Session I: Mechanisms of GIO

Chairmen: G. Minisola (Italy), G. Valesini (Italy)

09.00 – 09.30 OPENING LECTURE; Molecular Mechanisms of Glucocorticoids Action in Bone - *E. Canalis (USA)*

09.30 – 09.55 Neuroendocrine Effects of Glucocorticoids and Bone *A. Giustina (Italy)*

09.55 – 10.20 Glucocorticoids in the Management of Autoimmune Disorders - *L. Sinigaglia (Italy)*

10.20 – 10.45 Cortisol and the Muscle Bone Axis - *A. Scillitani (Italy)*

AGENDA

BONE MUSCLE UNIT

GLUCOCORTICOID AND BONE MUSCLE UNIT

THERAPY

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GLUCOCORTICOID AND BONE MUSCLE UNIT

THERAPY

Bone and muscle are integrated organs with shared functions e.g. in locomotion and growth, and both may act as endocrine organs. Development and maintenance of bone and muscle go hand in hand most of the time. Indeed, physical exercise can increase the strength and mass of muscle and bone, while both are compromised by ageing and situations of disuse like immobilization, stroke, paralysis, bed rest or spaceflight.

The concept of the "Bone–muscle unit" was evidenced phenotypically by the lifelong linear association between total body bone mineral content (BMC) and lean body mass.

A clinical study performed in boys and girls during pubertal development showed that the increase in bone strength was preceded by the increase in muscle strength.

Laurent MR et al, Mol Cell Endocinol 2016

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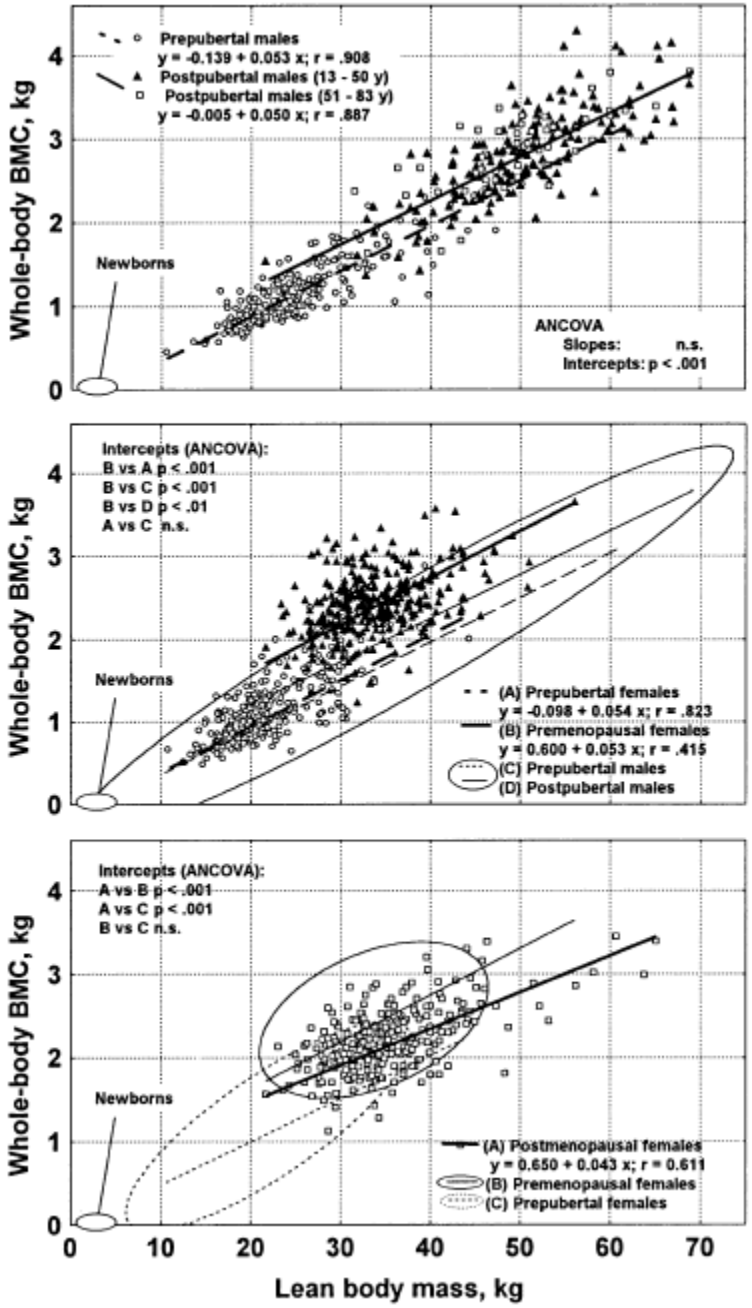
Laurent MR et al, Mol Cell Endocinol 2016

Correlations between the whole-body BMC (TBMC) and lean body mass (LBM) of all the prepubertal and postpubertal male individuals (upper), the prepubertal and postpubertal/premenopausal women (center), and the postmenopausal women studied (lower)



Ferretti JL et al, BONE 1998

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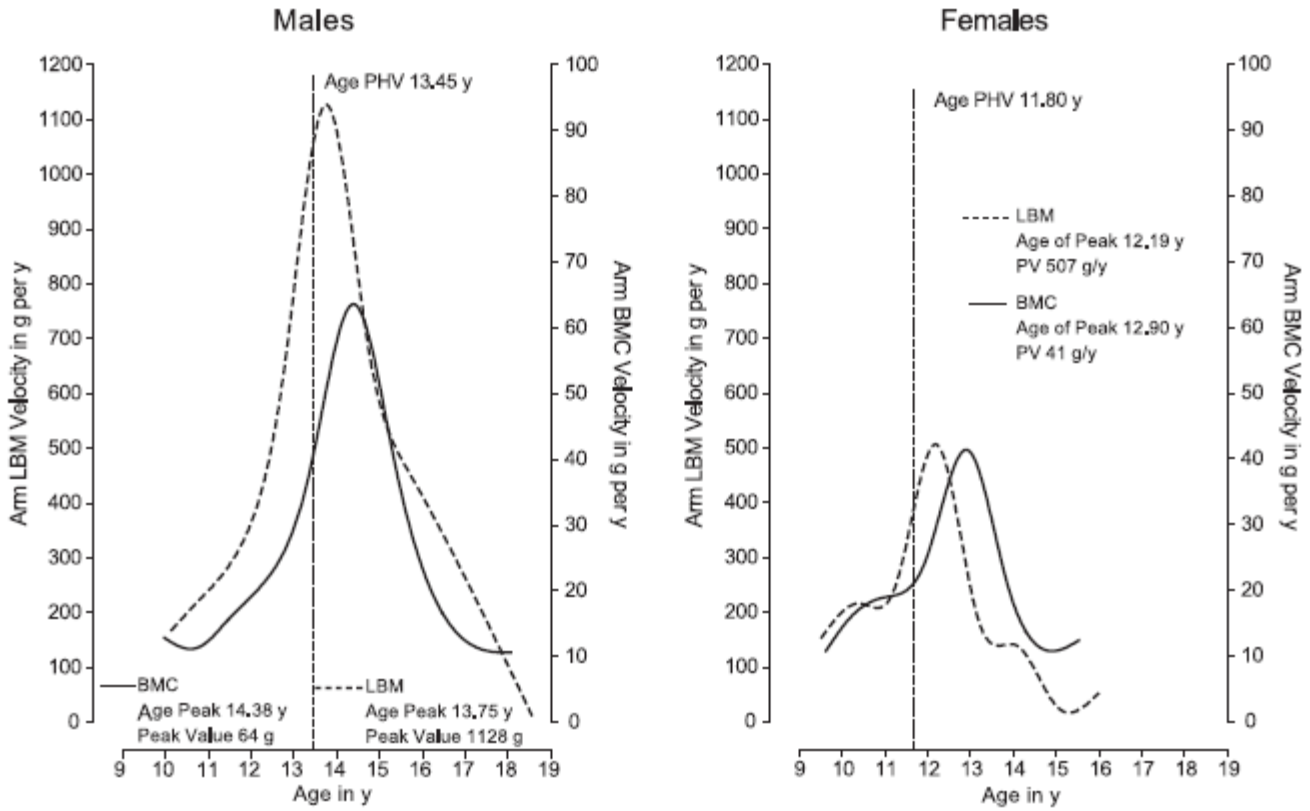
Laurent MR et al, Mol Cell Endocinol 2016

Velocities of upper extremity LBM and BMC accretion during the pubertal growth spurt



Rauch F et al, BONE 2004

Bone and muscle mass and functions are integrated at several levels:

biomechanical signals acting both directly on bone and muscle as well as indirectly via muscle contractions on bone

