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Potential Applications for rhIGF-I: Bone Disease and IGF-I

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Abstract

Growth hormone (GH) and insulin like growth factor-I (IGF-I) are key bone trophic hormones, whose rising levels during puberty are critical for pubertal bone accrual. Conditions of GH deficiency and genetic resistance impact cortical and trabecular bone deleteriously with reduced estimates of bone strength. In humans, conditions of undernutrition (as in anorexia nervosa (AN), or subsequent to chronic illnesses) are associated with low IGF-I levels, which correlate with disease severity, and also with lower bone mineral density (BMD), impaired bone structure and lower strength estimates. In adolescents and adults with AN, studies have demonstrated a nutritionally acquired GH resistance with low IGF-I levels despite high concentrations of GH. IGF-I levels go up with increasing body weight, and are associated with rising levels of bone turnover markers. In short-term studies lasting 6–10 days, recombinant human IGF-I (rhIGF-I) administration in physiologic replacement doses normalized IGF-I levels and increased levels of bone formation markers in both adults and adolescents with AN. In a randomized controlled trial in adults with AN in which participants were randomized to one of four arms: (i) rhIGF-I with oral estrogen-progesterone (EP), (ii) rhIGF-I alone, (iii) EP alone, or (iv) neither for 9 months, a significant increase in bone formation markers was noted in the groups that received rhIGF-I, and a significant decrease in bone resorption markers in the groups that received EP. The group that received both rhIGF-I and EP had a significant increase in bone density at the spine and hip compared to the group that received neither. Side effects were minimal, with no documented fingerstick glucose of < 50 mg/dl. These data thus suggest a potential role for rhIGF-I administration in optimizing bone accrual in states of undernutrition associated with low IGF-I.

Introduction

Growth hormone (GH) and insulin like growth factor-I (IGF-I) are key bone trophic hormones, whose rising levels during puberty are critical for pubertal bone accrual. In

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humans, conditionsof GH deficiency and genetic resistance impact cortical and trabecular bone deleteriously with reduced estimates of bone strength. Conditions of undernutrition (such as anorexia nervosa) are associated with low levels of IGF-I from an acquired state of GH resistance; these conditions are also associated with reduced bone density and an increased risk of fracture. This review discusses in detail the impact of GH and IGF-I deficiency and resistance on bone, and the potential role of IGF-I in improving bone outcomes.

Bone Trophic Effects of Growth Hormone (GH) and Insulin Like Growth Factor-I (IGF-I)

Growth hormone (GH) and insulin like growth factor-I (IGF-I) are key bone trophic hormones. In addition to promoting statural growth at the growth plate, both hormones increase muscle mass (which impacts bone favorably as the pull of muscle on bone has bone anabolic effects), and impact osteoblast and osteoclast differentiation and activity [1, 2]. GH, acting via IGF-I, stabilizes the canonical *wnt* signaling pathway in osteoblasts, thus resulting in osteoblast proliferation, differentiation and increased functional activity [3]. Whether or not GH has a direct (IGF-I independent) effect on this pathway is less clear. It does appear to have an IGF-I independent effect on periosteal bone apposition and diaphyseal bone growth [4].

GH increases osteoprotegerin secretion from osteoblasts, which in turn inhibits osteoclast differentiation and action. In contrast, IGF-I increases secretion of receptor activator of nuclear factor-κB ligand (RANKL) from osteoblasts, which increase differentiation and activation of osteoclasts [3]. One study demonstrated that the effect of IGF-I on osteoclasts is more rapid than its effect on osteoblasts, which may reflect its role in bone remodeling, where bone resorption is followed by bone formation [3]. Overall, GH is believed to impact both modeling and remodeling, while IGF-I likely has a greater impact on bone remodeling [5, 6]. Overall, the net effect of GH and IGF-I on bone is bone anabolic with a net increase in bone formation.

Further, IGF-I increases 1-α hydroxylase activity, leading to increased intestinal absorption of calcium and phosphorus, and also increases renal tubular absorption of phosphorus. Local IGF-I production may be necessary for the mechanosensor function of osteocytes [7, 8]. The increasein GH and IGF-I levels during puberty (in addition to rising levels of gonadal hormones) correlates with increased bone accrual during this time of life [9, 10]. Complex mouse models of GH and IGF-I deficiency and excess have clarified the effects of these hormones on bone outcomes and are detailed in reviews [4, 11]. Some data from these reviews are included in this paper.

Impact of GH Deficiency and Genetic Forms of GH Resistance Involving the GH Receptor and its Signaling Pathway on Bone Outcomes

Mouse Models:

Mouse models provide clues to the impact of systemic IGF-I deficiency on bone outcomes [11–15]. The mouse model of *Prop1*$^{-/-}$ (*dt/dt* Ames mouse) has GH and IGF-I deficiency with marked growth retardation. This mouse demonstrates reduced bone area and reduced bone mineral content. However, because this mouse also has reductions in prolactin and TSH levels, observed bone effects cannot be attributed entirely to GH [16].

