Autocrine/paracrine IGF-1 plays a critical role in determining bone size prenatally and early postnatally

Sébastien Elis, Hayden-William Courtland, Yingjie Wu, Hui Sun, Karl J. Jepsen, Shoshana Yakar

Elevated levels of serum IGF-1 restore peak bone properties and mechanical functionality in the absence of autocrine/paracrine IGF-1

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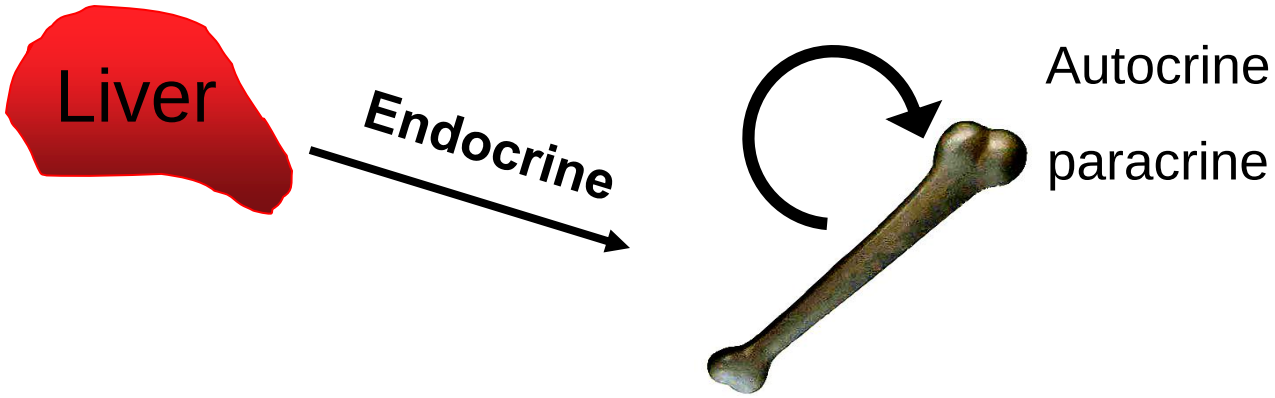
Department of Medicine
Division of Endocrinology, Diabetes and Bone Diseases

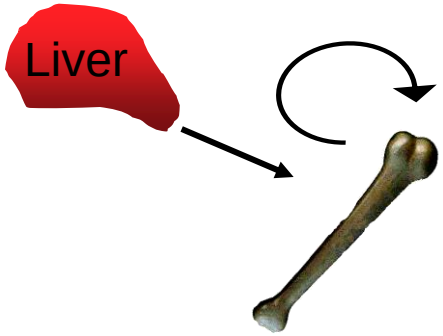
ENDO 09, Washington, 6.12.09

IGF-1 is an endocrine, and autocrine/paracrine modulator of growth and metabolism



Aim:
To test whether elevated serum IGF-1 levels can support skeletal growth and integrity in the complete absence of tissue IGF-1

Control



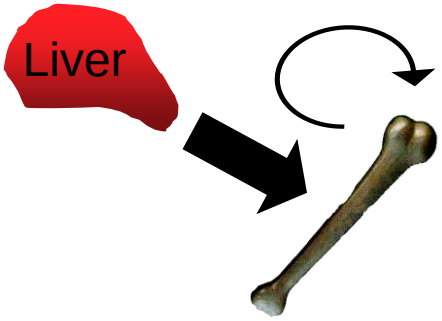
Normal serum IGF1 levels

Normal tissue IGF1 levels

HIT

Hepatic IGF-1 Transgene

TTR promoter



High serum IGF1 levels

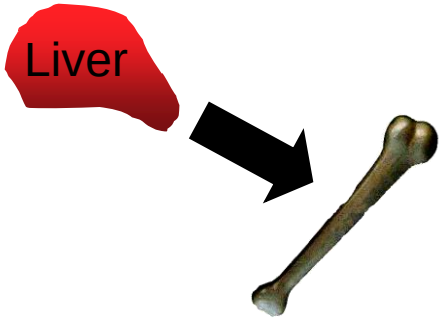
Normal tissue IGF1 levels

KO-HIT

Total IGF-1 KO+

Hepatic IGF-1 Transgene

TTR promoter

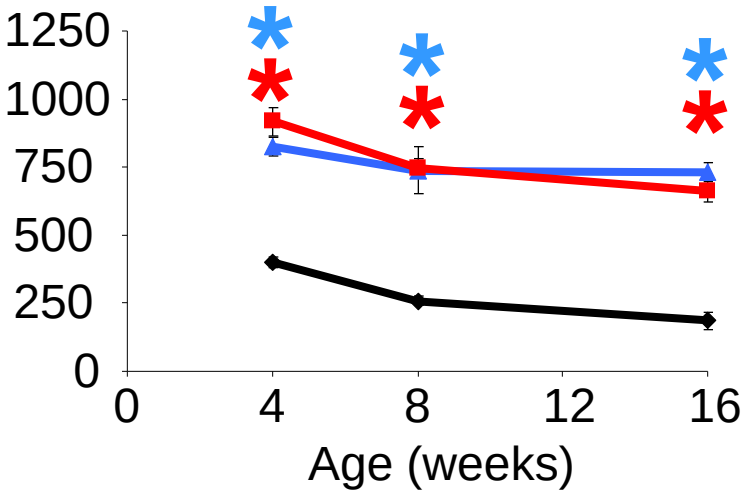


High serum IGF1 levels

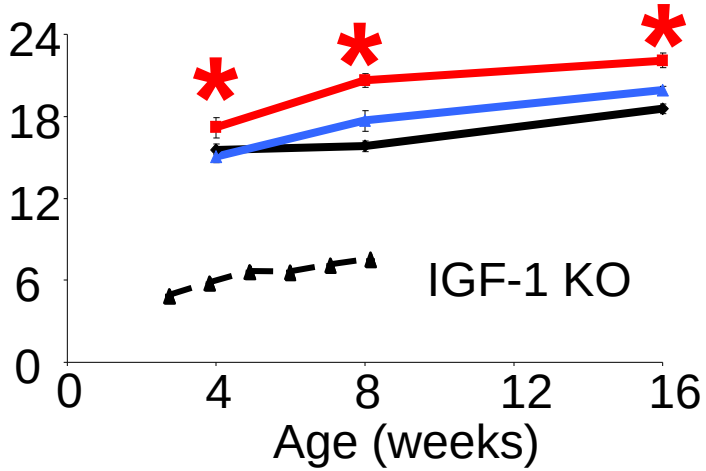
NO tissue IGF1

High levels of endocrine IGF-1 increase body weight

Serum IGF-1 (ng/mL)