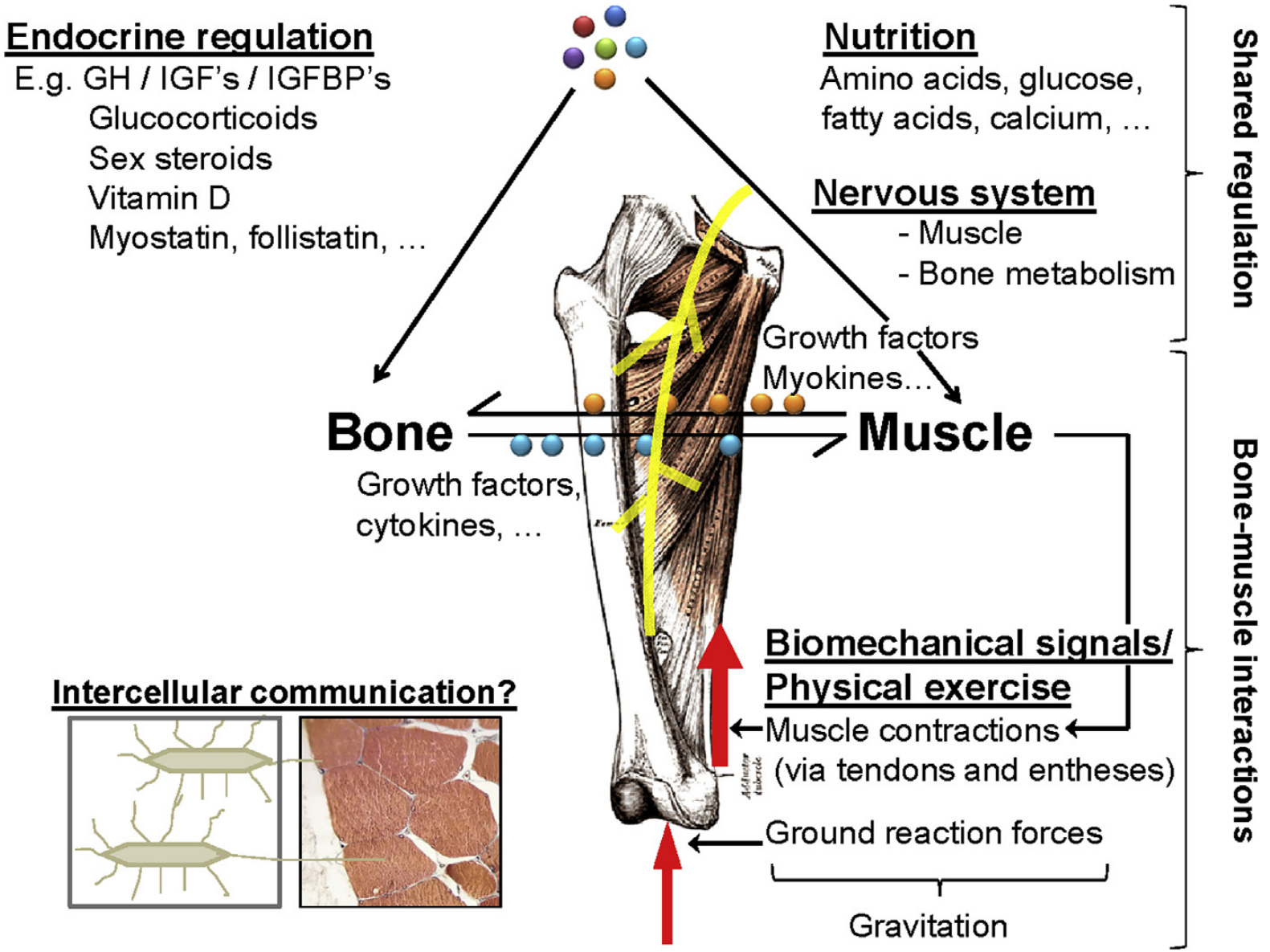
- **shared nutritional signals as well as endocrine regulation [e.g. growth hormone / insulin like growth factors and binding proteins (GH/IGFs/IGFBPs), glucocorticoids, sex steroids and vitamin D]**

- **central nervous system control of muscle and bone metabolism**

- **local hormones, growth factors and cytokines acting in both tissues as well as possibly via reciprocal muscle-bone paracrine actions**

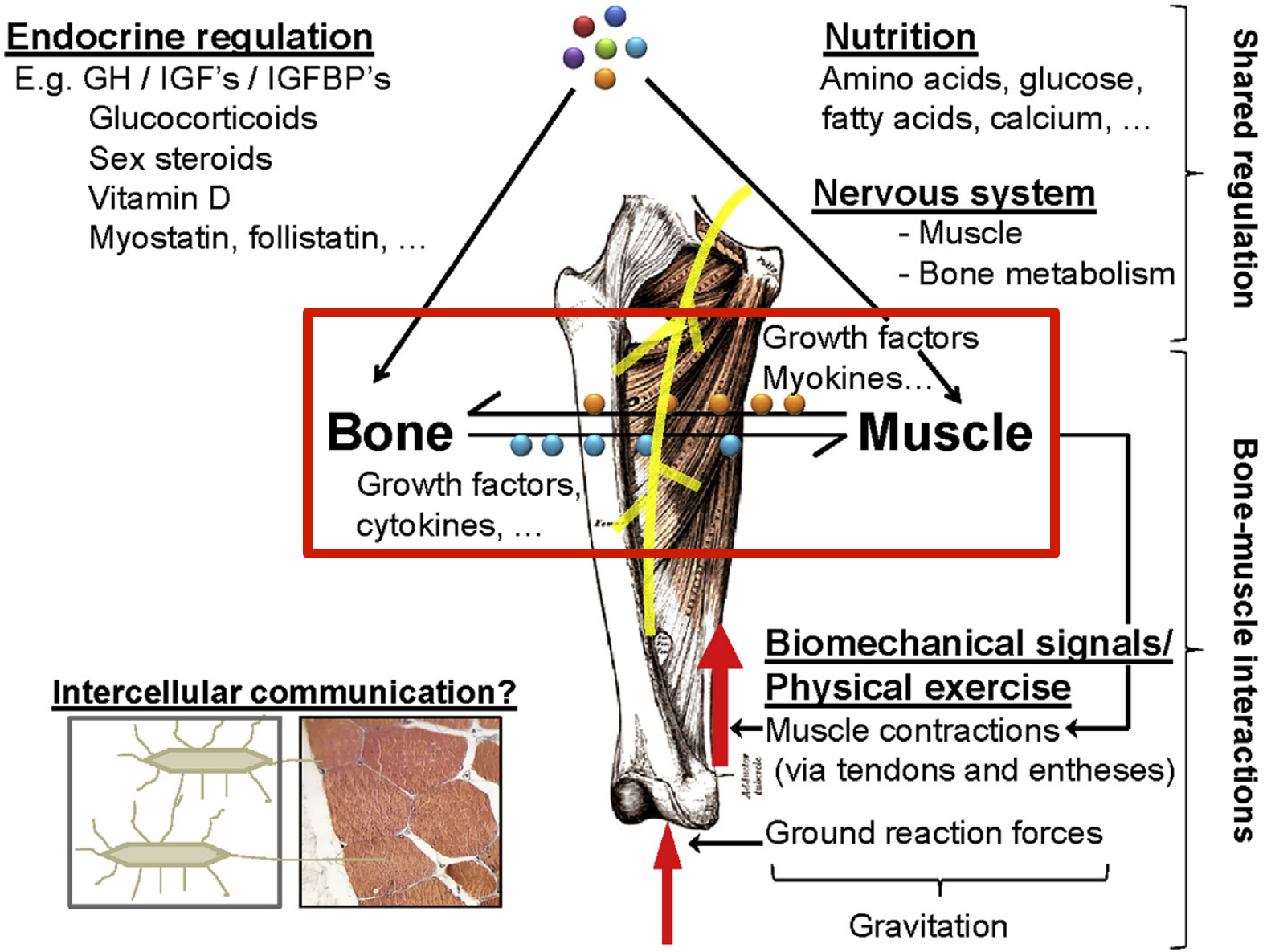
- **putative intercellular communication between bone and muscle cells**.

Schematic overview of mechanisms involved in muscle-bone interactions



Laurent MR et al, Mol Cell Endocinol 2016

Schematic overview of mechanisms involved in muscle-bone interactions



Laurent MR et al, Mol Cell Endocinol 2016

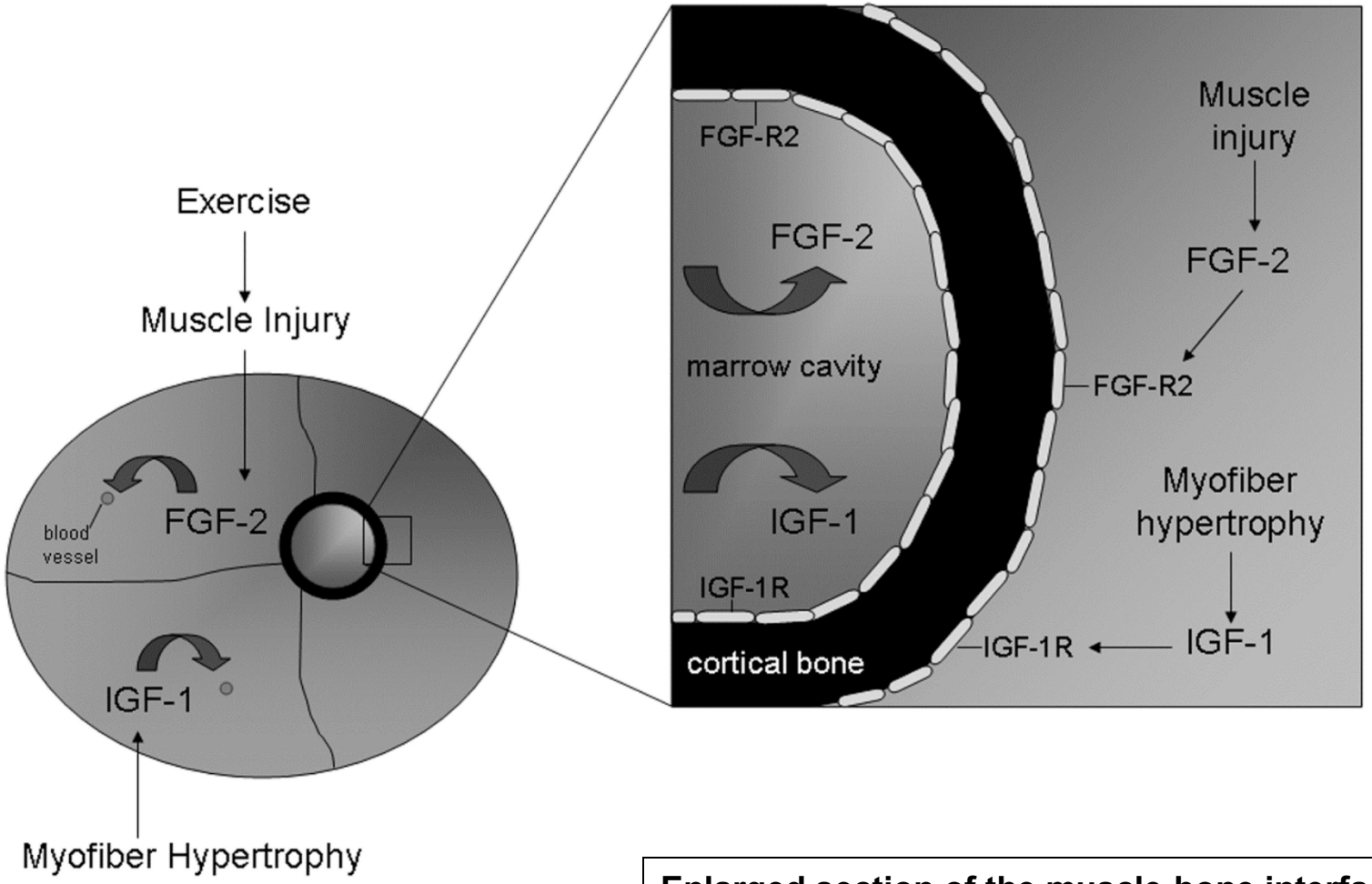
Growth factors, cytokines and other peptides secreted by muscle, the factors that influence their secretion and their potential effects on bone metabolism

