# Increased levels of serum IGF-1 can rescue the skeletal impairment of female IGF-1 null mice but are insufficient for the rescue of the male skeleton

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# Increased levels of serum IGF-1 can rescue the skeletal impairment of both male and female IGF-1 null mice.

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## BACKGROUND

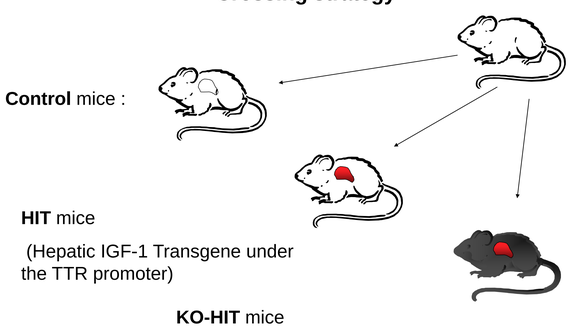
IGF-1 acts on the growing skeleton in an endocrine and autocrine/paracrine manner. IGF-1 null mice exhibit significant impairment of skeletal growth and development. Here, we studied whether increased levels of endocrine (serum) IGF-1 can rescue the severe skeletal phenotype of both male and female IGF-1 null mice. We performed skeletal analyses of three mouse models: 1) control mice, which express normal levels of autocrine/paracrine and endocrine IGF-1, 2) mice which express autocrine/paracrine IGF-1 as in control, but also overexpress *H*epatic *I*GF-1 *t*ransgene (HIT), and 3) IGF-1 null mice that overexpress the *H*epatic *I*GF-1 *t*ransgene (KO-HIT) and, thus, overexpress endocrine IGF-1.

## AIM

This study aimed at defining the skeletal response to increased levels of serum IGF-1 in the presence or absence of tissue IGF-1.

## MOUSE MODELS

**Crossing strategy**



**Control** mice :

**HIT** mice

(Hepatic IGF-1 Transgene under the TTR promoter)

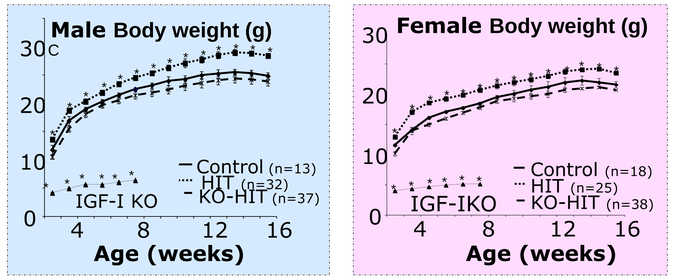
**KO-HIT** mice

(IGF-1 Knock Out + Hepatic IGF-1 Transgene)

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)

