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

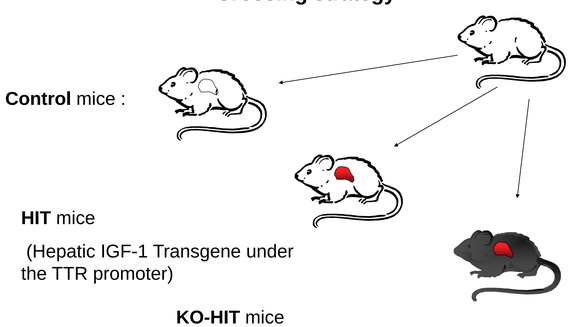
IGF-1 acts on the growing skeleton in an endocrine and autocrine/paracrine manner. IGF-1 null mice exhibit significant impairment of skeletal growth and development. Here, we studied whether increased levels of endocrine (serum) IGF-1 can rescue the severe skeletal phenotype of both male and female IGF-1 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)

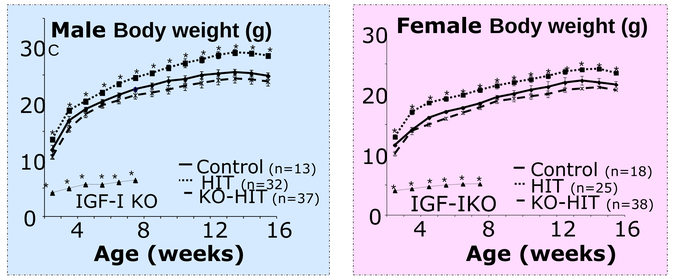
KO-HIT mice

(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)

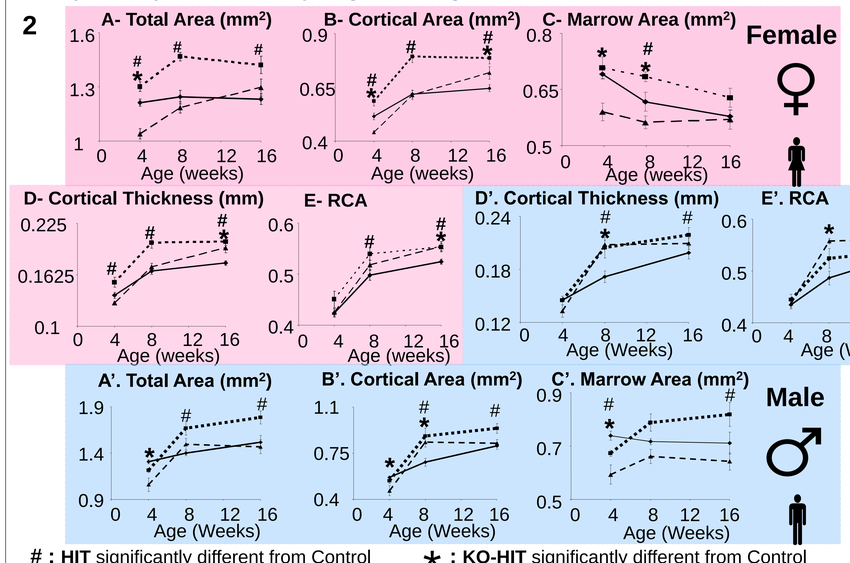
RESULTS

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

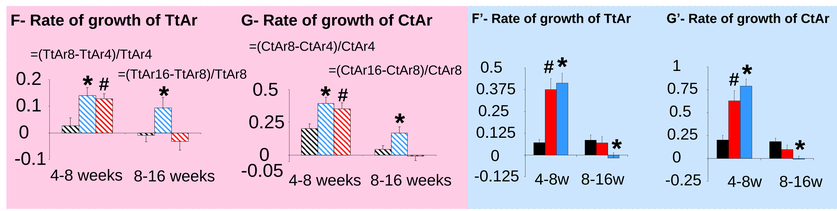


 # : HIT significantly different from Control *** : KO-HIT** significantly different from Control

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.

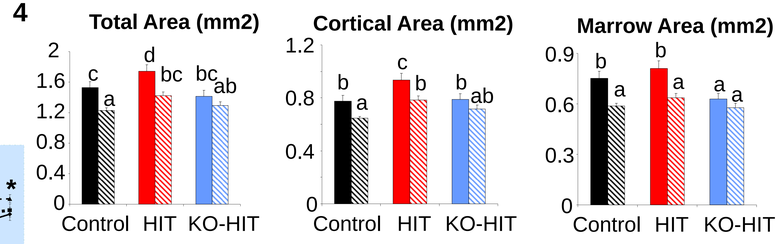
Control mice: local IGF1 normal + endocrine IGF1 normal
HIT mice : local IGF1 normal + endocrine IGF1 increased
KO-HIT mice : no local IGF1 + endocrine IGF1 increased

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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