type I collagen is an important component of bone matrix, and osteoblasts secrete its precursor procollagen molecule during bone formation, whereas degradation products of type 1 collagen are released during bone resorption. As a matter of fact, serum procollagen type I N propeptide (PINP) and carboxy-terminal cross-linking telopeptide of type I collagen (sCTX) are recommended as reference markers of bone formation and resorption, respectively, to be used in the clinical practice (Vasikaran et al. 2011). In the clinical practice, PINP and CTX are generally used for monitoring treatment of osteoporosis with bone-active drugs (Vasikaran et al. 2011). In pituitary diseases, such as in other forms of secondary osteoporosis, measurement of biochemical markers of bone turnover may also provide information on the type of skeletal disorder (i.e., increase or decrease in bone turnover) caused by pituitary hormone excess or defect.

In clinical practice, measurement of BMD at the lumbar spine, total hip, and femoral neck by dual-energy X-ray absorptiometry (DXA) is the mainstay for diagnosis of osteoporosis and prediction of fracture risk (Schousboe et al. 2013). Skeletal demineralization is graded according to the World Health Organization criteria based on comparisons of patient's BMD with the average for young adults, after adjusting for race and gender. A T-score less than or equal to −2.5 SD at the hip or spine is defined as osteoporosis, whereas osteopenia is defined as a T-score between −1 and −2.5 SD (Schousboe et al. 2013). These densitometric definitions are applicable only for postmenopausal women and men aged 50 and older, whereas for younger subjects the Z-score (i.e., the number of standard deviations from

age-matched controls) of -2.0 or lower is used to define a BMD "below the expected range for age" (Schousboe et al. 2013). Since pituitary diseases often occur in men under 50 and premenopausal women, diagnosis of osteoporosis cannot be easily performed on the basis of BMD alone in this clinical setting. Moreover, patients with pituitary diseases were shown to fracture even in the presence of normal BMD, consistently with the concept that bone quality more than bone quantity is affected by pituitary hormone excess and defect (Mazziotti et al. 2015a). This is a clinically relevant finding that prompted to the search for alternative diagnostic tools better reflecting quality of bone in these patients, such as quantitative ultrasonometry, high-resolution peripheral quantitative computed tomography, or measurement of trabecular bone score by DXA (Griffith and Genant 2012; Ulivieri et al. 2014). However, the feasibility and reliability of these methods in the clinical setting of pituitary diseases are still uncertain.

Vertebral fractures are the hallmark of osteoporosis, being the most common fragility fractures (Cooper et al. 1993; Wasnich 1996). In more than 50% of the cases, spine fractures occur without specific clinical symptoms, and the radiological and morphometric approach has emerged as the method of choice for evaluating the true prevalence and incidence of these fractures in the clinical practice (Griffith and Genant 2012). Vertebral fractures are identified marking the vertebral body with six points to describe the vertebral shape and heights. According to the quantitative morphometric approach, vertebral fractures are defined mild, moderate, and severe based on a height ratio decrease of 20–25%, 25–40%, and more than 40%, respectively (Genant et al. 1996). Quantitative morphometry is usually performed on spinal X-ray images, although quantitative approach may also be applied to images of the spine acquired by DXA (Clark et al. 2014).

Hypopituitarism

Adult patients with hypopituitarism have generally marked reduction in bone turnover as predominant effect of GH deficiency (GHD) on bone remodeling regardless of coexistent other pituitary hormone deficiencies (Kaufman et al. 1992). However, about half of hypopituitary patients with GHD have normal vertebral BMD (Giustina et al. 2008). In childhood-onset GHD, vertebral BMD is reduced with T-scores often between −1 and −2; about one third of the patients have T-scores of −2.5 or less (Molitch et al. 2006). In contrast, patients with adult-onset GHD have variable BMD values in relationship with age (e.g., lower BMD in younger patients) and duration and the severity of the disease (e.g., lower BMD in longer lasting and more severe GHD) (Murray et al. 2006). The reasons for the different degrees of bone loss may be that childhood-onset GHD occurs before the achievement of peak bone mass and due to its longer disease duration. However, some authors also argued that lower BMD in childhood-onset disease may be due to an underestimation of BMD related to low size and volume of bones in patients with GHD and short stature (Högler and Shaw 2010).

