Increased serum IGF-1 levels can rescue bone phenotype in female IGF-1 null mice

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Elevated levels of serum IGF-1 restore peak bone properties in the absence of tissue IGF-1 and enhance bone properties in its presence

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INTRODUCTION

The growth hormone (GH)/Insulin-like growth factor-1 (IGF-1) axis has major effects on skeletal growth and integrity. Studies of skeletal structure in the IGF-1 and GH receptor (GHR) null mice showed decreases in bone length, total cross-sectional bone area and cortical bone area. However, the IGF-1 null mice exhibit greater impairment in bone accretion than GHR or GH null mice, suggesting GH-independent effect of IGF-1 during postnatal growth. Moreover, while GH deficiency in human and mice does not affect birth size, mutations in the *igf-1* or the *igf-1* receptor (*igf-1r*) genes lead to severe intrauterine and postnatal growth retardation.

IGF-1 acts on the growing skeleton in an endocrine and autocrine/paracrine manner. In our previous study with the liver-IGF-1 deficient (LID) mice, which exhibit 75% reductions in serum IGF-1 and normal skeletal IGF-1 expression, we found that serum IGF-1 regulates periosteal bone growth, determines bone size and by inference bone strength.

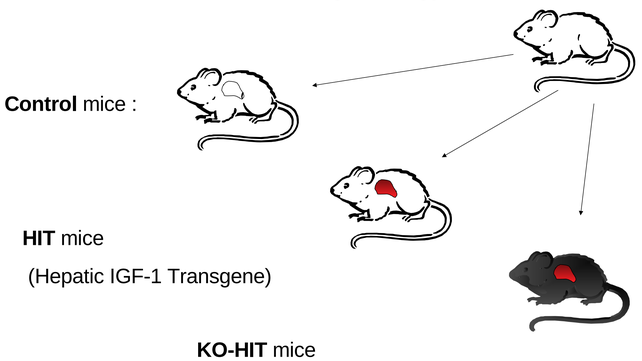
AIM

This study aimed to test whether elevated levels of IGF-1 in serum can rescue the severe growth phenotype of IGF-1 null mice.

MOUSE MODEL

We performed longitudinal analyses of three mouse models: 1) control mice, which express normal levels of autocrine/paracrine and endocrine IGF-1; 2) Hepatic IGF-1 transgenic (HIT) mice, which express normal levels of autocrine/paracrine IGF-1 but overexpress endocrine IGF-1 and 3) IGF-1 null mice, which do not express autocrine/paracrine IGF-1 but overexpress endocrine IGF-1 (KO-HIT)

Crossing strategy



Control mice :

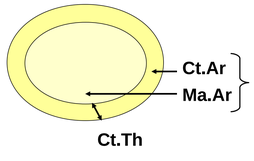
HIT mice

(Hepatic IGF-1 Transgene)

KO-HIT mice

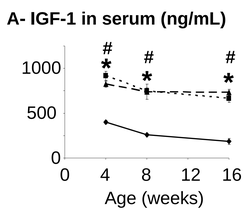
(Knock Out + Hepatic IGF-1 Transgene)

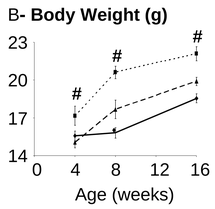
BONE PARAMETERS

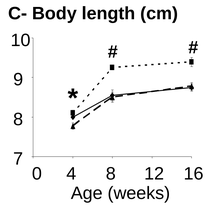


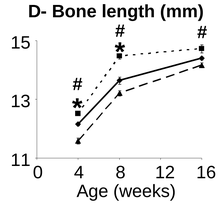
Slenderness is defined by Tt.Ar/Le, such as less slender bones (more robust bones) have greater TtAr/Le ratio.
The polar moment of inertia (Jo) is a measure of tissue distribution from the center of the bones and gives and indication of resisteance to bending.
Tissue mineral density (TMD), which is the average mineral value of the bone voxels only and is expressed in hydroxyapatite (HA) density equivalents.

RESULTS



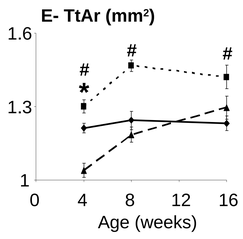


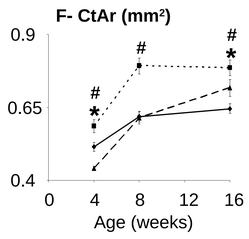


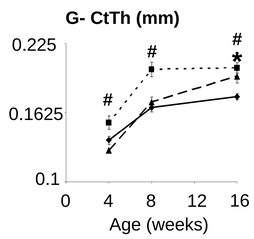


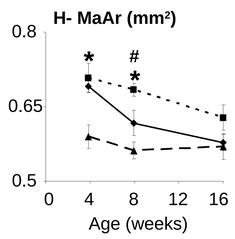
HIT and KO-HIT have 3 fold increase in IGF-1 level in serum