Muscle-derived peptides	*Factors that stimulate peptide secretion*	*Role(s) in bone metabolism*
Growth factors		
IGF-1	Resistance exercise	Stimulates bone formation
FGF-2	Eccentric muscle contraction	Stimulates bone formation
GDF-8	Muscle damage, cachexia, atrophy	Suppresses chondrogenesis and fracture healing
Extracellular matrix molecules		
SPARC	Resistance exercise, muscle regeneration	Promotes bone mineralization
MMP-2	Resistance exercise and re-loading	Fracture callus remodeling, bone formation
BMP-1	Blast trauma to muscle	Cleaving of procollagen and possibly heterotopic ossification
Inflammatory cytokines		
IL-6	Physical activity and muscle contraction	Bone resorption and turnover
IL-7	Physical activity and muscle contraction	Bone resorption
IL-15	Resistance exercise	Increase bone mass, decrease adiposity

Abbreviation: IL, interleukin.

Hamrick MW, BoneKey 2012

A Role for Myokines in Muscle-Bone Interactions

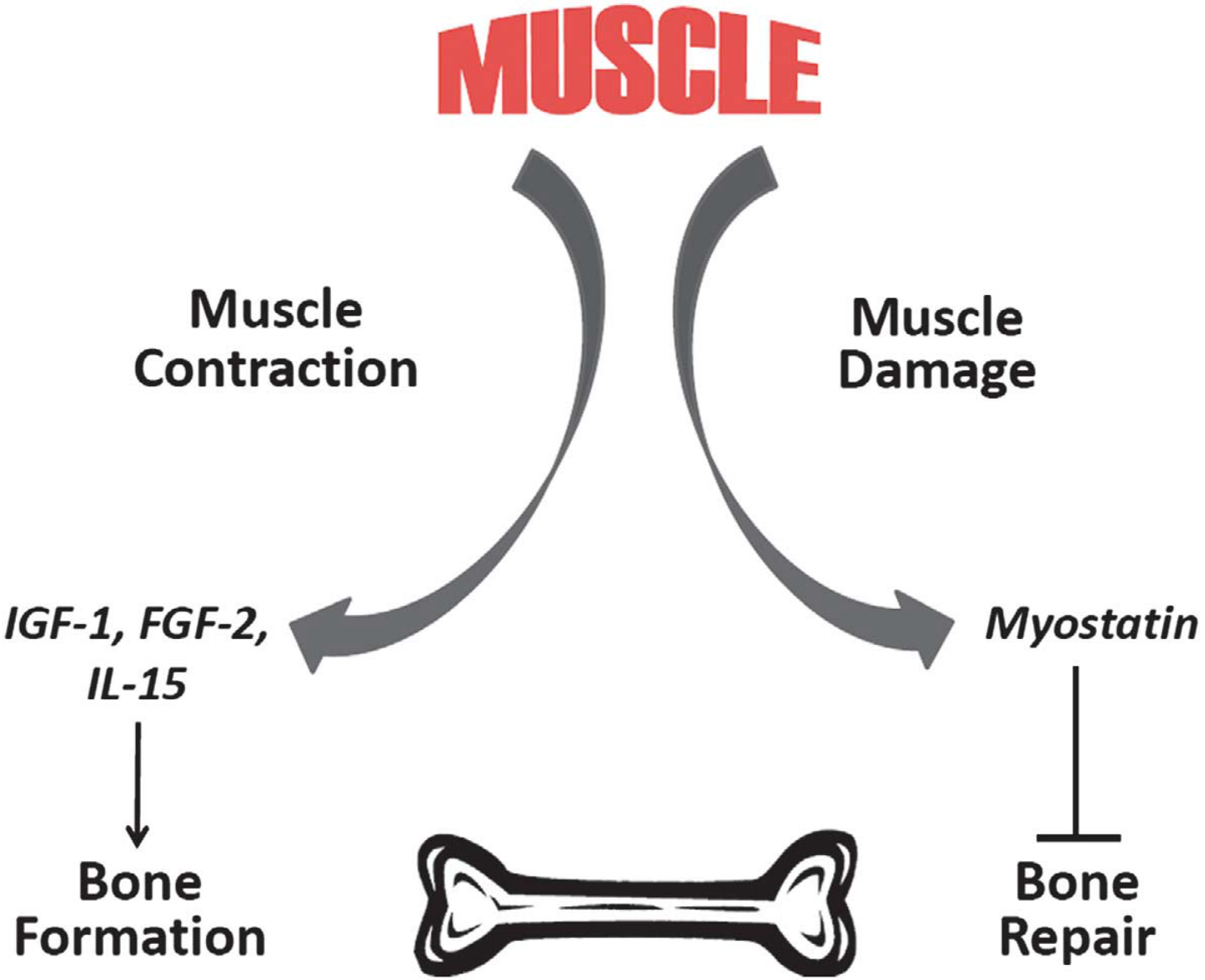


Cross-section of a proximal limb segment showing skeletal muscle surrounding bone

Enlarged section of the muscle-bone interface, showing osteoprogenitor cells lining the periosteal and endosteal surfaces of cortical bone

Hamrick WM, Exerc Sport Sci Rev 2011

Effect of resistance exercise and eccentric muscle contraction and of traumatic muscle injury and perhaps systemic inflammation and disuse

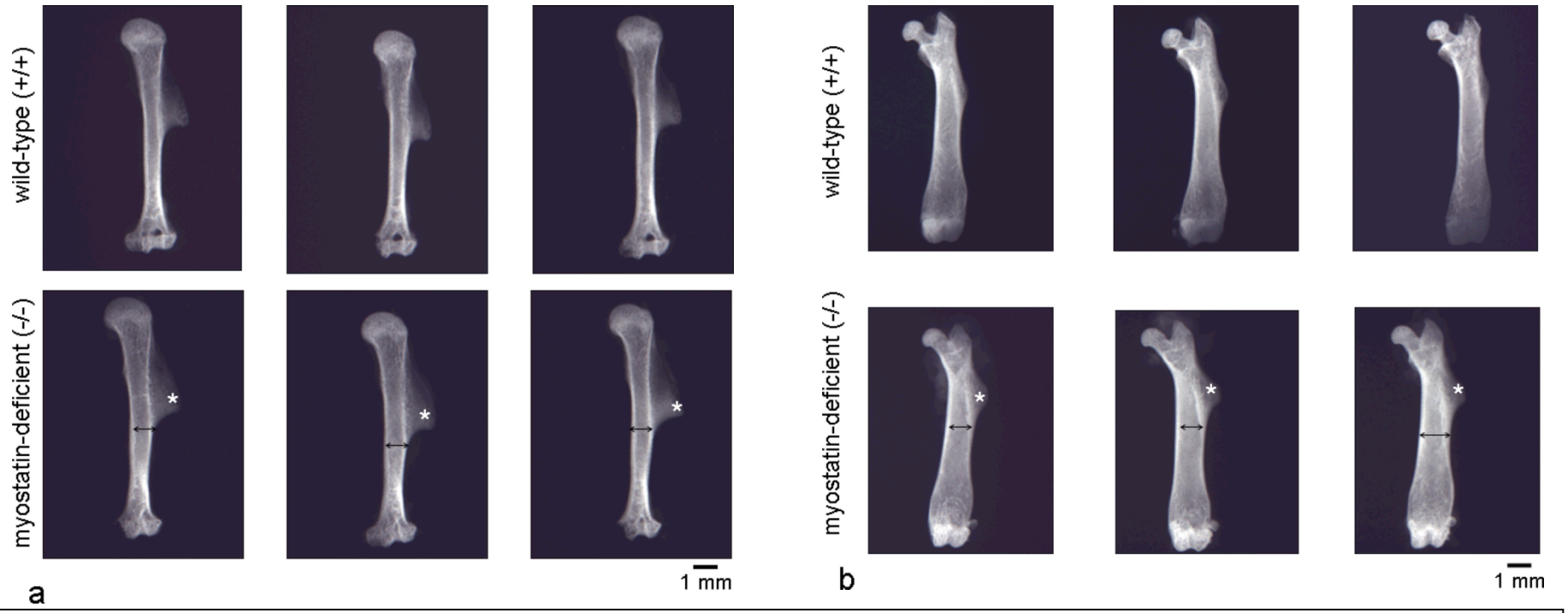


Hamrick MW, BoneKey 2012

J Musculoskelet Neuronal Interact. 2010 March ; 10(1): 56–63.