The rate of non-vertebral fractures is increased about threefold in untreated GHD patients (Rosen et al. 1997; Wuster et al. 2001). Using a radiological and

morphometric approach, prevalent vertebral fractures were found in more than one half of adult patients with GHD, and in about one third of them, fractures were moderate-severe causing back pain and functional impairment (Mazziotti et al. 2006b). The prevalence of vertebral fractures was related to the duration of GHD and did not seem to be significantly affected by the presence of other pituitary hormone deficiencies (Mazziotti et al. 2006b, 2008a). Vertebral fractures were shown to occur even in hypopituitary patients with normal BMD (Mazziotti et al. 2006b).

The effects of recombinant human GH (rhGH) replacement therapy on bone have been widely studied over the last 20 years. Replacement therapy with rhGH led to a dose-dependent increase in bone turnover markers (Abrahamsen et al. 2002). Indeed, the effects of rhGH on bone remodeling are biphasic, since after an initial (6–12 months) predominance of bone resorption, stimulation of formation became predominant when treatment was continued for longer period of time (Ohlsson et al. 1998). Therefore, the positive effects of rhGH on bone were shown to be evident after 12 months of treatment (Barake et al. 2014), whereas shorter-term trials revealed decrease or no change in BMD (Davidson et al. 2004). The beneficial effects of rhGH on BMD have been reported to persist after withdrawal of GH (Biller et al. 2000). A few studies reported densitometric outcomes when rhGH was given for a period equal or longer than 10 years (Arwert et al. 2005; Elbornsson et al. 2012).

Consistently with former observation that fracture rate was lower in treated GHD as compared to untreated patients (Mazziotti et al. 2006b), recent prospective studies reported a significant decrease in incident vertebral (Mazziotti et al. 2016c) and non-vertebral (Mo et al. 2015) fractures in adult GHD patients undergoing treatment with rhGH, suggesting that skeletal integrity could be an emerging critical end point in the decision-making process to initiate GH replacement in hypopituitary patients with GHD (Giustina and Mazziotti 2015).

Replacement therapies of central hypoadrenalism and hypothyroidism were shown to influence the fracture rate in patients with hypopituitarism (Mazziotti et al. 2010c, 2014). As a matter of fact, an overtreatment with these hormones may be frequent in patients with hypopituitarism since replacement therapies do not completely mirror the endogenous hormonal production and their monitoring is also made difficult by the lack of good biomarkers of their action. Higher prevalence of vertebral fractures was demonstrated in hypopituitary patients treated with hydrocortisone doses higher than 28 mg per day (Mazziotti et al. 2010c) and thyroxine doses higher than 1.35 μg/Kg per day (Mazziotti et al. 2014). The negative effects of glucocorticoid overtreatment were shown to be more evident in patients with untreated GHD, whereas the negative skeletal effects of thyroxine overtreatment were more evident in patients with replaced GHD (Mazziotti et al. 2015a).

GH-Secreting Adenomas

Consistently with the concept that GH excess stimulates bone remodeling, markers of bone formation and resorption are increased in patients with active acromegaly,

whereas data on BMD are rather variable in relation to the skeletal site, activity of disease, and gonadal status (Mazziotti et al. 2015b). As a matter of fact, low BMD is a relatively uncommon clinical finding in patients with acromegaly (Kayath and Vieira 1997), whereas several studies reported either increased (Kotzmann et al. 1993; Kaji et al. 2001) or similar (Longobardi et al. 1998) bone mass in acromegaly patients as compared to control subjects. The discrepancy resulted to be much more evident at the lumbar spine as compared to the femoral neck (Mazziotti et al. 2015b). Different factors may be involved in determining this variability. Firstly, patients with acromegaly are frequently affected by osteoarthritis with structural modifications of the spine consisting in osteophyte formation and facet-joint hypertrophy which may lead to an overestimation of BMD measured at lumbar spine (Claessen et al. 2016). Moreover, there is evidence that GH and IGF-I excess may exert deleterious effect on trabecular microarchitecture, whereas cortical bone density tends to be increased as effect of GH on periosteal ossification (Ueland et al. 2006). DXA does not distinguish between cortical and trabecular bone, and densitometric results are greatly influenced by the variable distribution of these two compartments in the different skeletal sites (Diamond et al. 1989).