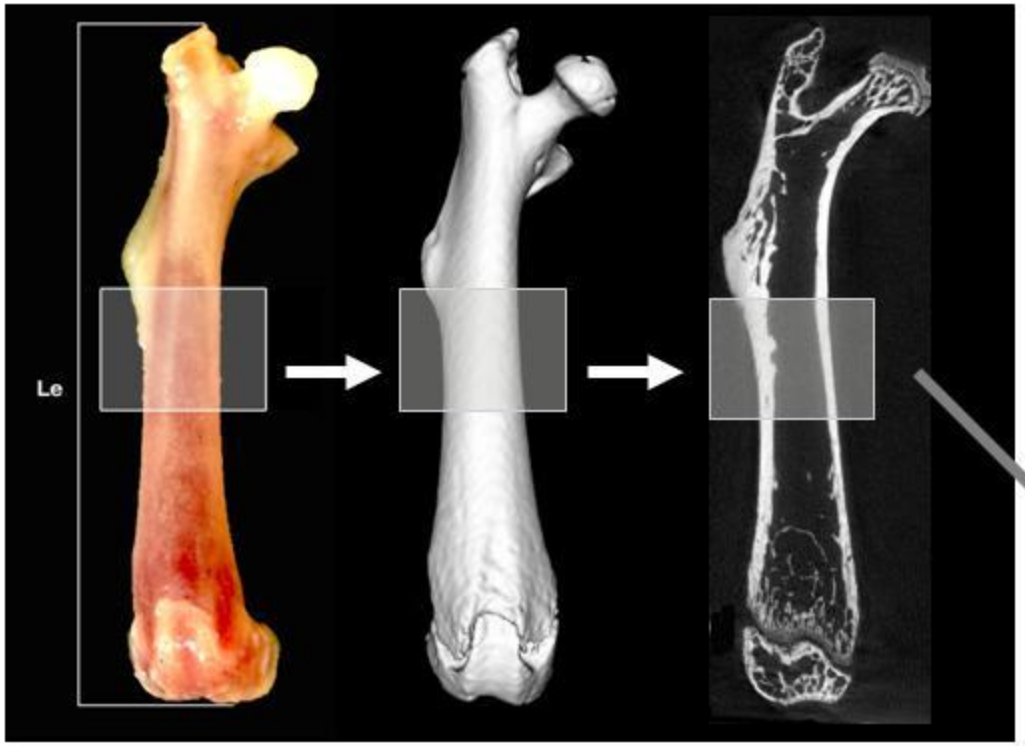


Body Weight (g)



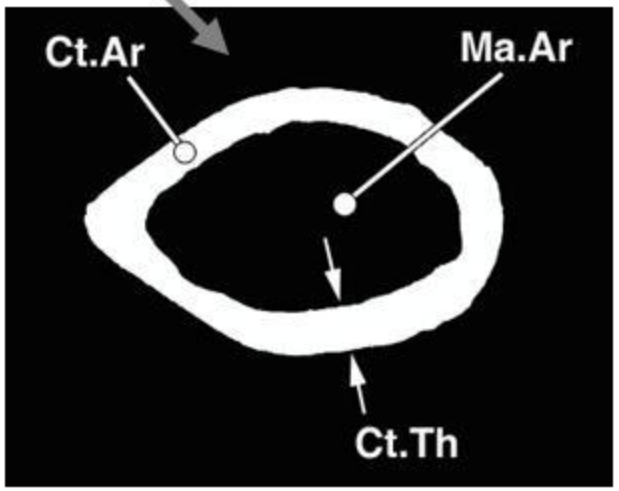
Legend	Serum	Tissue
Control	✓	✓
HIT	✓	✓
KO-HIT	✓	✗