The liver specific *Igf-I* $-/-$ (LID) mouse has an 80% reduction in serum IGF-I levels with a 3-fold increase in GH, a 7-fold increase in acid labile subunit (ALS), and a 50% decrease in IGFBP-3. Despite the marked reduction in circulating IGF-I, length is not significantly compromised. Yet, these mice have a 10% reduction in trabecular number and volumetric BMD, a 5% decrease in cortical thickness and volumetric BMD and a decrease in polar moment of inertia (a strength estimate) [15]. These data suggest a key role for systemic IGF-I in optimizing bone density and bone strength, even when longitudinal growth is not significantly affected.

Similarly, the ALS knockout (ALSKO) mouse has a 60% reduction in circulating IGF-I with normal levels of GH, low levels of ALS and a 90% reduction in IGFBP-3 levels. These mice have an 8% reduction in length, a 20% reduction in trabecular vBMD, a 5% reduction in cortical thickness and volumetric BMD, and a decrease in strength estimates; again demonstrating a greater impact on trabecular bone density and bone strength than on longitudinal growth [15].

In contrast, the IGFBP-3 knockout (BP3KO) mouse has mixed effects on bone. These mice have a 40% reduction in systemic IGF-I, normal GH, a 3-fold increase in ALS and low IGFBP-3. They have a 5% increase in body length, and while these mice demonstrate a 30% reduction in trabecular vBMD, their trabecular thickness is increased. Cortical thickness, cortical volumetric BMD, and strength estimates are not impacted [15]. Interestingly, overexpression of various IGF binding proteins can impact bone by reducing IGF-I bioavailability (despite normal IGF-I levels). Overexpression of *Igfbp-1* results in poor growth and delay in mineralization in several bones [17]. *Igfbp2* transgenics have reduced whole body, femoral and tibial bone mineral content and femoral volume [18], and *Igfbp3* transgenics have decreased body weight, and reduced cortical BMD, bone volume and thickness [19] (similar changes have been reported in *Igfbp-5* transgenics [20]).

Finally, the LID/ALSKO/BP3KO (LAB) mice have a 97.5% reduction in serum IGF-I, with a 6-fold increase in GH concentrations, and low ALS and IGFBP-3. These mice have a 6% reduction in body length, 10% reduction in trabecular and cortical vBMD, and significant reduction in strength estimates [15].

Rodent models overall suggest that systemic IGF-I may be less important than autocrine/paracrine IGF-I for linear growth, however, both systemic and autocrine/paracrine IGF-I

(with intact direct effects of GH) appear to be necessary for optimizing bone mineral density (BMD), and bone structure and strength [11–14].

For human data, we know that adults with childhood onset acquired GH deficiency, in whom GH replacement was discontinued after completion of statural growth, have lower total cortical and trabecular volumetric BMD, lower cortical area, and lower cortical and trabecular thickness at both the distal radius and tibia than controls (assessed using high resolution peripheral quantitative computed tomography (HRpQCT)), leading to reduced strength estimates at both sites (after adjusting for height) [21]. They also have lower muscle strength. Most bone parameters are reported to be associated positively with IGF-I levels. Patients with GH receptor mutations have reduced trabecular connectivity (as assessed using dynamic bone histomorphometry), though height adjusted BMD measures at the spine and femoral neck (bone mineral apparent density, a surrogate for volumetric bone density) are not decreased [22]. Both adults and children with GH receptor mutations demonstrate low levels of the surrogate markers of bone turnover, which increase following IGF-I replacement [23].

Impact of Mutations in the IGF-I Gene or its Receptor on Bone Outcomes

The mouse model of IGF-I gene deletion or haploinsufficiency has a 24% reduction in cortical bone size, reduced cortical thickness and volumetric BMD, but increased trabecular elements and trabecular volumetric BMD [11, 24]. Human patients with IGF-I gene deletions exhibit growth retardation and reduced BMD but mainly because of reduced bone volume. Consistent with this, IGF-I replacement therapy has a greater effect on bone volume than on bone density [25].

The mouse model of IGF-I receptor haploinsufficiency has low BMD [11]. One human case report of IGF-I receptor haploinsufficiency indicated reduced cortical, but increased trabecular volumetric BMD (but normal DXA measures of areal BMD), associated with reduced polar moment of inertia (an estimate of bone strength) [26].

GH levels are typically high with normal direct GH effects in patients with IGF-I gene deletions and IGF-I receptor haploinsufficiency- this brings up the possibility that lower cortical but higher trabecular volumetric BMD in these patients may be explained by IGF-I deficiency/resistance versus higher GH concentrations (with normal direct effects of GH) respectively.