Although BMD is not generally decreased, recent studies have demonstrated that GH excess may cause abnormalities in bone microstructure (Madeira et al. 2013; Maffezzoni et al. 2016), predisposing patients with acromegaly to develop a specific bone metabolic disease, i.e., "acromegalic osteopathy," characterized by high bone turnover, deterioration of bone microarchitecture, and high risk of vertebral fractures (Mazziotti et al. 2017). Using a radiological and morphometric approach, increased prevalence of vertebral fractures was demonstrated in postmenopausal women (Bonadonna et al. 2005) and males (Mazziotti et al. 2008b) with acromegaly. This finding was confirmed by other cross-sectional studies (Mazziotti et al. 2017), and more recently two independent prospective studies provided evidence for an increased risk of vertebral fractures in male and female patients with acromegaly (Mazziotti et al. 2013a; Claessen et al. 2013). The occurrence of vertebral fractures in acromegaly correlated with the duration of active disease and serum IGF-I levels, but not with BMD, since they were found to develop even in patients with normal or minimally decreased BMD (Mazziotti et al. 2017). Biochemical control of acromegaly improves skeletal health (Mazziotti et al. 2015b), although the risk of vertebral fractures may persist high in some patients with well-controlled or cured acromegaly in relationship with preexistent vertebral fractures and untreated hypogonadism (Mazziotti et al. 2013a; Claessen et al. 2013). Therefore, guidelines for the diagnosis and follow-up of acromegaly complications now include not only DXA (Giustina et al. 2003) but also morphometric spine X-ray evaluation (Melmed et al. 2013).

PRL-Secreting Adenomas

Patients with prolactinomas have high-bone-turnover osteoporosis (Mazziotti et al. 2015a). Bone loss occurs predominantly at the lumbar spine (Naliato et al. 2008) in close relationship with the duration of disease, serum values of PRL, and

bone turnover markers (Mazziotti et al. 2015a). Patients with prolactinomas may develop vertebral and non-vertebral fractures (Mazziotti et al. 2011a, b; Vestergaard et al. 2002a). High prevalence of vertebral fractures was reported even in postmenopausal women with prolactinomas (Mazziotti et al. 2011a) and in men with normal testosterone values (Mazziotti et al. 2011b), supporting the hypothesis that PRL excess per se may contribute to skeletal fragility regardless of gonadal status. The frequency of vertebral fractures was significantly associated with duration of disease independently of the effects of hypopituitarism, age of patients, and serum PRL levels (Mazziotti et al. 2015a). Patients with fractures were shown to have lower BMD as compared to those without fractures, but only a minority of patients had either osteoporosis or BMD below the expected range for age (Mazziotti et al. 2011a, b).

Improvement of BMD was reported during medical treatment of prolactinomas with dopaminergic drugs (Klibanski and Greenspan 1986), although a partial recovery of osteopenia and osteoporosis was observed in some patients with prolactinomas (Di Somma et al. 1998). Few data from cross-sectional studies suggest that correction of hyperprolactinemia may lead to a significant decrease of fracture risk in women with prolactinomas (D'Sylva et al. 2015), although there is also evidence that fracture risk may remain high in some patients, especially if males and/or with long-standing hyperprolactinemia, independently of medical treatment (Mazziotti et al. 2011a, b).

ACTH-Secreting Adenomas

Skeletal fragility is a frequent complication of Cushing disease (Mazziotti et al. 2016a). At the diagnosis of Cushing disease, the skeletal phenotype is usually characterized by low-bone turnover and normal or low-normal BMD (Mazziotti et al. 2016a). However, fracture risk increases rapidly after few months of exposure to endogenous hypercortisolism, and fragility fractures may be the first clinical manifestation of Cushing disease (Abdel-Kader et al. 2012). Fractures involve more frequently the vertebrae, and they may occur in 30–50% of patients with Cushing disease in close relationship with the severity of hypercortisolism (Vestergaard et al. 2002b; Trementino et al. 2014). Moreover, vertebral fractures were shown to occur more frequently in males as compared to females (Valassi et al. 2011).