Micro Computational Tomography



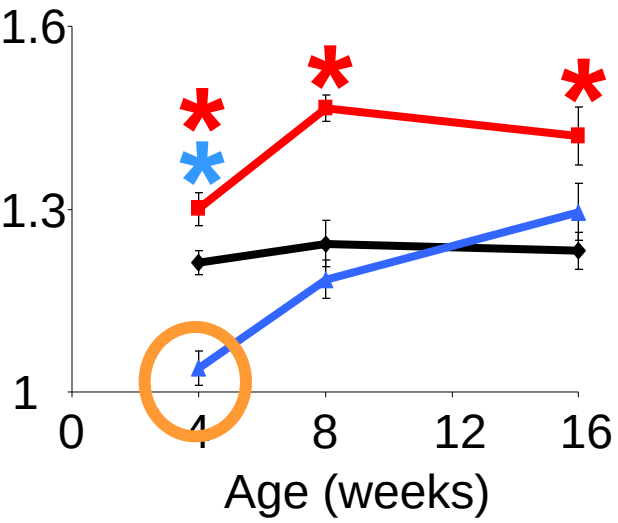
Morphology

- Dynamic μCT
- Midshaft of femur
- Bone Compartment size

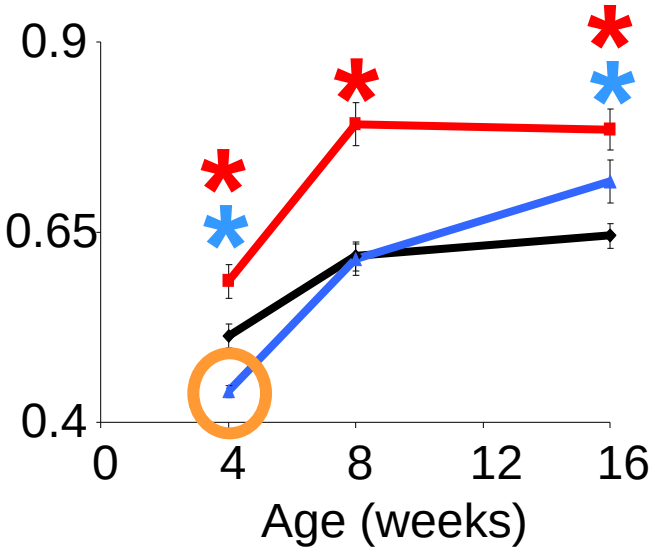


Cortical bone

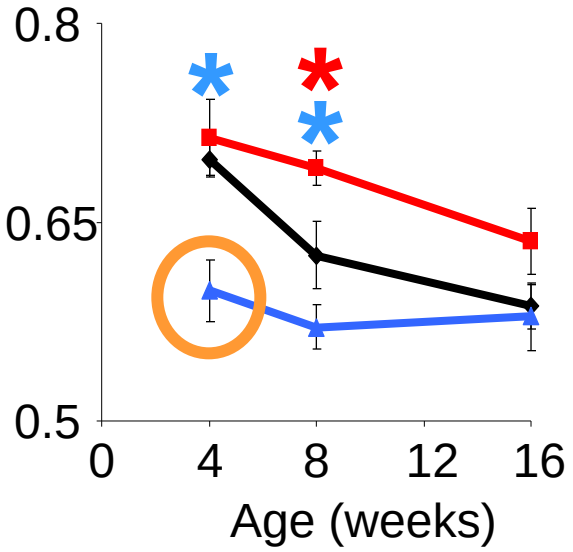
Total Area (mm2)

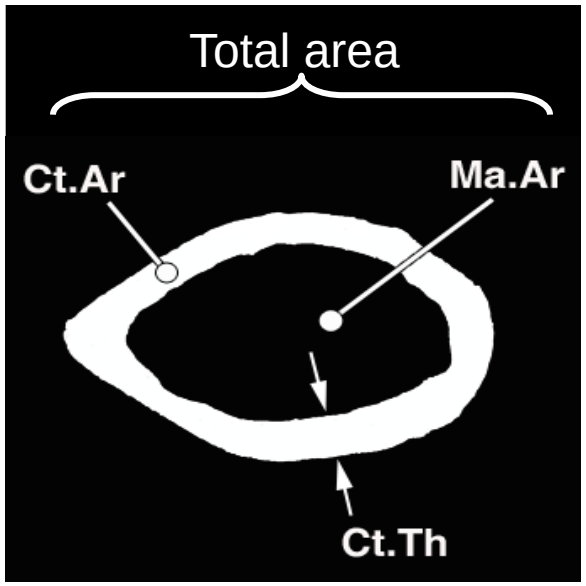


Cortical Area



Marrow Area



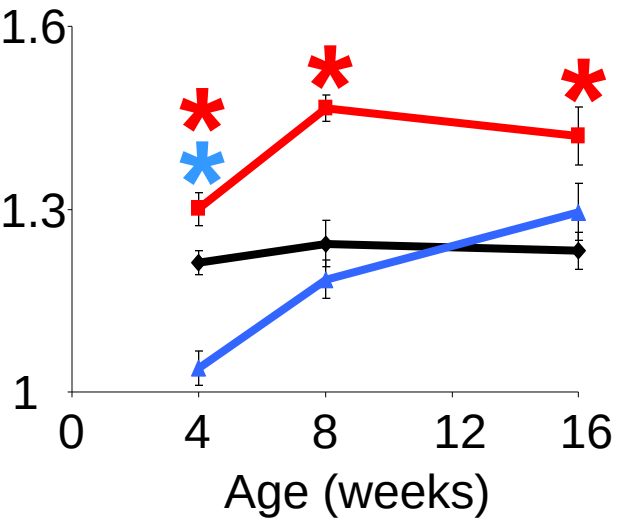


Autocrine/paracrine IGF-1 critical for early growth (before 4w)

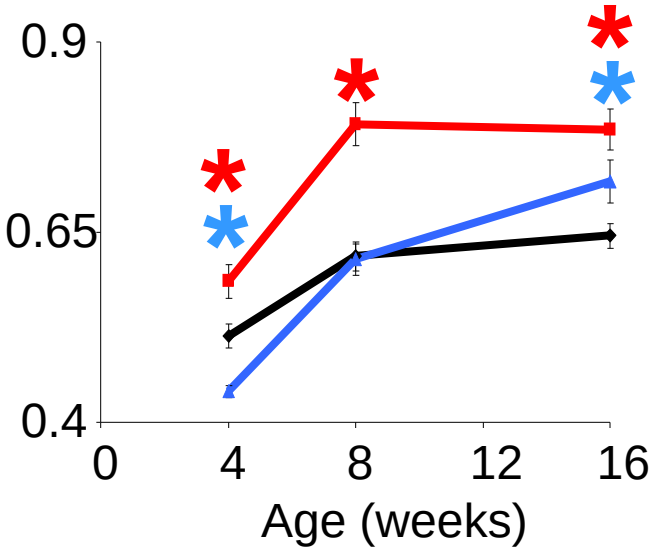
Legend	Serum	Tissue
Control	✓	✓
HIT	✓	✓
KO-HIT	✓	✗