Spontaneous mutations have been reported in mice in the *Irs1* gene resulting in failure to translate relevant proteins resulting in growth retardation, low BMD, reduced cortical and trabecular thickness and low bone-formation rates [27]. The human phenotype is very similar [28].

Conditions of Undernutrition: Effects on the GH-IGF-I Axis and Bone (Anorexia Nervosa as a Model of Undernutrition)

In humans, conditions of undernutrition [as in anorexia nervosa (AN) [29, 30], or subsequent to chronic illnesses such as inflammatory bowel disorders [31], celiac disease [32, 33], cystic fibrosis [34], liver disease [35], uncontrolled diabetes [36–38] and cerebral palsy [39]] are associated with low IGF-I levels, which correlate with disease severity, and also with lower areal BMD [29, 30, 40]. AN, in particular, has been studied extensively as a model of chronic undernutrition and will be described in detail here. Compared to normal-weight controls, in addition to lower DXA measures of areal BMD, young women with AN are at risk for reduced volumetric BMD (vBMD) and impaired bone structure [as assessed using high resolution peripheral quantitative computed tomography (HRpQCT)], and reduced bone strength estimates [assessed using microfinite element analysis (FEA)] [40–44].

Specifically, at the distal radius (non-weight bearing site), adolescent girls with AN have lower total and trabecular vBMD, lower cortical area and thickness, and higher cortical porosity and trabecular separation compared with controls [41]. Failure load and stiffness (by FEA), were 15% and 16% lower in AN, indicating reduced bone strength. In addition to these changes, adults with AN have lower cortical thickness, trabecular number and/or thickness than controls [43, 44]. At the distal tibia (weight-bearing site), adolescents with AN have been reported to have greater cortical porosity, lower total and cortical vBMD, and lower cortical area, thickness, trabecular number and strength estimates than controls [40]. A study in adults found lower cortical thickness and estimated failure load in AN, more pronounced at the tibia than the radius [45]. Estimated vertebral strength (assessed using QCT scanning) has been noted to be lower in low-weight women with AN than in normal-weight controls, and intermediate in atypical AN [46]. Another study assessed vertebral bone texture using a low-dose single-section quantitative CT of the L4 vertebral body, and reported altered bone texture in adult women with AN [47]. Changes in bone density, geometry and structure, in turn, are associated with a higher risk of fracture [48, 49].

GH concentrations, as assessed by frequent sampling overnight or over 24-hours, are higher in AN compared to controls [50–53]. Further, following an oral glucose load, GH concentrations suppress appropriately in normal-weight controls, but mean levels of nadir GH are significantly higher in girls with AN [54]. Low systemic IGF-I levels despite these high GH concentrations indicate a hepatic resistance to GH that is nutritionally acquired [50–53], believed to be consequent to reduced expression of the GH receptor, as evidenced by lower circulating levels of GH binding protein (the cleaved extracellular component of the GH receptor) [55]. FGF21 may also mediate the resistance to GH observed in states of undernutrition [56]. Consistent with this ‘resistance’ being nutritionally acquired, IGF-I levels increase with increasing body weight [29].

In addition to a hepatic resistance to GH in AN, there appears to be resistance to GH effects at the level of bone. In healthy controls, increasing levels of GH are associated with increasing levels of markers of bone formation and resorption [50]. However, this association of GH concentrations with bone turnover markers is lost in girls with AN.

A positive association of systemic IGF-I levels with bone density has been reported in adolescents and adults with AN [29, 30, 57]. Similarly, a positive association of IGF-I levels with radial trabecular parameters (bone trabecular volume, trabecular number and thickness) has been demonstrated in adults with AN [44].

Resolution of the state of GH resistance with weight gain is associated with an increase in markers of bone formation and resorption (associated with increases in IGF-I) [29]. Importantly, in this study in adolescents with AN, an increase in bone turnover markers in the first six months following weight gain predicted an increase in BMD in the subsequent six months [29]. Weight gain also results in improvement in total and trabecular vBMD and cortical thickness at the distal radius in adults with AN [42].

In recent years, there has been an increasing interest in the bone-fat connection, which refers to the common mesenchymal stem cell origin of adipocytes and osteoblasts in bone marrow. Increased differentiation along the adipocyte lineage may be associated with decreased differentiation along the osteoblast lineage, and, in fact, marrow adiposity is higher in AN than in controls, with lower bone density being associated with greater marrow adiposity [58].

Importantly, inverse associations of marrow fat with IGF-I levels have been reported in both AN and obesity [57, 59].