Bone health does not always completely recover after correction of endogenous hypercortisolism (Scillitani et al. 2014). In fact, some patients may experience an increase in bone formation soon after resolution of glucocorticoid excess with secondary improvement of BMD and decrease in fracture risk (Mancini et al. 2010; Szappanos et al. 2010; Randazzo et al. 2012), whereas in other patients the risk of fracture may persist elevated long-term after the cure of disease (Faggiano et al. 2001). Therefore, a single-case evaluation is often needed for the therapeutic management of osteoporosis induced by endogenous hypercortisolism also because specific guidelines are not available and data of the literature do not allow an evidence-based approach (Mazziotti et al. 2016b).

Summary

Pituitary hormones may negatively impact bone health. Pathophysiological and clinical relevance of these actions is well depicted by the often severe skeletal damage which is observed in pituitary diseases characterized by either hypo- or hyperfunction of the gland. Based on these findings, a novel area of research and of clinical activity has developed over the last years which has been defined "neuroendocrinology of bone." Contribution of neuroendocrine axes to pathophysiology of bone loss outside the classic field to pituitary diseases is still unknown but currently under active investigation.

References

Abdallah BM, Ding M, Jensen CH, et al. Dlk1/FA1 is a novel endocrine regulator of bone and fat mass and its serum level is modulated by growth hormone. Endocrinology. 2007;148:3111–21.

Abdel-Kader N, Cardiel MH, Navarro Compan V, et al. Cushing's disease as a cause of severe osteoporosis: a clinical challenge. Reumatol Clin. 2012;8:278–9.

Abe E, Marians RC, Yu W, et al. TSH is a negative regulator of skeletal remodeling. Cell. 2003;115:151–62.

Abrahamsen B, Hangaard J, Horn HC, et al. Evaluation of the optimum dose of growth hormone (GH) for restoring bone mass in adult-onset GH deficiency: results from two 12-month randomized studies. Clin Endocrinol. 2002;57:273–81.

Arwert LI, Roos JC, Lips P, et al. Effects of 10 years of growth hormone (GH) replacement therapy in adult GH-deficient men. Clin Endocrinol. 2005;63:310–6.

Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. J Clin Endocrinol Metab. 2014;99:852–60.

Biller BMK, Sesmilo G, Baum HBA, Hayden D, Schoenfeld D, Klibanski A. Withdrawal of long-term physiological growth hormone (GH) administration: differential effects on bone density and body composition in men with adult-onset GH deficiency. J Clin Endocrinol Metab. 2000;85:970–6.

Bonadonna S, Mazziotti G, Nuzzo M, et al. Increased prevalence of radiological spinal deformities in active acromegaly: a cross-sectional study in postmenopausal women. J Bone Miner Res. 2005;20:1837–44.

Canalis E, Giustina A, Bilezikian JP. Mechanisms of anabolic therapies for osteoporosis. N Engl J Med. 2007a;35:905–16.

Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007b;18:1319–28.

Claessen KM, Kroon HM, Pereira AM, et al. Progression of vertebral fractures despite long-term biochemical control of acromegaly: a prospective follow-up study. J Clin Endocrinol Metab. 2013;98:4808–15.

Claessen KM, Mazziotti G, Biermasz NR, Giustina A. Bone and joint disorders in acromegaly. Neuroendocrinology. 2016;103:86–95.

Clark EM, Carter L, Gould VC, et al. Vertebral fracture assessment (VFA) by lateral DXA scanning may be cost-effective when used as part of fracture liaison services or primary care screening. Osteoporos Int. 2014;25:953–64.

Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ III. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985–1989. J Bone Miner Res. 1993;7:221–7.