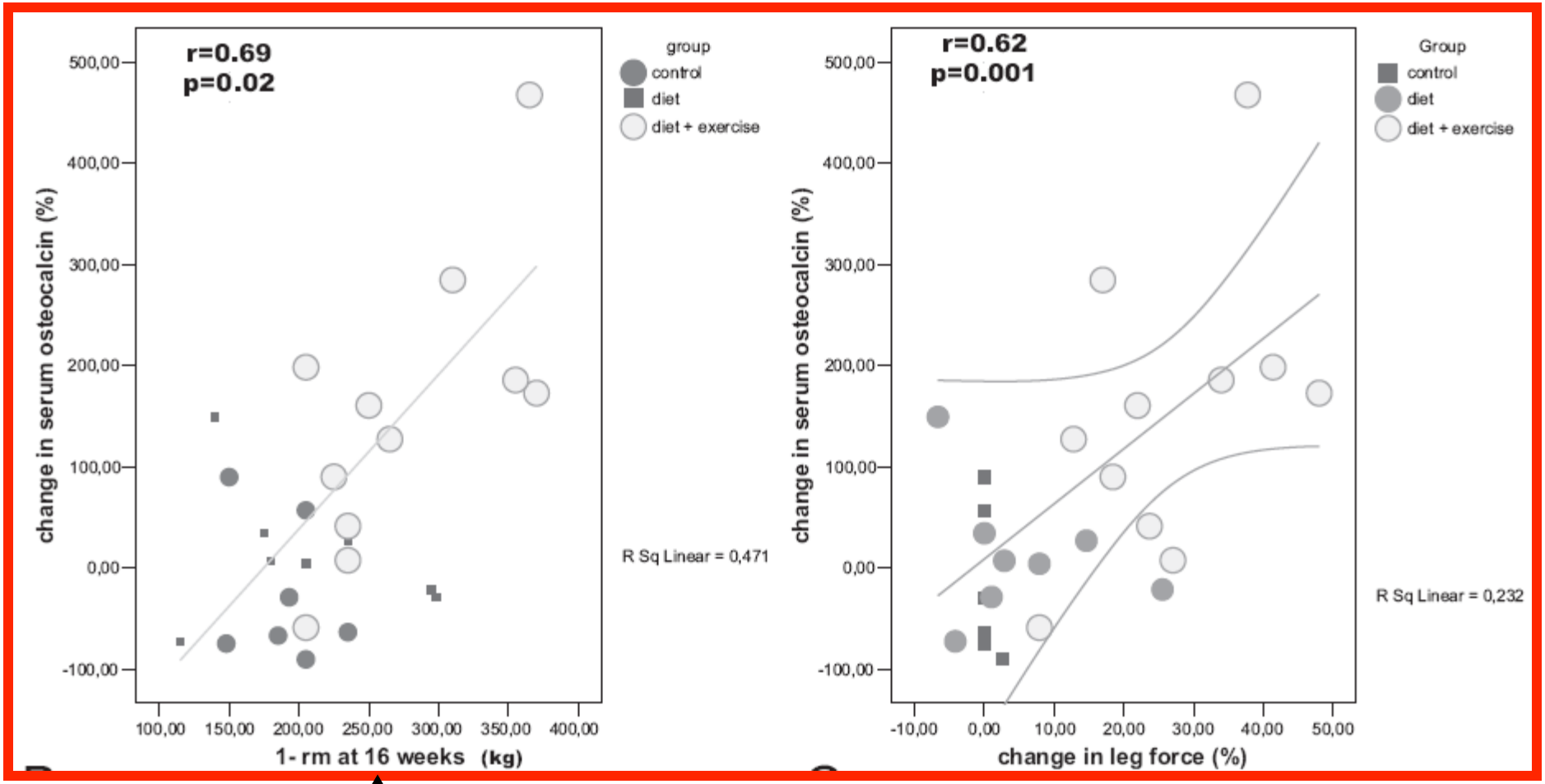
Myostatin (GDF-8) as a Key Factor Linking Muscle Mass and Skeletal Form

Moataz N. Elkasrawy* and **Mark W. Hamrick**



Radiographs demonstrating increased shaft diameter and increased muscle attachment site at the deltoid crest in humerus (a), and the third trochanter in femur (b) in Myostatin−/− mice compared to wild type. Notice the extension of the articular surface towards the neck of the femur (b)

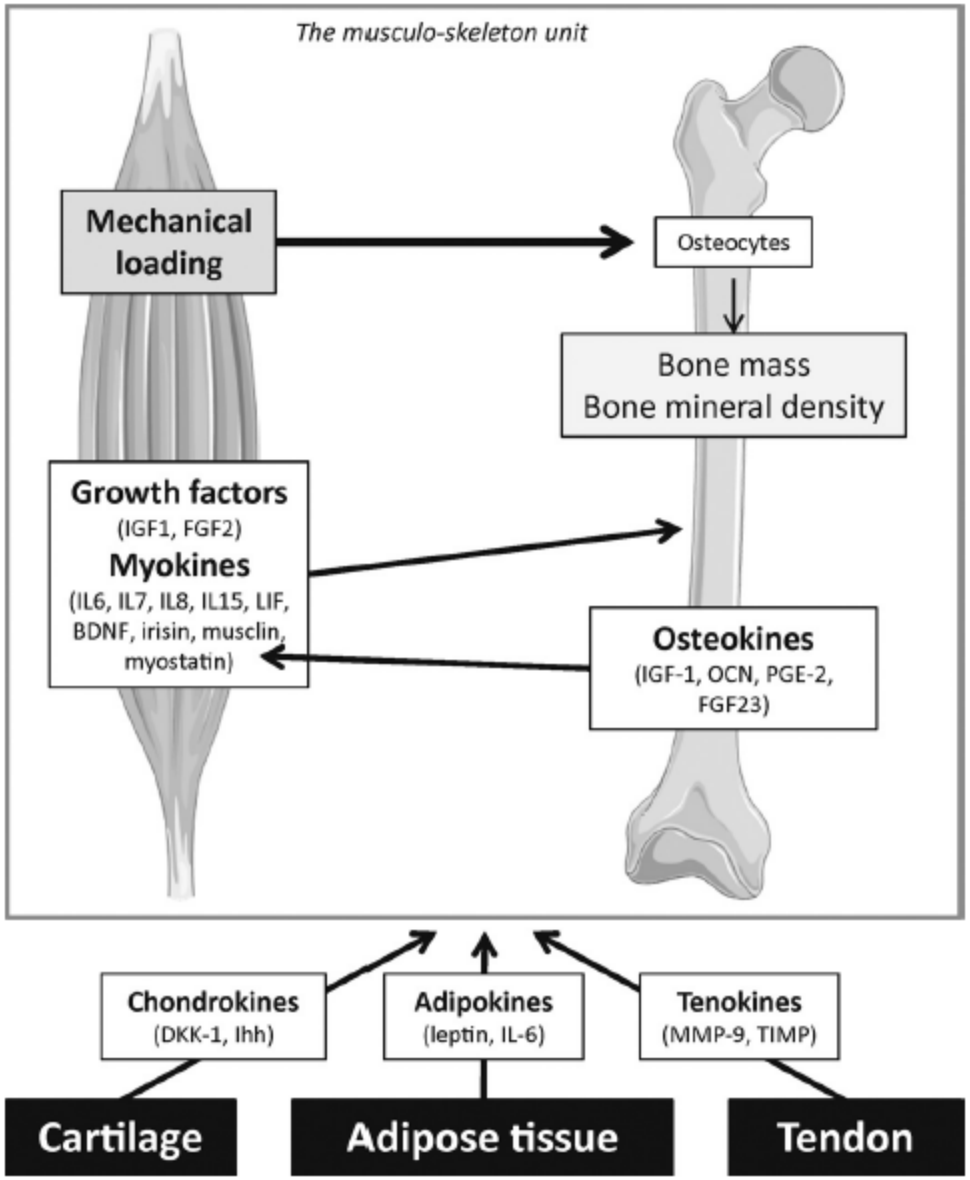
Factors associated with changing osteocalcin in obese women enrolled in the slight weight loss intervention



absolute leg force (1-rm)