Cortical bone

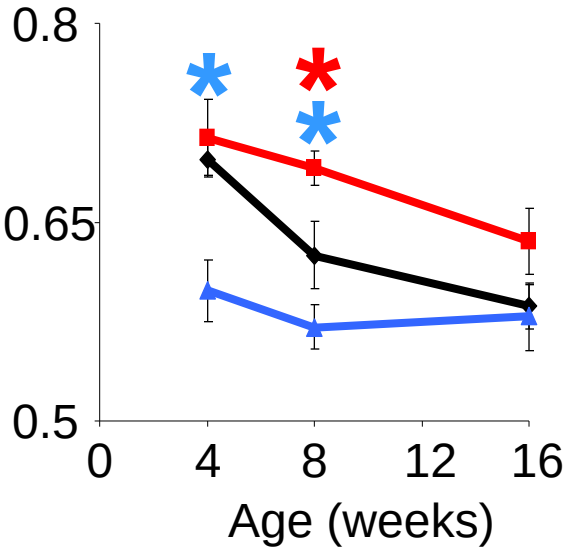
Total Area (mm2)



Cortical Area



Marrow Area



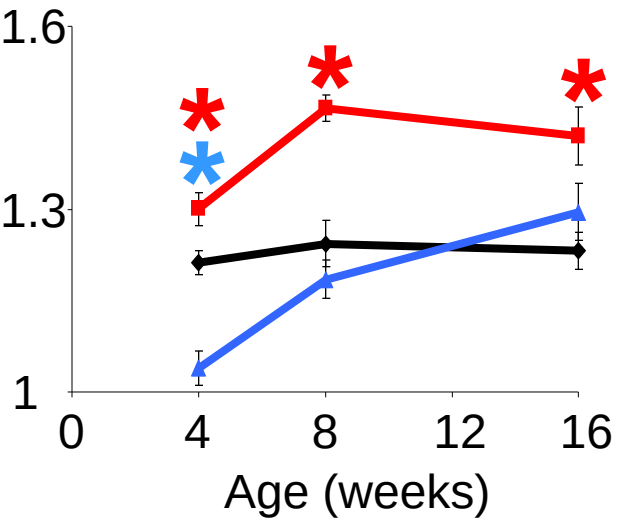
Control

Serum	Tissue
✓	✓

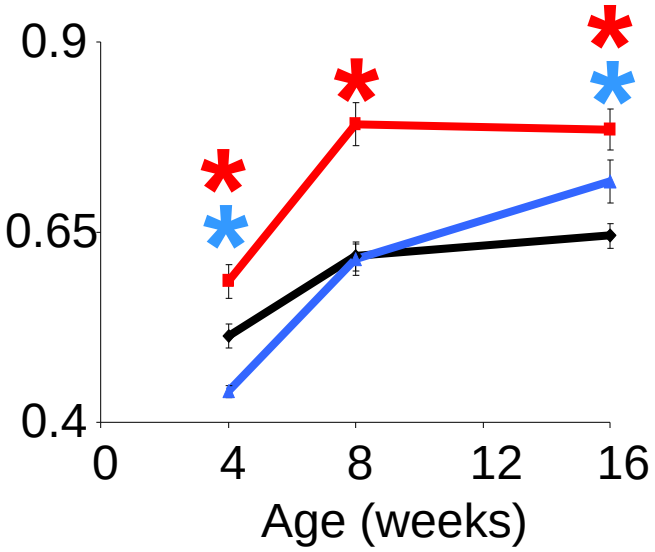
Legend	Serum	Tissue
Control	✓	✓
HIT	✓	✓
KO-HIT	✓	✗

Cortical bone

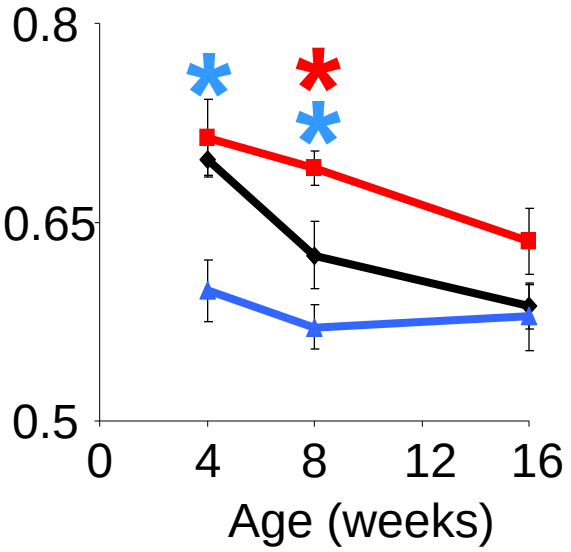
Total Area (mm2)