Coss D, Yang L, Kuo CB, et al. Effects of prolactin on osteoblast alkaline phosphatase and bone formation in the developing rat. Am J Physiol Endocrinol Metab. 2000;279: E1216–25.
D'Sylva C, Khan T, Van Uum S, Fraser LA. Osteoporotic fractures in patients with untreated hyperprolactinemia vs. those taking dopamine agonists: a systematic review and meta-analysis. Neuro Endocrinol Lett. 2015;36:745–9.
Davidson P, Milne R, Chase D, et al. Growth hormone replacement in adults and bone mineral density: a systematic review and meta-analysis. Clin Endocrinol. 2004;60:92–8.
Devleta B, Adem B, Senada S. Hypergonadotropic amenorrhea and bone density: new approach to an old problem. J Bone Miner Metab. 2004;22:360–4.
Di Somma C, Colao A, Di Sarno A, et al. Bone marker and bone density responses to dopamine agonist therapy in hyperprolactinemic males. J Clin Endocrinol Metab. 1998;83:807–13.
Diamond T, Nery L, Posen S. Spinal and peripheral bone mineral densities in acromegaly: the effects of excess growth hormone and hypogonadism. Ann Intern Med. 1989;111:567–73.
Digirolamo DJ, Mukherjee A, Fulzele K, et al. Mode of growth hormone action in osteoblasts. J Biol Chem. 2007;282:31666–74.
Drake MT, McCready LK, Hoey KA, Atkinson EJ, Khosla S. Effects of suppression of follicle-stimulating hormone (FSH) secretion on bone resorption markers in postmenopausal women. J Clin Endocrinol Metab. 2010;95:5063–8.
Elbornsson M, Gotherstrom G, Bosaeus I, et al. Fifteen years of GH replacement increases bone mineral density in hypopituitary patients with adult-onset GH deficiency. Eur J Endocrinol. 2012;166:787–95.
Faggiano A, Pivonello R, Filippella M, et al. Spine abnormalities and damage in patients cured from Cushing's disease. Pituitary. 2001;4:153–61.
Genant HK, Jergas M, Palermo L, et al. Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 1996;11:984–96.
Giavoli C, Libé R, Corbetta S, et al. Effect of recombinant human growth hormone (GH) replacement on the hypothalamic-pituitary-adrenal axis in adult GH-deficient patients. J Clin Endocrinol Metab. 2004;89:5397–401.
Giustina A, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev. 1998;19:717–97.
Giustina A, Casanueva FF, Cavagnini F, et al. Diagnosis and treatment of acromegaly complications. J Endocrinol Invest. 2003;26:1242–7.
Giustina A, Mazziotti G, Canalis E. Growth hormone, insulin-like growth factors, and the skeleton. Endocr Rev. 2008;29:535–59.
Giustina A, Mazziotti G. Growth hormone replacement therapy and fracture risk. Lancet Diabetes Endocrinol. 2015;3:307–8.
Gogakos AI, Duncan Bassett JH, Williams GR. Thyroid and bone. Arch Biochem Biophys. 2010;503:129–36.
Griffith JF, Genant HK. New advances in imaging osteoporosis and its complications. Endocrine. 2012;42:39–51.
Högler W, Shaw N. Childhood growth hormone deficiency, bone density, structures and fractures: scrutinizing the evidence. Clin Endocrinol. 2010;72:281–9.
Hubina E, Lakatos P, Kovacs L, et al. Effects of 24 months of growth hormone (GH) treatment on serum carboxylated and undercarboxylated osteocalcin levels in GH-deficient adults. Calcif Tissue Int. 2004;74:55–9.
Iqbal J, Blair HC, Zallone A, et al. Further evidence that FSH causes bone loss independently of low estrogen. Endocrine. 2012;412:171–5.
Isales CM, Zaidi M, Blair HC. ACTH is a novel regulator of bone mass. Ann N Y Acad Sci. 2010;1192:110–6.
Kaji H, Sugimoto T, Nakaoka D, et al. Bone metabolism and body composition in Japanese patients with active acromegaly. Clin Endocrinol. 2001;55:175–81.