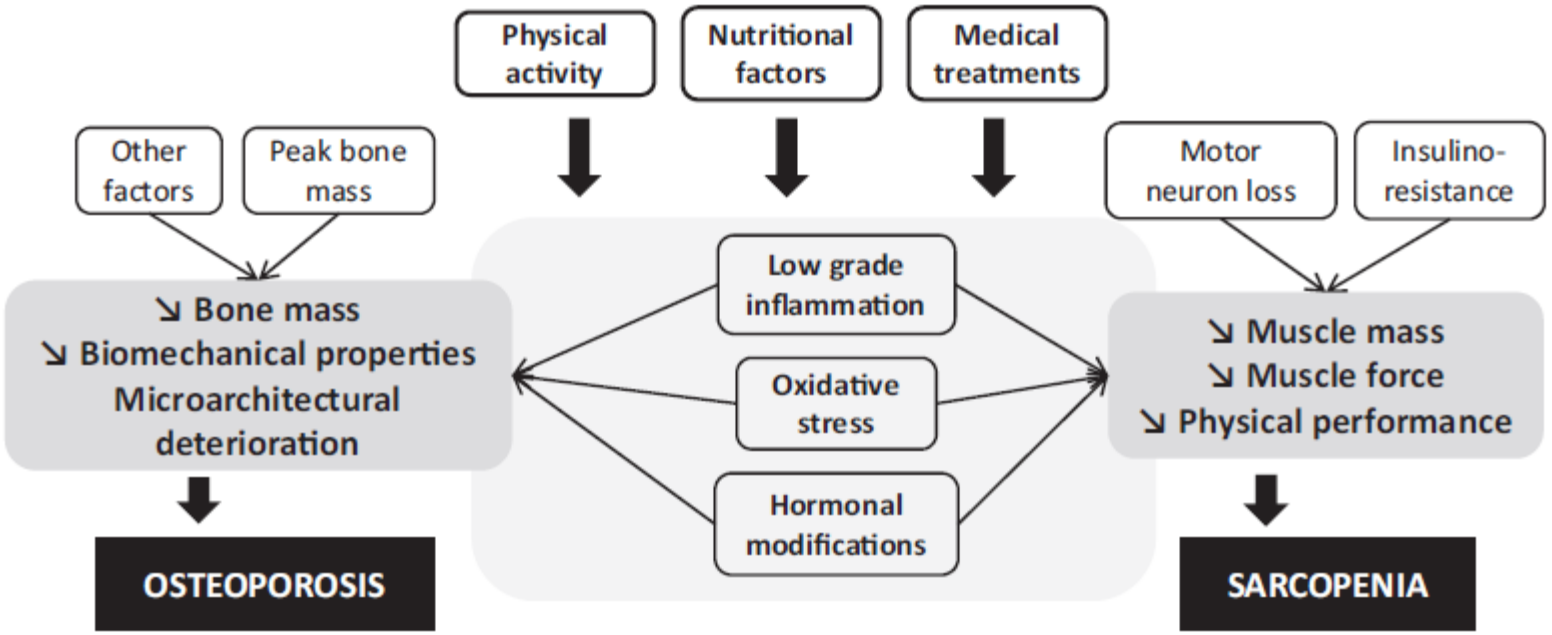
Fernandez-Real JM et al, JCEM 2009

The muscle-bone unit



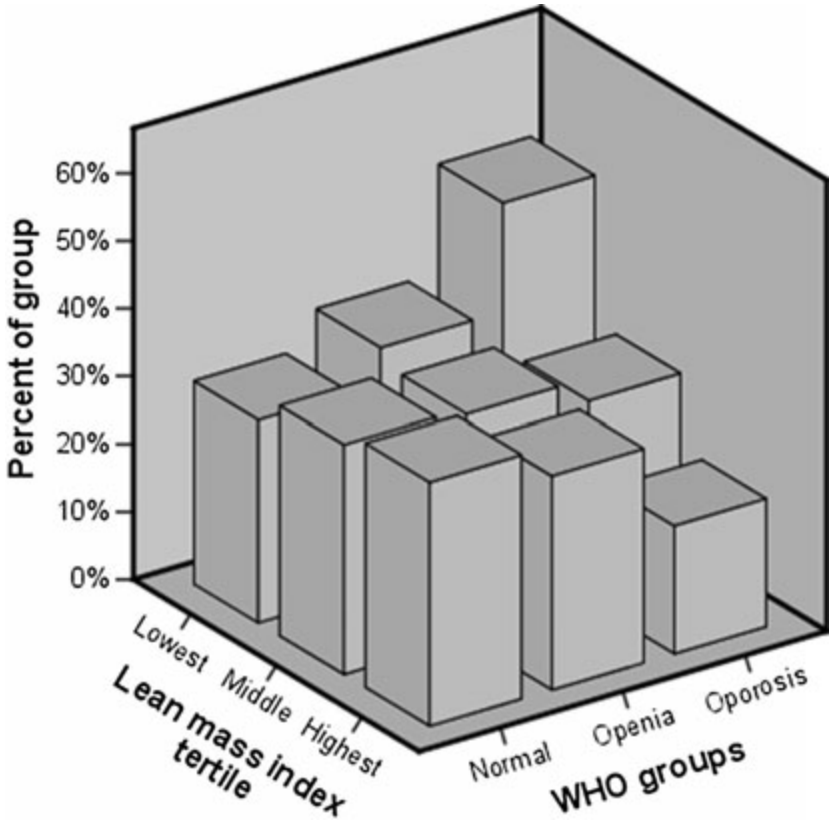
Tagliaferri C et al, Ageing Research Reviews 2015

Common and separate causes of osteoporosis and sarcopenia



Tagliaferri C et al, Ageing Research Reviews 2015

Muscle Strength and Body Composition Are Clinical Indicators of Osteoporosis



Rikkonen T et al, CTI 2012

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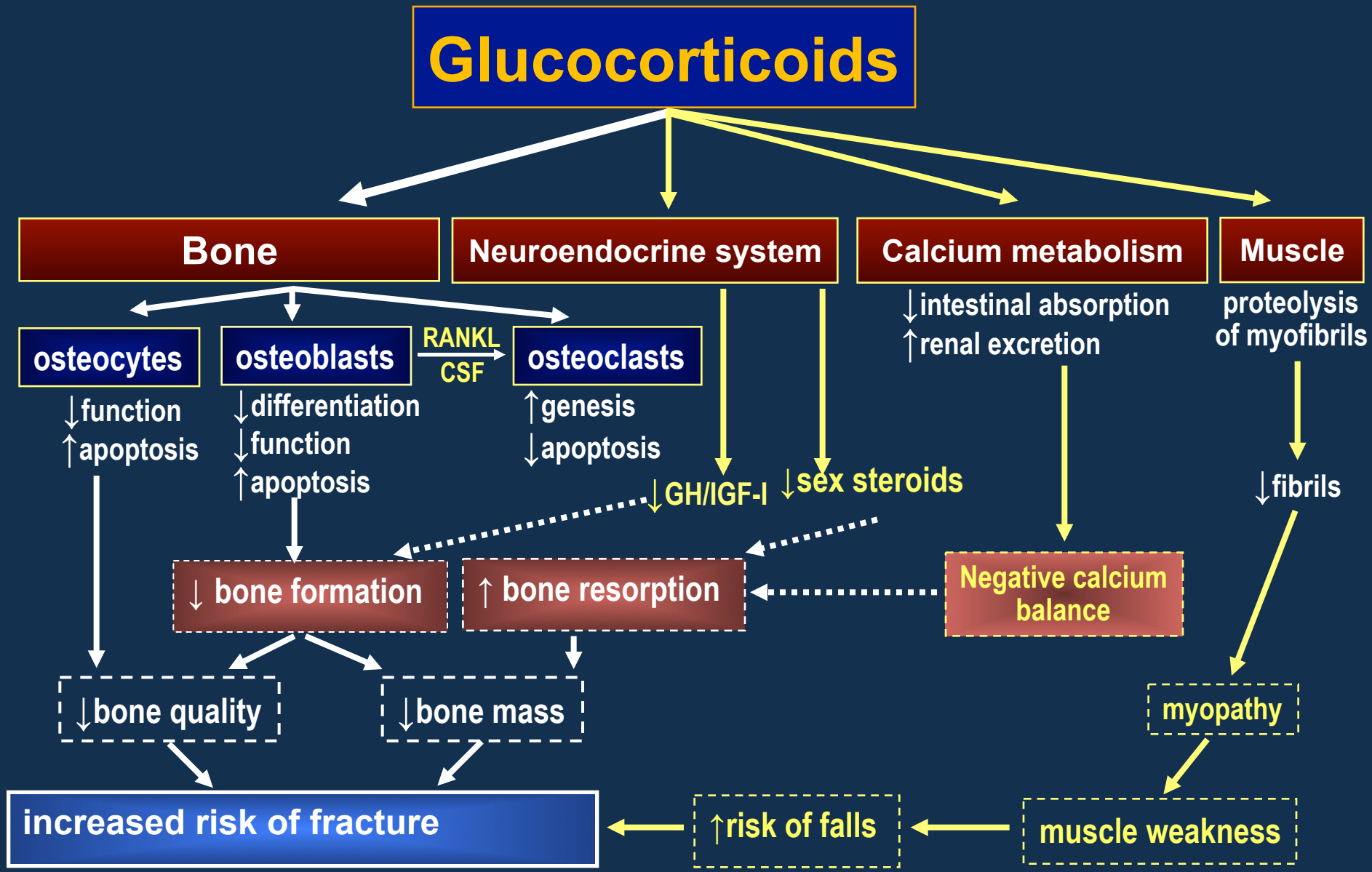
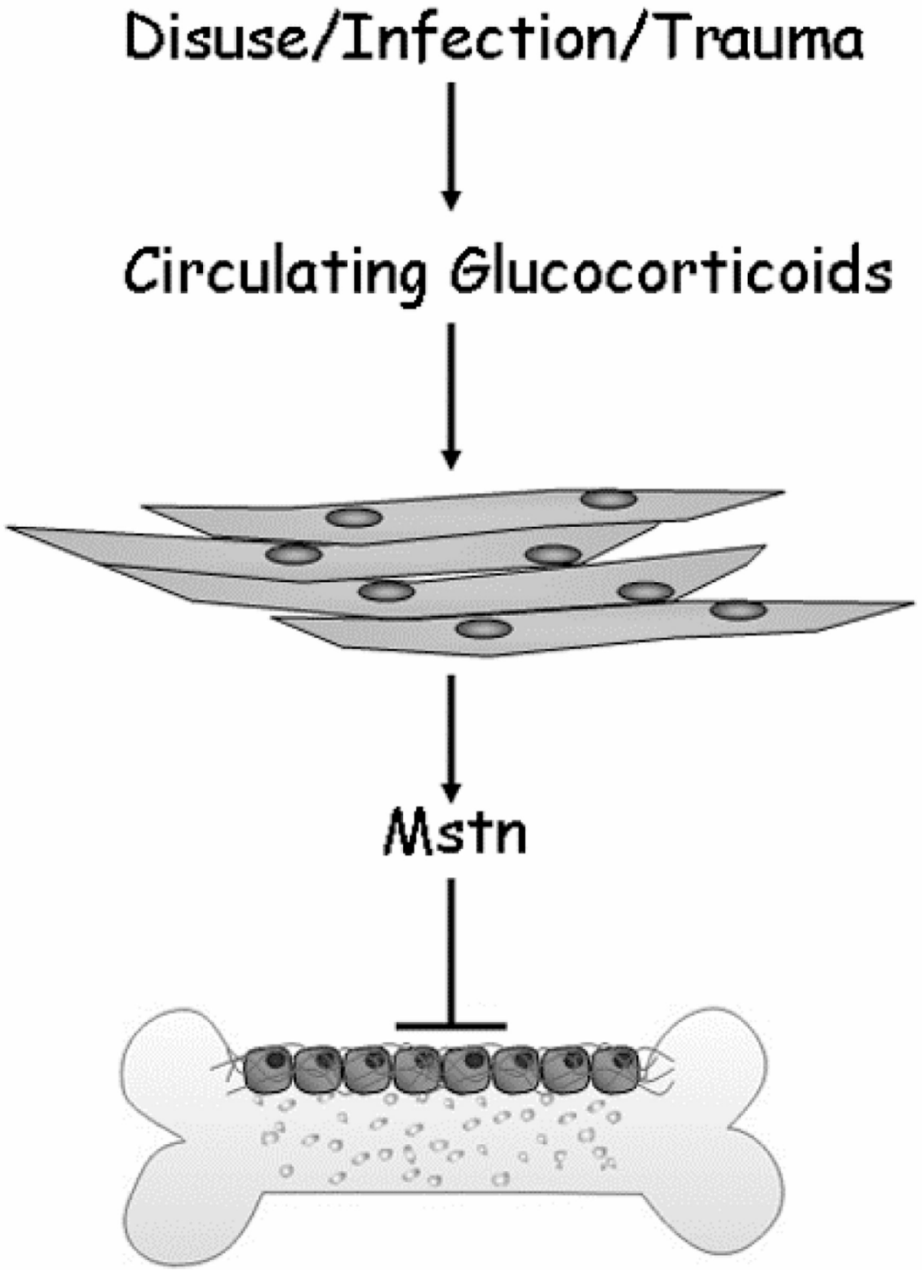
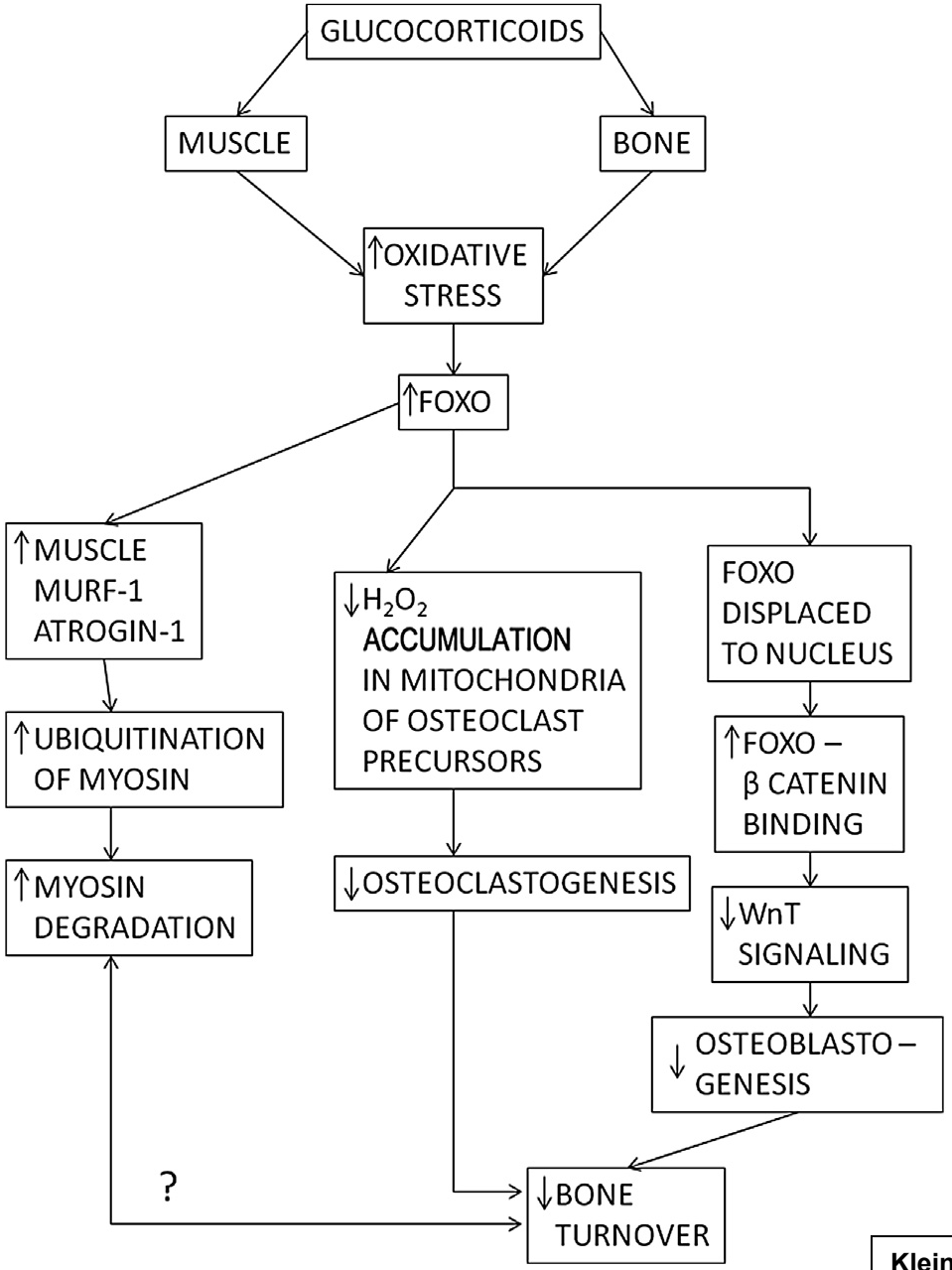