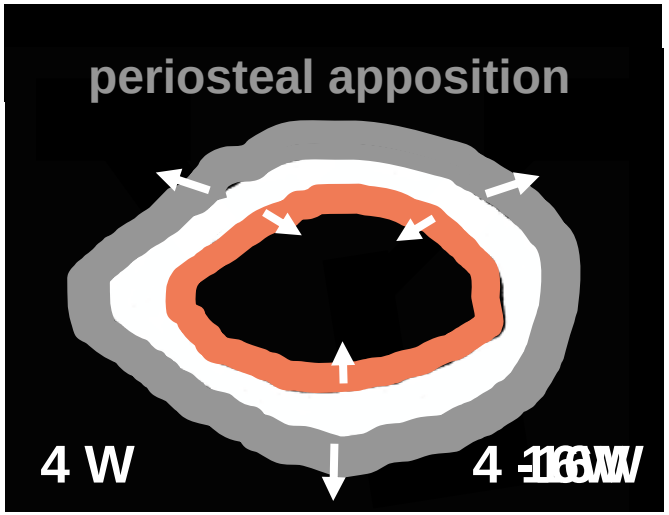


Cortical Area



Marrow Area





Control

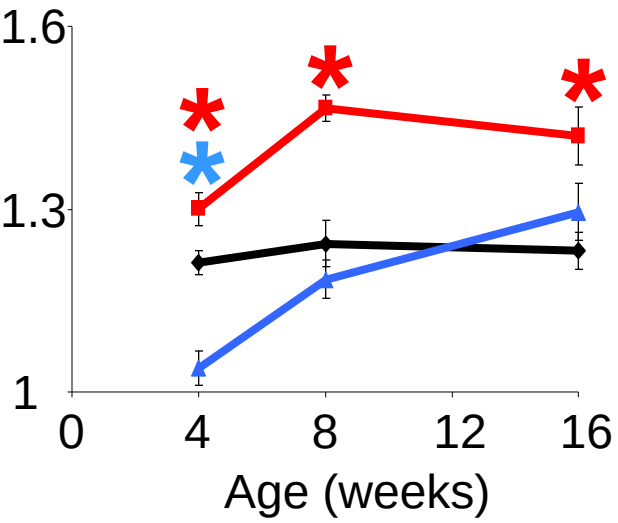
Serum ✓ **Tissue** ✓

HIT

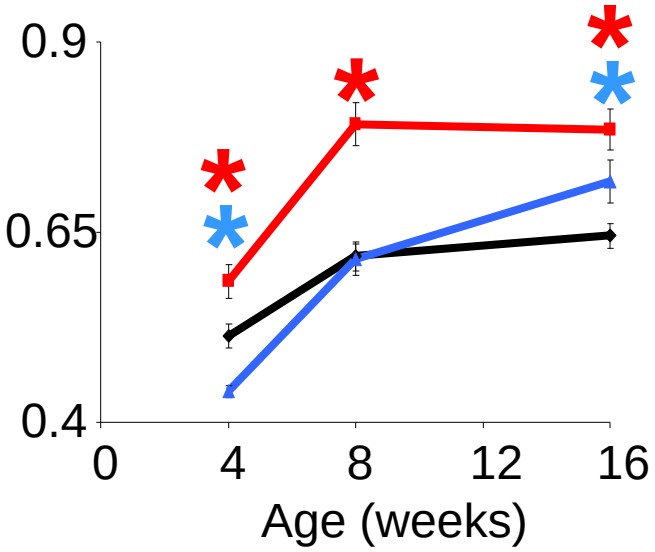
Serum ✓ **Tissue** ✓

Cortical bone

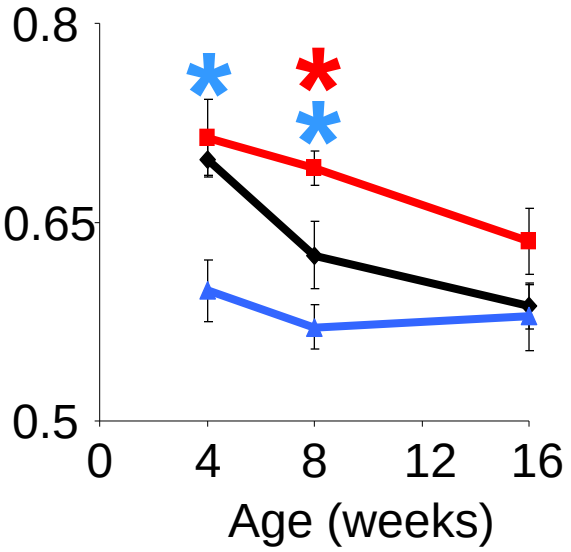
Total Area (mm2)