Kamenický P, Mazziotti G, Lombès M, Giustina A, Chanson P. Growth hormone, insulin-like growth factor-1, and the kidney: pathophysiological and clinical implications. Endocr Rev. 2014;35:234–81.
Kassem M, Blum W, Ristelli J, et al. Growth hormone stimulates proliferation and differentiation of normal human osteoblast-like cells in vitro. Calcif Tissue Int. 1993;52:222–6.
Kaufman JM, Taelman P, Vermeulen A, Vandeweghe M. Bone mineral status in growth hormone-deficient males with isolated and multiple pituitary deficiencies of childhood onset. J Clin Endocrinol Metab. 1992;74:118–23.
Kayath MJ, Vieira JG. Osteopenia occurs in a minority of patients with acromegaly and is predominant in the spine. Osteoporos Int. 1997;7:226–30.
Klibanski A, Greenspan SL. Increase in bone mass after treatment of hyperprolactinemic amenorrhea. N Engl J Med. 1986;315:542–6.
Klibanski A, Biller BM, Rosenthal DI, et al. Effects of prolactin and estrogen deficiency in amenorrheic bone loss. J Clin Endocrinol Metab. 1988;67:124–30.
Kotzmann H, Bernecker P, Hubsch P, et al. Bone mineral density and parameters of bone metabolism in patients with acromegaly. J Bone Miner Res. 1993;8:459–65.
Longobardi S, Di Somma C, Di Rella F, et al. Bone mineral density and circulating cytokines in patients with acromegaly. J Endocrinol Invest. 1998;21:688–93.
Madeira M, Neto LV, de Paula Paranhos Neto F, et al. Acromegaly has a negative influence on trabecular bone, but not on cortical bone, as assessed by high-resolution peripheral quantitative computed tomography. J Clin Endocrinol Metab. 2013;98:1734–41.
Maffezzoni F, Maddalo M, Frara S, et al. Cone beam tomography analysis of bone microarchitecture in patients with acromegaly and vertebral fractures. Endocrine. 2016;54:532–42.
Mancini T, Porcelli T, Giustina A. Treatment of Cushing disease: overview and recent findings. Ther Clin Risk Manag. 2010;6:505–16.
Martins MR, Doin FC, Komatsu WR, et al. Growth hormone replacement improves thyroxine biological effects: implications for management of central hypothyroidism. J Clin Endocrinol Metab. 2007;92:4144–53.
Mazziotti G, Sorvillo F, Piscopo M, et al. Recombinant human TSH modulates in vivo C-telopeptides of type-1 collagen and bone alkaline phosphatase, but not osteoprotegerin production in postmenopausal women monitored for differentiated thyroid carcinoma. J Bone Miner Res. 2005;20:480–6.
Mazziotti G, Angeli A, Bilezikian JP, et al. Glucocorticoid-induced osteoporosis: an update. Trends Endocrinol Metab. 2006a;17:144–9.
Mazziotti G, Bianchi A, Bonadonna S, et al. Increased prevalence of radiological spinal deformities in adult patients with GH deficiency: influence of GH replacement therapy. J Bone Miner Res. 2006b;21:520–8.
Mazziotti G, Bianchi A, Cimino V, et al. Effect of gonadal status on bone mineral density and radiological spinal deformities in adult patients with growth hormone deficiency. Pituitary. 2008a;11:55–61.
Mazziotti G, Bianchi A, Bonadonna S, et al. Prevalence of vertebral fractures in men with acromegaly. J Clin Endocrinol Metab. 2008b;93:4649–55.
Mazziotti G, Porcelli T, Patelli I, et al. Serum TSH values and risk of vertebral fractures in euthyroid post-menopausal women with low bone mineral density. Bone. 2010a;46:747–51.
Mazziotti G, Canalis E, Giustina A. Drug-induced osteoporosis: mechanisms and clinical implications. Am J Med. 2010b;123:877–84.
Mazziotti G, Porcelli T, Bianchi A, et al. Glucocorticoid replacement therapy and vertebral fractures in hypopituitary adult males with GH deficiency. Eur J Endocrinol. 2010c;163:15–20.
Mazziotti G, Mancini T, Mormando M, et al. High prevalence of radiological vertebral fractures in women with prolactin-secreting pituitary adenomas. Pituitary. 2011a;14:299–306.
Mazziotti G, Porcelli T, Mormando M, et al. Vertebral fractures in males with prolactinoma. Endocrine. 2011b;39:288–93.
Mazziotti G, Bilezikian J, Canalis E, et al. New understanding and treatments for osteoporosis. Endocrine. 2012;41:58–69.