Canalis E. et al., Osteoporos. Int., 2007



Hamrich MW, Exerc Sport Sci Rev. 2011

Proposed common pathway of oxidative damage to both bone and muscle



Klein GL, Osteopor osSarcop enia 2015

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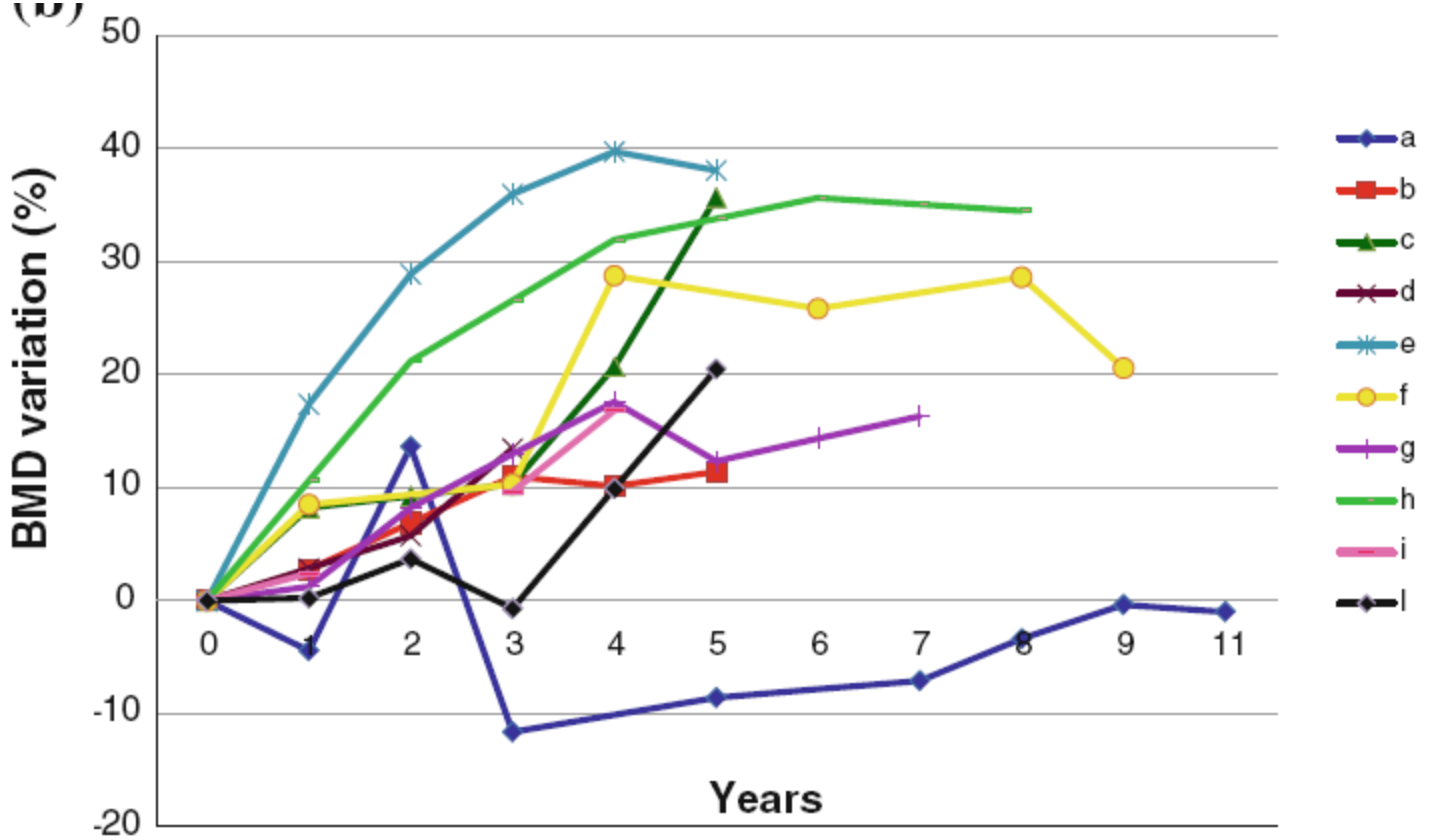
Spontaneous recovery of bone mass after cure of endogenous hypercortisolism



Randazzo ME et al, Pituitary 2012

Body Composition and Cardiovascular Risk Markers after Remission of Cushing's Disease: A Prospective Study Using Whole-Body MRI

Eliza B. Geer, Wei Shen, Erika Strohmayer, Kalmon D. Post, and Pamela U. Freda

TABLE 2. Body composition measurements

Measure (kg)	Active CD	Remission	Difference	Change (%)	Value decreased (no. of patients)	*P* value[a]
VAT	4.59 ± 2.68	3.21 ± 2.05	−1.38	−29.3	12	0.004
Pelvic BMAT[b]	0.26 ± 0.11	0.19 ± 0.09	−0.07	−20.5	11	0.012
TrSAT	19.54 ± 7.35	15.72 ± 7.92	−3.82	−21.9	12	0.0005
Limb SAT	13.82 ± 7.33	12.01 ± 7.29	−1.81	−14.8	13	0.001
Total SAT	33.36 ± 14.10	27.69 ± 14.33	−5.67	−19.1	13	0.0001
TAT	39.21 ± 14.15	32.00 ± 15.43	−7.21	−20.5	12	0.0002
IMAT	1.18 ± 0.46	1.10 ± 0.57	−0.08	−4.8	9	0.512
SM	21.18 (19.4–22.9)	19.58 (18.6–23.2)	−1.60	−4.5	10	0.02
Limb SM	11.04 (9.92–12.66)	10.86 (9.84–11.67)	−0.18	−2.9	10	0.12
VAT/SM	0.20 ± 0.09	0.14 ± 0.07	−0.06	−26.1	12	0.006
VAT/TAT	0.13 ± 0.09	0.11 ± 0.08	−0.02	−13.9	13	0.04

Data are presented as mean ± SD or median (interquartile range). *P* values are from Ln (natural logarithm) values.

