Sex-specific effects of endocrine IGF-1 on skeletal morphology and peak bone acquisition

Sébastien Elis, Yingjie Wu, Hayden-William Courtland

P1 – 265

Sex−Specific Effects of Endocrine IGF−1 on Skeletal Morphology and Peak Bone Acquisition

Sebastien Elis, Yingjie Wu, Hayden-William Courtland, Hui Sun, Valerie Williams, Karl Jepsen and Shoshana Yakar

Division of Endocrinology, Diabetes and Bone disease, Mount Sinai School of Medicine, New York, NY 10029

BACKGROUND

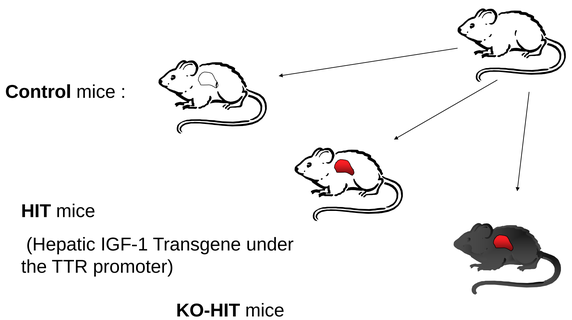
IGF-1 acts on the growing skeleton in an endocrine and autocrine/paracrine manner. IGF-1 null mice exhibit significant impairment of skeletal growth and development. Here, we studied whether increased levels of endocrine (serum) IGF-1 can rescue the severe skeletal phenotype of both male and female IGF-1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

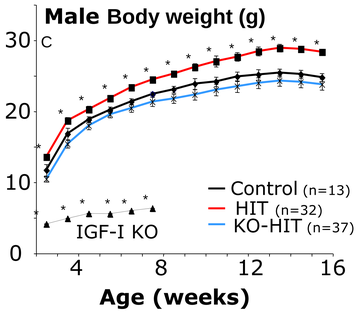
(Hepatic IGF-1 Transgene under the TTR promoter)

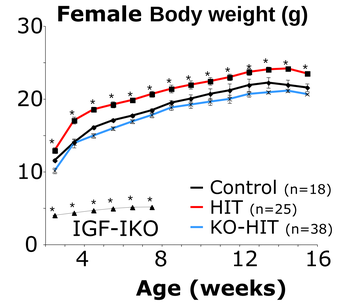
KO-HIT mice

(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

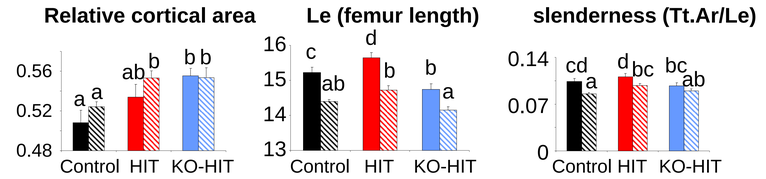


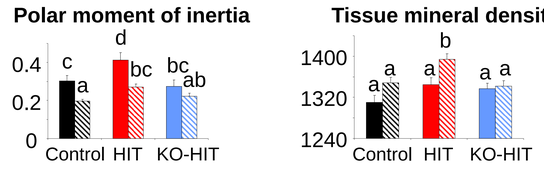


Control mice: local IGF1 normal + endocrine IGF1 normal

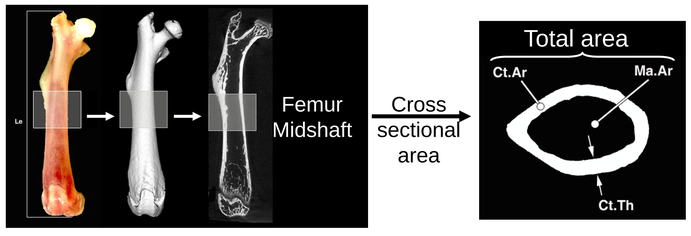
HIT mice : local IGF1 normal + endocrine IGF1 increased

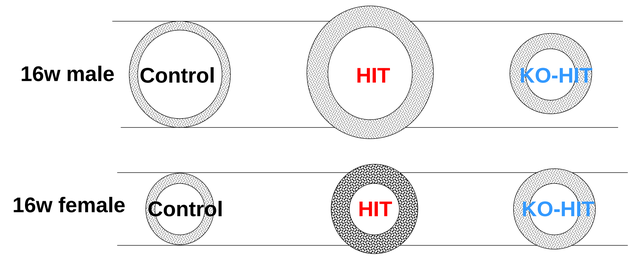
KO-HIT mice : no local IGF1 + endocrine IGF1 increased

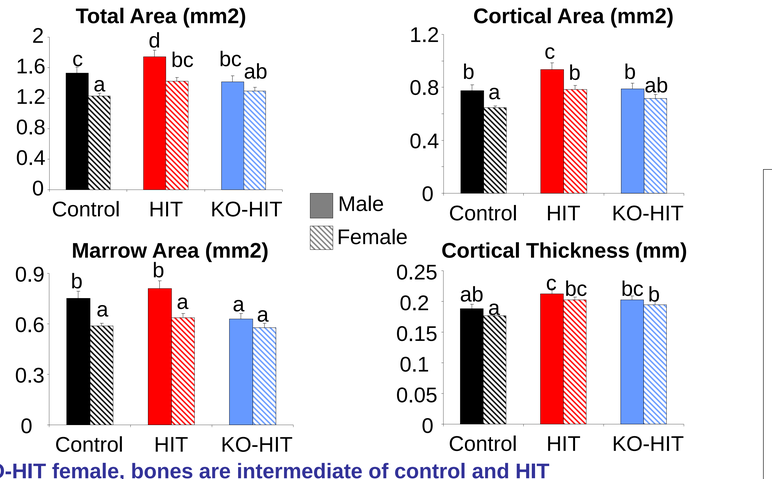




Bone morphology at 16w
Micro Computational Tomography







In KO-HIT female, bones are intermediate of control and HIT

In KO-HIT male bones are significantly smaller than HIT (trend to be smaller than control)

CONCLUSIONS

These data suggest that in the absence of tissue IGF-1, increased levels of serum IGF-1 are sufficient to rescue the body weight and transverse bone size in both male and female mice (KO-HIT). However, we show that in the absence of tissue IGF-1, increased levels of serum IGF-1 in males are insufficient for normal longitudinal bone growth.

GRANTS

National Institutes of Health : R01AR055141- R01AR054919