Mazziotti G, Giustina A. Glucocorticoids and the regulation of growth hormone secretion. Nat Rev Endocrinol. 2013a;95:265–76.
Mazziotti G, Bianchi A, Porcelli T, et al. Vertebral fractures in patients with acromegaly: a 3-year prospective study. J Clin Endocrinol Metab. 2013b;98:3402–10.
Mazziotti G, Mormando M, Cristiano A, et al. Association between l-thyroxine treatment, GH deficiency, and radiological vertebral fractures in patients with adult-onset hypopituitarism. Eur J Endocrinol. 2014;170:893–9.
Mazziotti G, Chiavistelli S, Giustina A. Pituitary diseases and bone. Endocrinol Metab Clin North Am. 2015a;44:171–80.
Mazziotti G, Biagioli E, Maffezzoni F, et al. Bone turnover, bone mineral density, and fracture risk in acromegaly: a meta-analysis. J Clin Endocrinol Metab. 2015b;100:384–94.
Mazziotti G, Delgado A, Maffezzoni F, Formenti AM, Giustina A. Skeletal fragility in endogenous hypercortisolism. Front Horm Res. 2016a;46:66–73.
Mazziotti G, Formenti AM, Adler RA, et al. Glucocorticoid-induced osteoporosis: pathophysiological role of GH/IGF-I and PTH/vitamin D axes, treatment options and guidelines. Endocrine. 2016b;54:603–11.
Mazziotti G, Doga M, Frara S, et al. Incidence of morphometric vertebral fractures in adult patients with growth hormone deficiency. Endocrine. 2016c;52:103–10.
Mazziotti G, Maffezzoni F, Frara S, Giustina A. Acromegalic osteopathy. Pituitary. 2017;20:63–9.
Melmed S, Casanueva FF, Klibanski A, et al. A consensus on the diagnosis and treatment of acromegaly complications. Pituitary. 2013;16:294–302.
Mo D, Fleseriu M, Qi R, et al. Fracture risk in adult patients treated with growth hormone replacement therapy for growth homone deficiency: a prospective cohort study. Lancet Diabetes Endocrinol. 2015;3:331–8.
Molitch ME, Clemmons DR, Malozowski S, et al. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2006;91:1621–34.
Mrak E, Villa I, Lanzi R, Losa M, Guidobono F, Rubinacci A. Growth hormone stimulates osteoprotegerin expression and secretion in human osteoblast-like cells. J Endocrinol. 2007;192:639–45.
Murray RD, Adams JE, Shalet SM. A densitometric and morphometric analysis of the skeleton in adults with varying degrees of growth hormone deficiency. J Clin Endocrinol Metab. 2006;91:432–8.
Naliato EC, Violante AH, Caldas D, et al. Bone density in women with prolactinoma treated with dopamine agonists. Pituitary. 2008;11:21–8.
Ohlsson C, Bengtsson BA, Isaksson OG, et al. Growth hormone and bone. Endocr Rev. 1998;19:55–79.
Omodei U, Mazziotti G, Donarini G, et al. Effects of recombinant follicle-stimulating hormone on bone turnover markers in infertile women undergoing in vitro fertilization procedure. J Clin Endocrinol Metab. 2013;981:330–6.
Randazzo ME, Grossrubatscher E, Dalino Ciaramella P, et al. Spontaneous recovery of bone mass after cure of endogenous hypercortisolism. Pituitary. 2012;15:193–201.
Riggs BL, Khosla S, Melton LJ 3rd. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev. 2002;23:279–302.
Rosen T, Wilhelmsen L, Landin-Wilhelmsen K, et al. Increased fracture frequency in adult patients with hypopituitarism and GH deficiency. Eur J Endocrinol. 1997;137:240–5.
Rubin J, Ackert-Bicknell CL, Zhu L, et al. IGF-I regulates osteoprotegerin (OPG) and receptor activator of nuclear factor-kappaB ligand in vitro and OPG in vivo. J Clin Endocrinol Metab. 2002;87(9):4273.
Schousboe JT, Shepherd JA, Bilezikian JP, et al. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. J Clin Densitom. 2013;16:455–66.
Scillitani A, Mazziotti G, Di Somma C, et al. Treatment of skeletal impairment in patients with endogenous hypercortisolism: when and how? Osteoporos Int. 2014;25:441–6.