[a] From paired *t* test.

[b] For pelvic BMAT, n = 13 (patient 12 had metal artifact in right femur).

Treatment of glucocorticoid-induced osteoporosis

Growth hormone

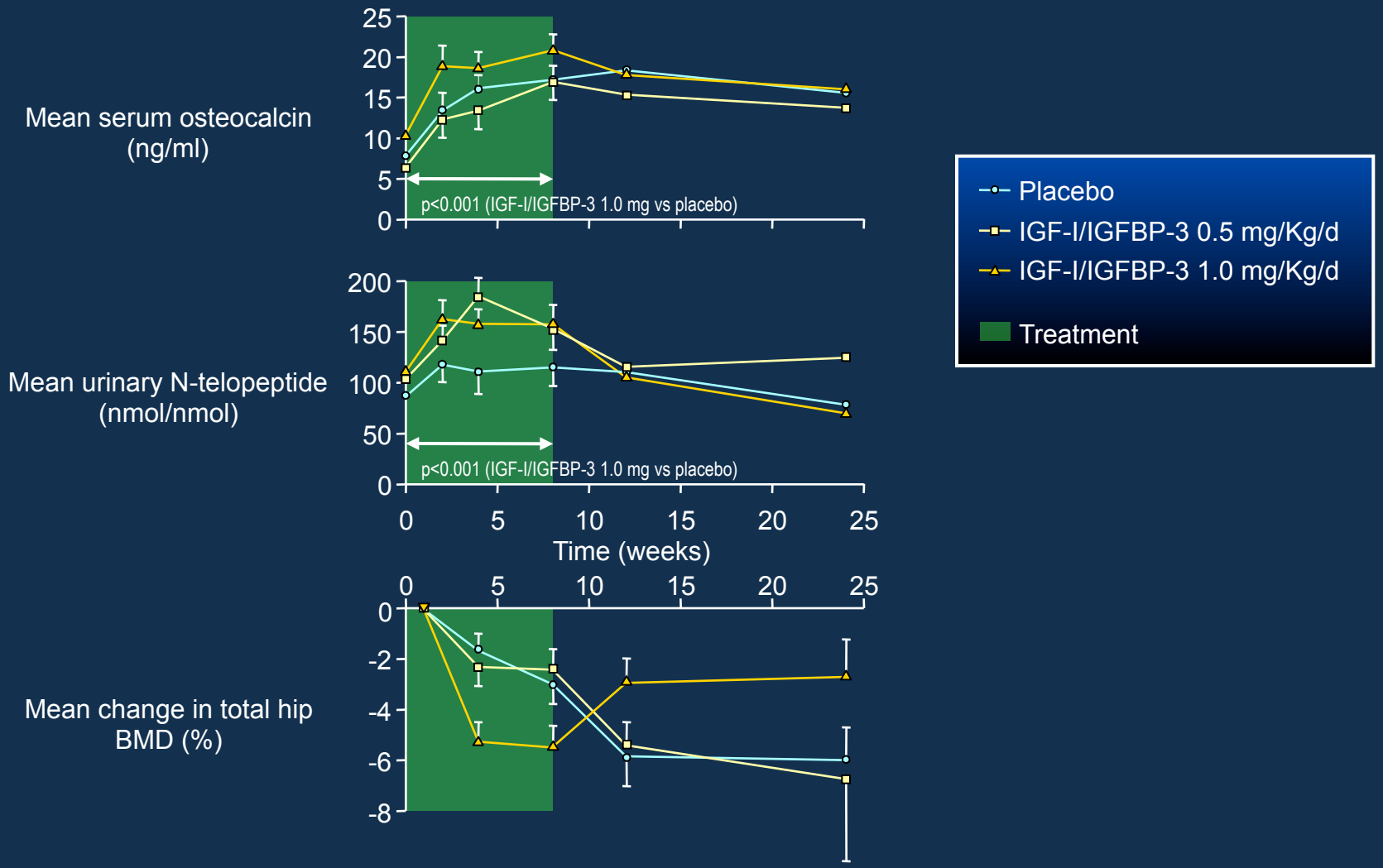
Glucocorticoids decrease the skeletal production of IGF-1, exert negative effects on GH secretion and cause a state of 'functional GH deficiency'. GH deficiency may contribute to.GIO.
Consequently, GH or IGF-I administration could revert some of the negative effects of chronic glucocorticoids on the skeleton. However, glucocorticoids decrease the activity of GH on skeletal cells and there are no controlled trials to determine the effectiveness of either GH or IGF-I as treatments for GIO.

Combined therapy of GH and IGF-I counteracts selected negative effects of glucocorticoids on bone in healthy volunteers, receiving short-term glucocorticoid therapy.

However, the efficacy and safety of GH and IGF-I treatment in GIO is unknown and well-designed prospective controlled studies are necessary before their use can be recommended.

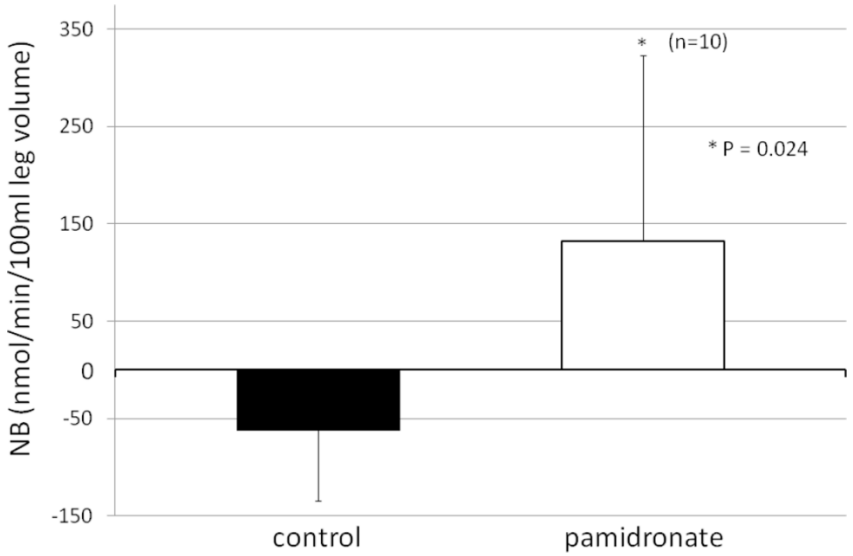
Mazziotti G et al, Therapeutic Advances in Musculoskeletal Disease