Cortical Area

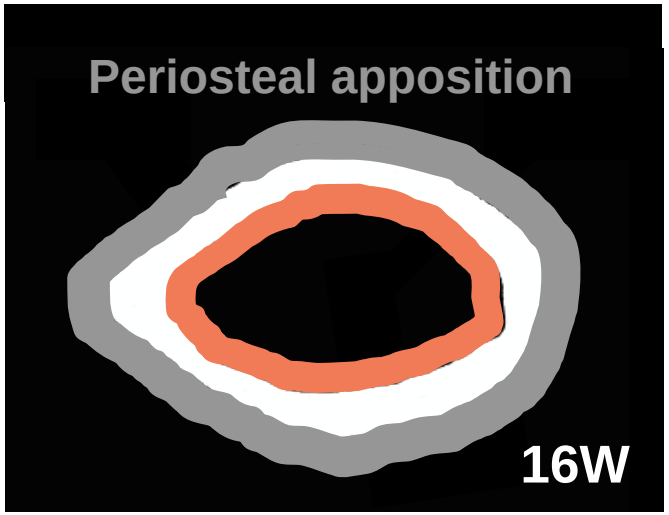


Marrow Area



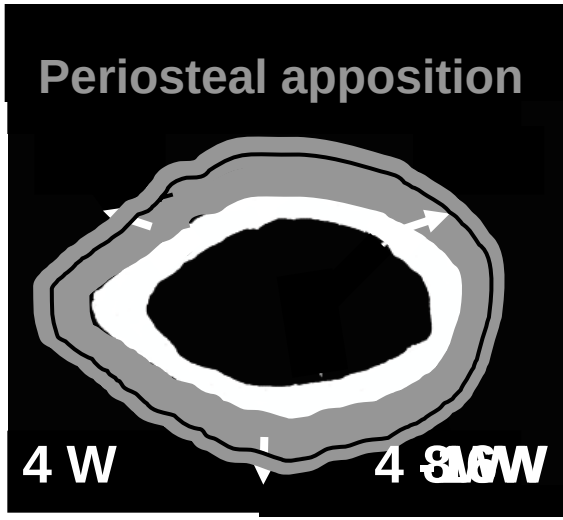
Control

Serum ✓ Tissue ✓



HIT

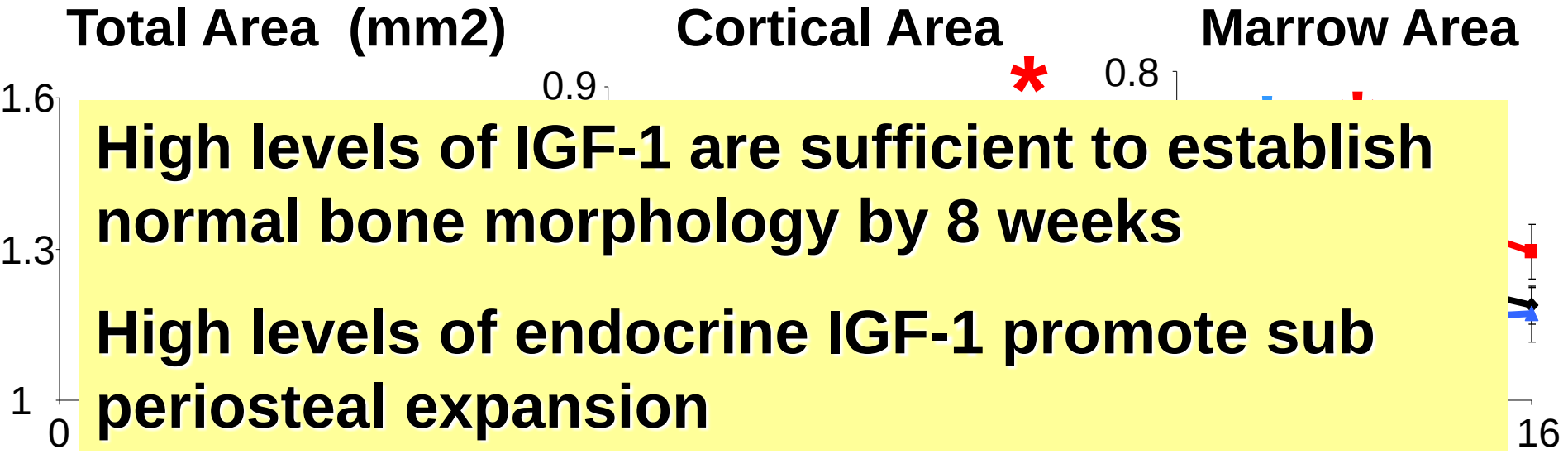
Serum ✓ Tissue ✓



KO-HIT

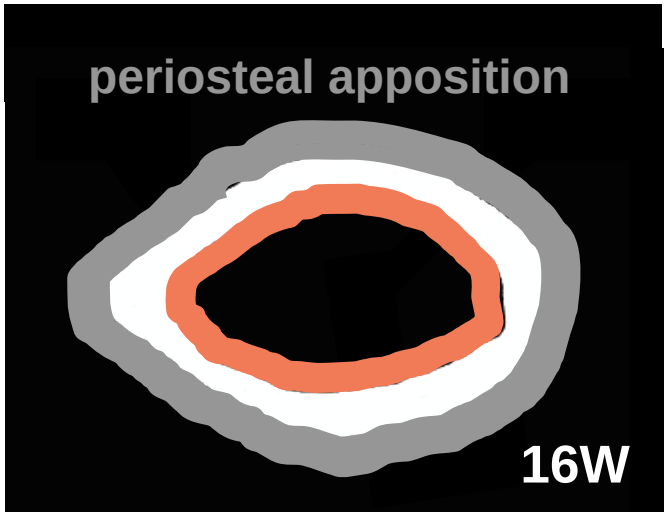
Serum ✓ Tissue ✗

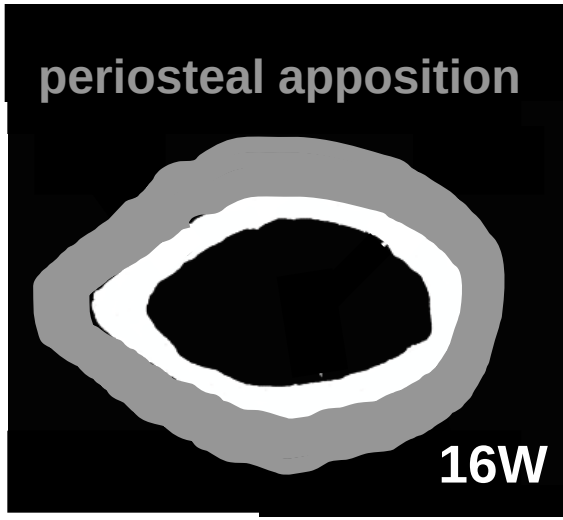
Cortical bone



High levels of IGF-1 are sufficient to establish normal bone morphology by 8 weeks