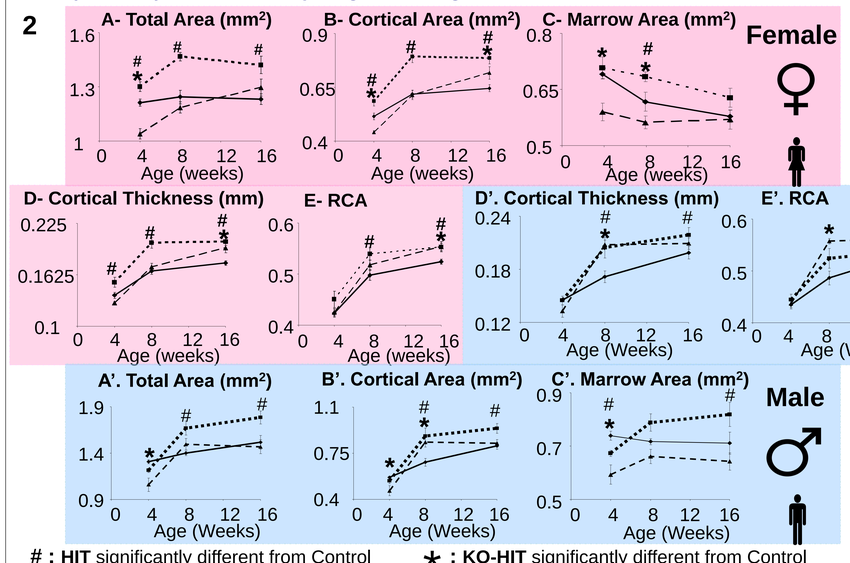
## RESULTS

1




**IGF-1 null mice have severe growth retardation and exhibit 70% reduction in body weight throughout growth. However, elevations in serum IGF-1 levels in IGF-1 null mice where tissue IGF-1 expression is blunted (KO-HIT mice) restore body weight to controls in both genders. Furthermore, when tissue IGF-1 expression is normal, elevations in serum IGF-1 levels (HIT mice) increase in body weight of both genders.**

2

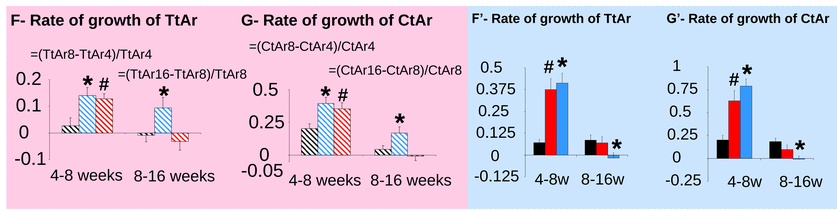



**# : HIT** significantly different from Control *** : KO-HIT** significantly different from Control

**Increases in serum IGF-1 levels enhance skeletal growth (HIT mice) in both genders, indicated by increase in total cross-sectional area, cortical area, cortical thickness and relative cortical area (RCA). When tissue IGF-1 expression is blunted, elevations in serum IGF-1 (KO-HIT mice) fail to restore those skeletal properties early postnatally, evident by decreases in total cross-sectional area, cortical area and thickness at 4 weeks of age.**
**Nonetheless, at 8 weeks of age KO-HIT mice show catch up growth and their skeletal traits are similar to controls.**
**Of note, trabecular architecture, assessed at the distal femur, did not reveal differences between the groups at 4, 8 or 16 weeks of age in both males and females.**

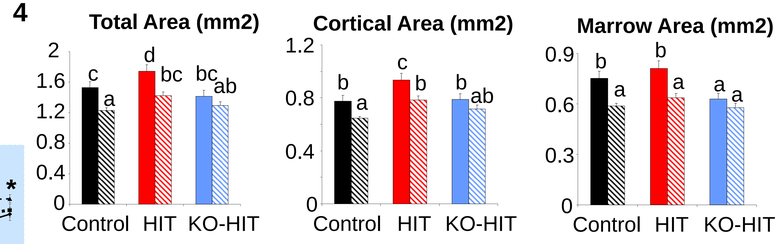
**Control mice: local IGF1 normal + endocrine IGF1 normal**
**HIT mice : local IGF1 normal + endocrine IGF1 increased**
**KO-HIT mice : no local IGF1 + endocrine IGF1 increased**

3




**Elevations in serum IGF-1 lead to increased transversal bone growth rate (total cross-sectional area and cortical area) during puberty (4-8 weeks of age) in both HIT and KO-HIT male and female mice. However, while control and HIT mice "cease" transversal bone growth after puberty (8-16 weeks), KO-HIT females show prolongation of transversal bone growth.**

4




**In the absence of tissue IGF-1, elevations in serum IGF-1 levels (KO-HIT mice) diminish sex-related differences in skeletal properties. At 16 weeks of age total cross-sectional area, cortical area and marrow area in control and HIT mice differ between males and females. In contrast, femural parameters of KO-HIT male and female at 16 weeks of age are indistinguishable.**

## CONCLUSIONS

***The KO-HIT model show that elevations in serum IGF-1 are insufficient to restore body weight and skeletal size early postnataly.**
***During puberty and adult age, elevations in serum IGF-1 result in increased transversal bone growth rate leading to restoration of body weight and skeletal size, despite blunted tissue IGF-1 expression.**
*** When tissue IGF-1 expression is blunted, elevations in serum IGF-1 (KO-HIT mice) diminish sex-related differences in skeletal properties.**

**GRANTS**
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