Changes during treatment and follow-up

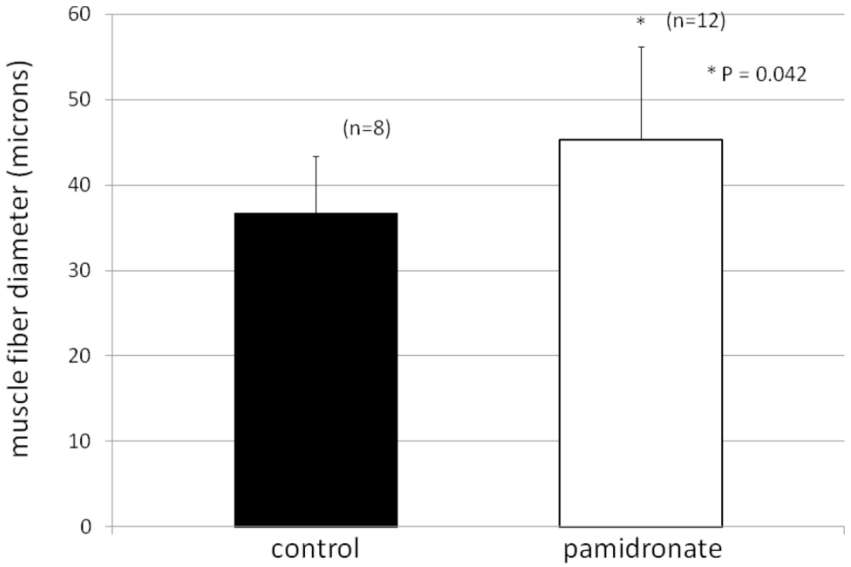


Boonen S. et al., J. Clin. Endocrinol. Metab., 2002

PAMIDRONATE ATTENUATES MUSCLE LOSS FOLLOWING PEDIATRIC BURN INJURY



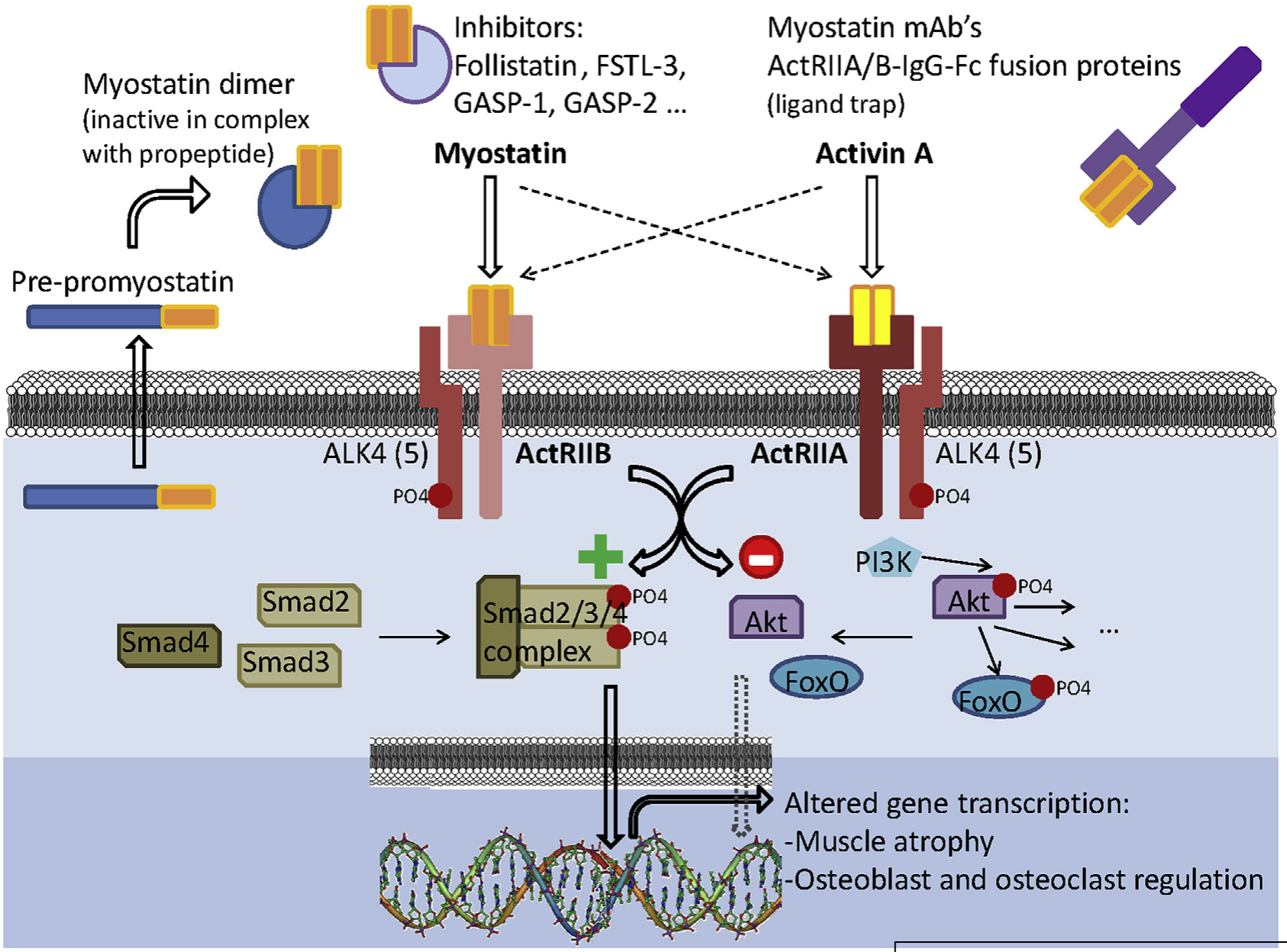
Net balance (NB, synthesis minus breakdown) of phenylalanine as calculated from the arterio-venous difference in phenylalanine concentration multiplied by the blood flow and expressed as nmol/min/100 ml leg volume.



Muscle fiber diameter from m. vastus lateralis biopsies of subjects receiving either pamidronate or placebo and expressed in microns.

Børsheim E et al, JBMR 2014

Schematic overview of myostatin and activin A signaling via activin receptors



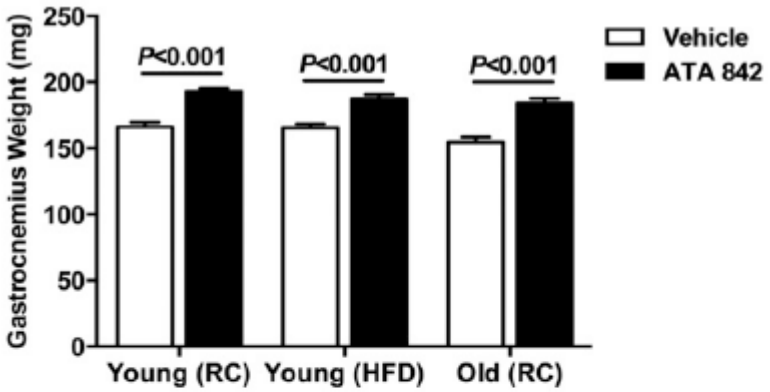
Laurent MR et al, Mol Cell Endocinol 2016

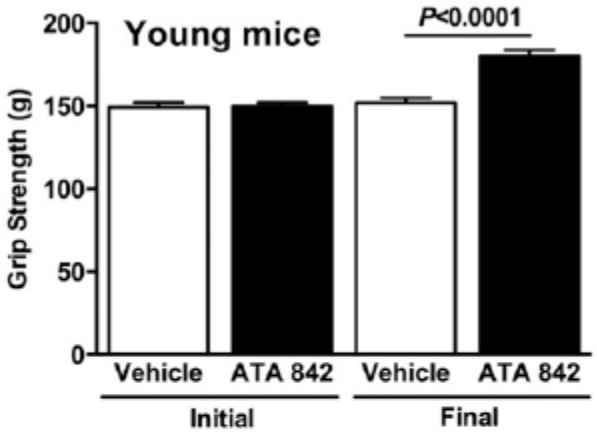
Anti-myostatin antibody increases muscle mass and strength and improves insulin sensitivity in old mice

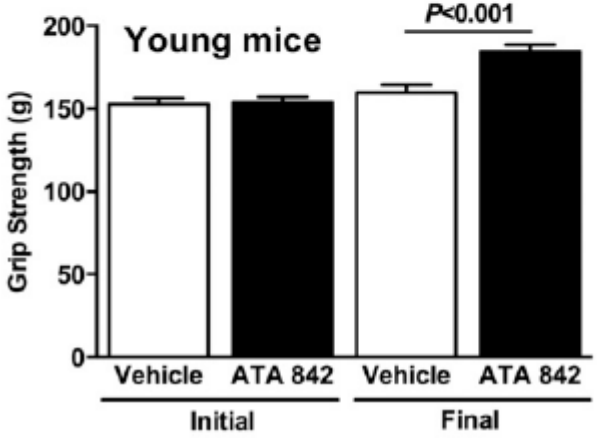
João-Paulo G. Camporez[a], Max C. Petersen[a,b], Abulizi Abudukadier[a], Gabriela V. Moreira[a], Michael J. Jurczak[c], Glenn Friedman[d], Christopher M. Haqq[d], Kitt Falk Petersen[a], and Gerald I. Shulman[a,b,e,1]

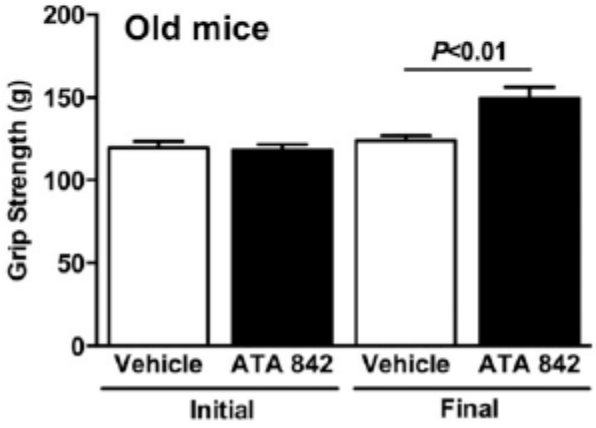
[a]Department of Internal Medicine, Yale University School of Medicine, New Haven, CT 06520; [b]Department of Cellular and Molecular Physiology, Yale University School of Medicine, New Haven, CT 06520; [c]Division of Endocrinology and Metabolism, Department of Medicine, University of Pittsburgh, Pittsburgh, PA 15261; [d]Atara Biotherapeutics, Westlake Village, CA 91363; and [e]Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT 06520

Contributed by Gerald I. Shulman, January 12, 2016 (sent for review November 29, 2015; reviewed by Se-Jin Lee and Michael O. Thorner)

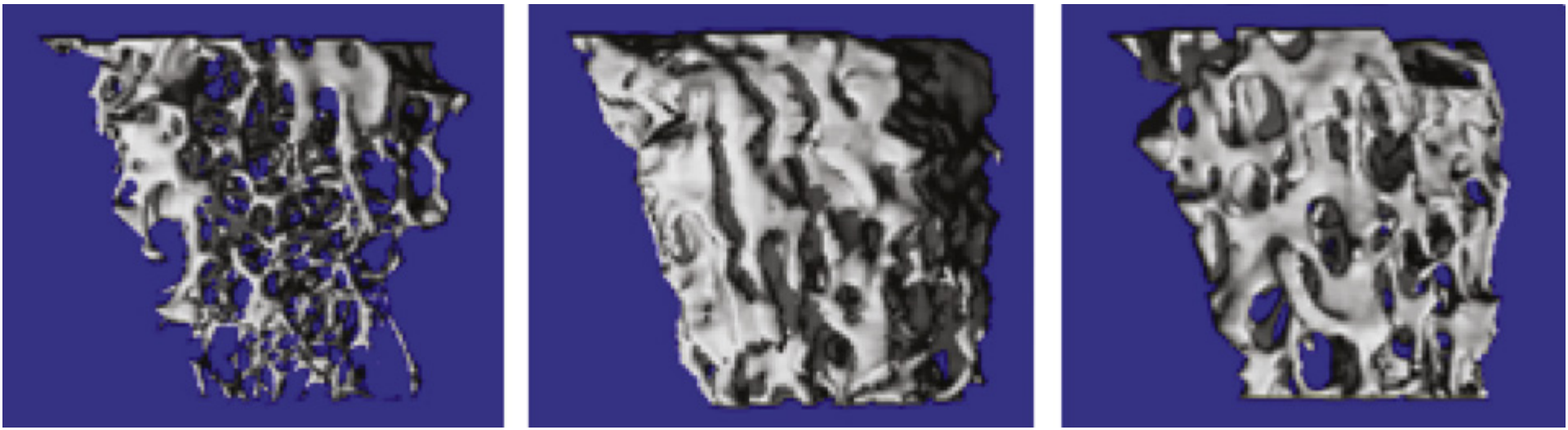








A myostatin and activin decoy receptor enhances bone formation in mice



Vehicle

ActRIIB-Fc

PTH

ActRIIB-Fc increases both muscle and bone mass in mice

Bialek P et al, Bone 2014

BIMAGRUMAB

- ✓ A human antiActRIIB antibody, is currently investigated for muscle wasting disorders

- ✓ It has been found effective in a randomized trial subjects with inclusion body myositis and was recently granted FDA orphan drug approval based on this trial

- ✓ It Prevents glucocorticoid-induced muscle wasting in animal model