High levels of endocrine IGF-1 promote sub periosteal expansion



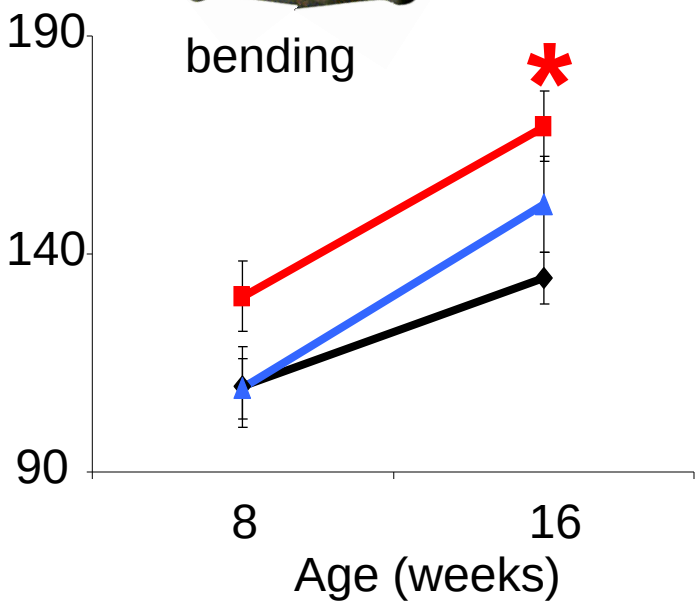


Control	HIT	KO-HIT
Serum ✓ Tissue ✓	Serum ✓ Tissue ✓	Serum ✓ Tissue ✗

Mechanical properties

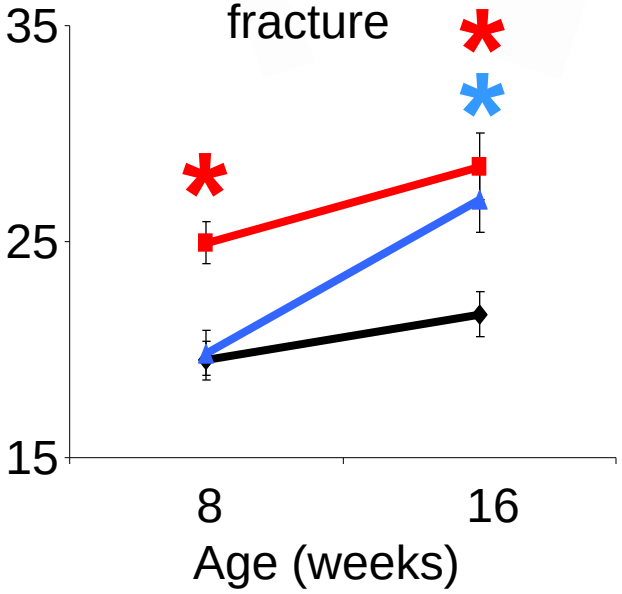
Stiffness (N)

bending



Max load (g)

fracture



4-point bending test

8 weeks :

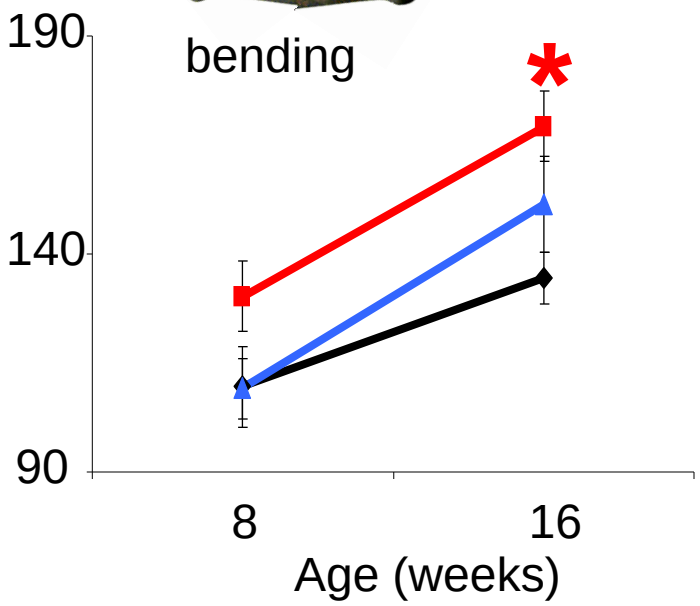
HIT	cortices	↗	max load	↗
KO-HIT	cortices	=	max load	=

Legend	Serum	Tissue
Control	✓	✓
HIT	✓	✓
KO-HIT	✓	✗

Mechanical properties

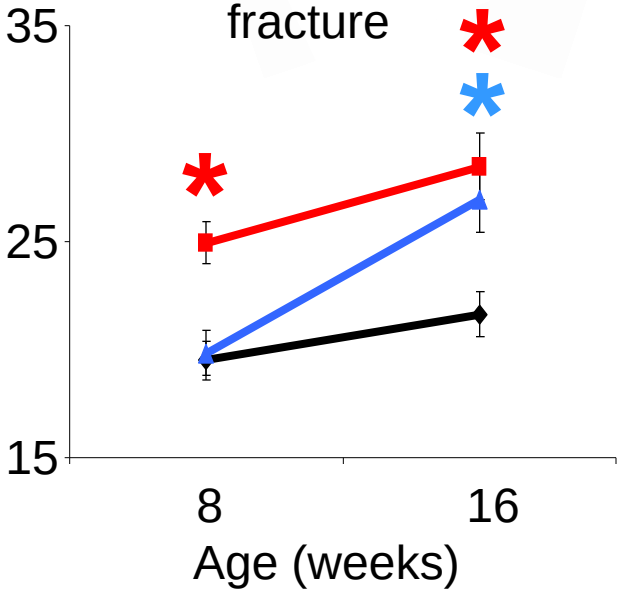
Stiffness (N)

bending



Max load (g)

fracture



4-point bending test

16 weeks :