At 4w, KO-HIT are smaller, but then they caught up body weight, length and bone length by 8 w

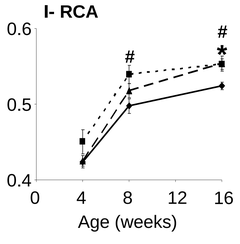


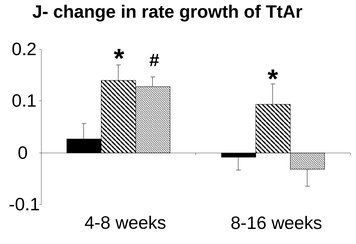


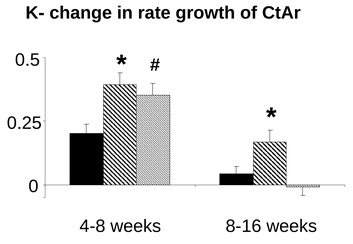




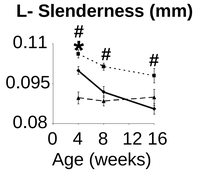
At 4w, all KO-HIT bone compartment are smaller, but then they caught up by 8w, and have increased Ct.Ar and Ct.Th by 16w

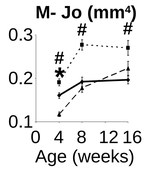


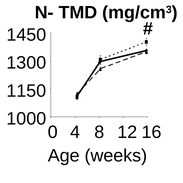


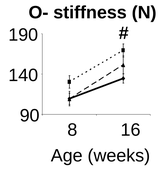


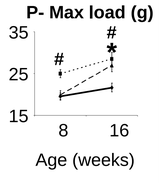
Between 4 and 8w and between 8 and 16w, KO-HIT have higher growth rate of Tt.Ar and Ct.Ar than control. KO-HIT is the only group that keep a high growth rate between 8 and 16w.











Although KO-HIT mice exhibit a less robust phenotype at 4w, they show an increase in Max load at 16w, compare to control

DISCUSSIONS

Increased level of IGF-1 lead to a bigger bone and more robust phenotype in HIT mice, by affecting bone size (Tt.Ar, Ct.Ar, Le) but also mineralization (increased TMD). Those modifications lead to stronger bones, as showed by the mechanical testing (stiffer bones and increased max load).

HIT mice reach a plateau of the morphological bone parameters at 8 weeks old. Nevertheless, mineralization and thus strength, continue to increase till 16 weeks old.

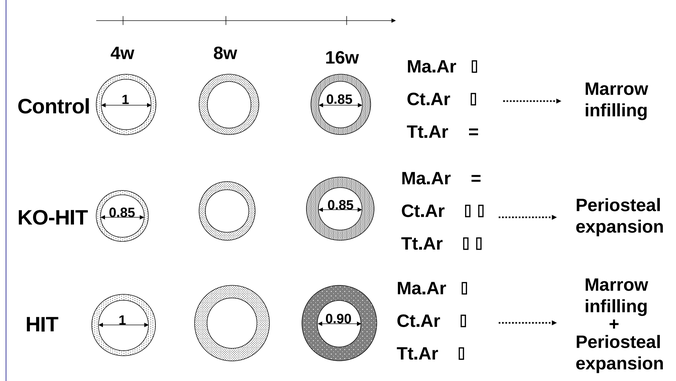
KO-HIT mice exhibit a delay in bone growth, as they have smaller bones at 4 weeks old (Tt.Ar, Ct.Ar, Ma.Ar, Le) and thus, probably weaker bones as suggested by their slenderness and J_o (10 and 23% decrease, respectively).

Increased endocrine IGF-1 lead to a catch up of the bone at 8 weeks old on most of the morphological parameters. This is explained by an increase in growth rate observed in both HIT in KO-HIT.

KO-HIT mice, as oppose to HIT mice and control, keep a high growth rate between 8 and 16 weeks of age, so that they reach an intermediate phenotype between control and HIT by 16 weeks of age.

High level of IGF-1 can lead to increase in mineralization but only if the autacrine/paracrine IGF-1 is at a normal level, as suggested by the absence of difference in TMD between KO-HIT and control mice.

The longitudinal modification of the bone also suggest that increased endocrine IGF-1 lead to an increase in size of the bone.



- **Endocrine IGF-1 mostly affects cortical bone**
- **Autocrine/paracrine IGF-1 is critical early postnatally**
- **High endocrine IGF-1 is sufficient to restore a normal phenotype**
- **High endocrine IGF-1 lead to more robust bones, by affecting Tt.Ar, Ct.Ar and TMD**
- **Endocrine IGF-1 may be related to pathways of periosteal bone apposition**
- **Autocrine/paracrine IGF-1 may be related to pathways of endosteal bone apposition**

CONCLUSION

Elevated level of endocrine IGF-1 restore the severe bone phenotype of IGF-1 null mice at 8 weeks of age. Nevertheless, autocrine/paracine IGF-1 levels are important to establish bone size early postnatally.

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