Seriwatanachai D, Charoenphandhu N, Suthiphongchai T, et al. Prolactin decreases the expression ratio of receptor activator of nuclear factor kappaB ligand/osteoprotegerin in human fetal osteoblast cells. Cell Biol Int. 2008a;32:1126–35.

Seriwatanachai D, Thongchote K, Charoenphandhu N, et al. Prolactin directly enhances bone turnover by raising osteoblast-expressed receptor activator of nuclear factor kappaB ligand/osteoprotegerin ratio. Bone. 2008b;42:535–46.

Seriwatanachai D, Krishnamra N, van Leeuwen JP. Evidence for direct effects of prolactin on human osteoblasts: inhibition of cell growth and mineralization. J Cell Biochem. 2009;107:677–85.

Sun L, Peng Y, Sharrow AC, et al. FSH directly regulates bone mass. Cell. 2006;125:247–60.

Szappanos A, Toke J, Lippai D, et al. Bone turnover in patients with endogenous Cushing's syndrome before and after successful treatment. Osteoporos Int. 2010;21:637–45.

Tamma R, Colaianni G, Zhu LL, et al. Oxytocin is an anabolic bone hormone. Proc Natl Acad Sci U S A. 2009;106:7149–54.

Tamma R, Sun L, Cuscito C, et al. Regulation of bone remodeling by vasopressin explains the bone loss in hyponatremia. Proc Natl Acad Sci U S A. 2013;110:18644–9.

Trementino L, Appolloni G, Ceccoli L, et al. Bone complications in patients with Cushing's syndrome: looking for clinical, biochemical, and genetic determinants. Osteoporos Int. 2014;25:913–21.

Ueland T, Bollerslev J, Flyvbjerg A, et al. Effects of 12 months of growth hormone (GH) treatment on cortical and trabecular bone content of insulin like growth factors (IGF) and osteoprotegerin in adults with acquired GH deficiency: a double-blind, randomized, placebo-controlled study. J Clin Endocrinol Metab. 2002;87:2760–3.

Ueland T, Fougner SL, Godang K, Schreiner T, Bollerslev J. Serum GH and IGF-I are significant determinants of bone turnover but not bone mineral density in active acromegaly: a prospective study of more than 70 consecutive patients. Eur J Endocrinol. 2006;155:709–15.

Ulivieri FM, Silva BC, Sardanelli F, et al. Utility of the trabecular bone score (TBS) in secondary osteoporosis. Endocrine. 2014;47:435–48.

Valassi E, Santos A, Yaneva M, et al. The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. Eur J Endocrinol. 2011;165:383–92.

Vasikaran S, Eastell R, Bruyère O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int. 2011;22:391–420.

Vestergaard P, Mosekilde L. Hyperthyroidism, bone mineral, and fracture risk – a meta-analysis. Thyroid. 2003;13:585–93.

Vestergaard P, Jørgensen JO, Hagen C, et al. Fracture risk is increased in patients with GH deficiency or untreated prolactinomas – a case-control study. Clin Endocrinol. 2002a;56:159–67.

Vestergaard P, Lindholm J, Jørgensen JO, et al. Increased risk of osteoporotic fractures in patients with Cushing's syndrome. Eur J Endocrinol. 2002b;146:51–6.

Wasnich RD. Vertebral fracture epidemiology. Bone. 1996;18:179S–83S.

Wuster C, Abs R, Bengtsson BA, et al. The influence of growth hormone deficiency, growth hormone replacement therapy, and other aspects of hypopituitarism on fracture rate and bone mineral density. J Bone Miner Res. 2001;16:398–405.

Zaidi M. Skeletal remodeling in health and disease. Nat Med. 2007;13:791–801.