HIT cortices ↗ max load ↗

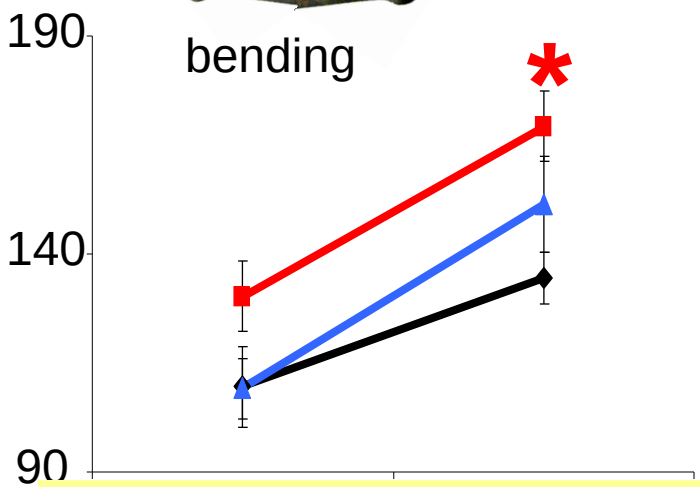
KO-HIT cortices ↗ max load ↗

Legend	Serum	Tissue
Control	✓	✓
HIT	✓	✓
KO-HIT	✓	✗

Mechanical properties

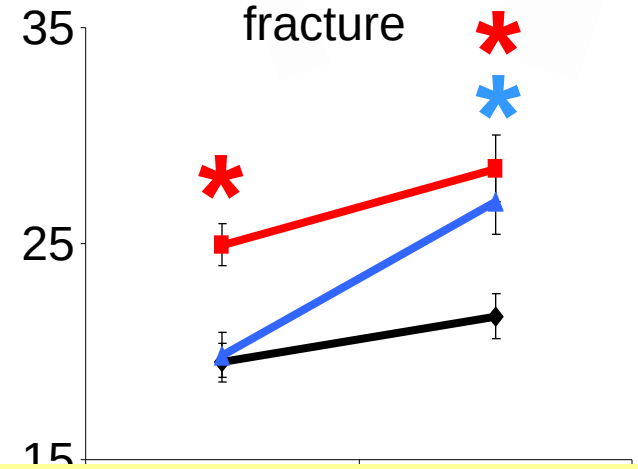
Stiffness (N)

bending



Max load (g)

fracture



4-point bending test

Elevated levels of IGF-1 in serum increase bone mechanical properties

Elevated levels of IGF-1 compensate for a lack of local IGF-1 both morphologically and mechanically

Tissue
✓
✓
✗

Summary

Postnatally, elevated serum IGF-1 levels :

- **increase in body weight.**
- **increase bone morphological traits**
- **increase in mechanical properties.**

Tissue IGF-1 is critical for neonatal and early postnatal growth (before 4w).

Elevated serum IGF-1 levels fully compensate for a postnatal absence of tissue IGF-1 :

Morphologically & Mechanically

Acknowledgments

Endocrinology division, Mount Sinai School of Medecine

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Hayden-William Courtland

Hui Sun

Yingjie Wu

Clifford Rosen

Valerie Williams

Karl J Jepsen

Orthopaedics department, Mount Sinai School of Medecine

U.S. Department of Health and Human Services

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National Institutes of Health

NIAMS National Institute of Arthritis and Musculoskeletal and Skin Diseases

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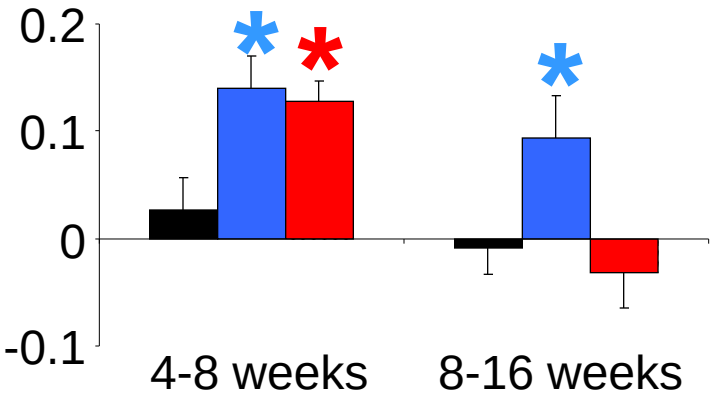
R01AR054919

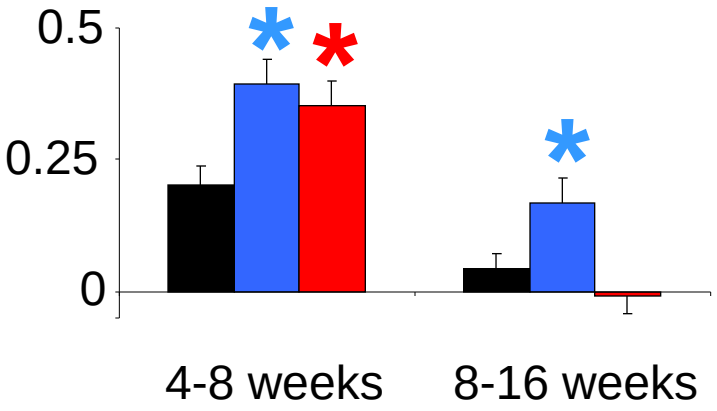
THANK YOU

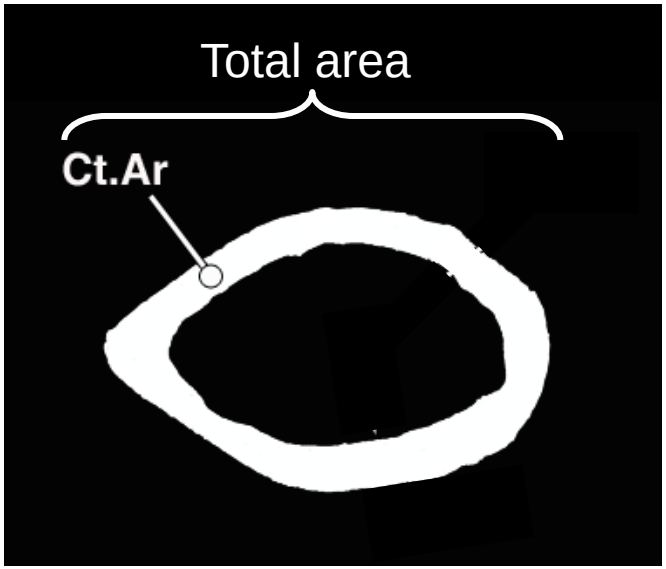
Increased serum IGF-1 levels accelerate growth rate

Growth rate of TtAr



Growth rate of CtAr





Legend		Serum	Tissue
	Control	✓	✓
	HIT	✓	✓
	KO-HIT	✓	×