Impact of Supraphysiological GH Doses on Levels of IGF-I and Bone Turnover Markers in Anorexia Nervosa

One study has examined whether the state of GH resistance in AN can be overcome by administration of supraphysiological doses of recombinant human GH (rhGH) [60]. In a three-month randomized controlled trial of supraphysiological doses of rhGH vs. placebo in adult women with AN, administration of rhGH at 5–6 times physiological doses failed to cause a significant increase in levels of IGF-I or bone turnover markers [60]. Interestingly, this study did demonstrate a decrease in fat mass in the rhGH arm compared to placebo, indicating that direct GH effects on adipocytes are preserved in AN. These data are consistent with those from a cross-sectional study in adolescents with AN, in which girls with higher overnight GH concentrations had lower trunk fat [61]. Yet another study has reported an increase in statural growth following administration of rhGH in teenage girls with AN in whom height was impacted by restricted eating [62]. These data suggest that the growth plate prechondrocytes and chondrocytes in AN may remain somewhat responsive to GH vs. a profound resistance to GH at the level of osteoblasts and osteoclasts.

Impact of IGF-I Administration on Levels of Bone Turnover Markers and Bone Mineral Density in Anorexia Nervosa

In short-term studies, administration of recombinant human IGF-I (rhIGF-I) has been demonstrated to normalize IGF-I levels and increase levels of bone formation markers in adults and adolescents with AN [63, 64]. In a six-day study of rhIGF-I given at a high dose (100 mcg/kg twice daily) vs. a more physiologic dose (30 mcg/kg twice daily) vs. placebo to

adult women with AN, the high dose led to a marked increase in IGF-I levels (to supraphysiologic levels), and an increase in markers of both bone formation and resorption [63]. In contrast, the lower dose or rhIGF-I led to a normalization of IGF-I levels and an increase in C-terminal propeptide of type 1 procollagen (P1CP) only (a marker of bone formation), with no increase in markers of bone resorption. These data suggested that the lower dose of rhIGF-I may avoid the coupled increase in bone turnover, and therefore, may have a greater impact on bone health long-term than the higher dose of rhIGF-I.

Similarly, a study of adolescent girls with AN administered rhIGF-I at a dose of 30–40 mcg/kg twice daily (depending on pubertal stage) for a period of 7–10 days. Compared to girls with AN followed without intervention, the group that received rhIGF-I had an increase in IGF-I levels to the upper half of the normal range, and levels of N-terminal propeptide of type 1 procollagen (P1NP: a bone formation marker) increased significantly, while levels of carboxy-terminal collagen crosslinks (CTX: a bone resorption marker) did not [64]. The increase in IGF-I level was strongly and positively correlated with changes in P1NP, but not CTX.

Pilot studies of rhIGF-I were followed by a nine-month randomized controlled trial in adults with AN in which participants were randomized to one of four arms: (i) rhIGF-I with oral estrogen-progesterone (EP), (ii) rhIGF-I alone, (iii) EP alone, or (iv) neither for 9 months [65]. A significant increase in bone formation markers was noted in the groups that received rhIGF-I, and a significant decrease in bone resorption markers in the groups that received EP (consistent with the anti-resorptive effects of estrogen). The group that received both rhIGF-I and EP had a significant increase in bone density at the spine and hip compared to the group that received neither, with the other two groups demonstrating intermediate changes in BMD. RhIGF-I administration led to a significant decrease in circulating levels of IGFBP-3 and an increase in levels of IGFBP-2 [66]. Side effects were minimal, with no documented fingerstick glucose of < 50 mg/dl [65].

Conclusion

GH and IGF-I are bone trophic hormones, and reduced GH/IGF-I secretion or action results in impaired bone health. Conditions of nutritional deficiency are associated with an acquired state of GH resistance and low IGF-I levels, associated with lower levels of bone formation markers and lower BMD. This has been extensively studied in low-weight young women with anorexia nervosa, in whom weight gain results in an increase in IGF-I levels, associated with an increase in levels of bone turnover markers. RhIGF-I administration in physiologic doses increases levels of bone formation markers in adults and adolescents with anorexia nervosa, and when given with a combined estrogen-progesterone contraceptive pill, increases areal BMD in adults. Available data thus suggest a potential role for rhIGF-I in optimizing bone accrual in states of undernutrition.

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Highlights

- Growth hormone (GH) and insulin like growth factor-I (IGF-I) are bone trophic hormones that are critical for pubertal bone accrual
- GH deficiency impacts cortical and trabecular bone deleteriously with reduced estimates of bone strength
- Genetic resistance to GH is associated with reduced trabecular connectivity; however, height adjusted measures of bone density are not deleteriously impacted
- Anorexia nervosa (AN) is associated with a nutritionally acquired GH resistance
- Administration of recombinant human (rh) IGF-I to individuals with AN results in increased markers of bone formation
- In adult women with AN, rhIGF-I with estrogen results in a significant increase in bone density