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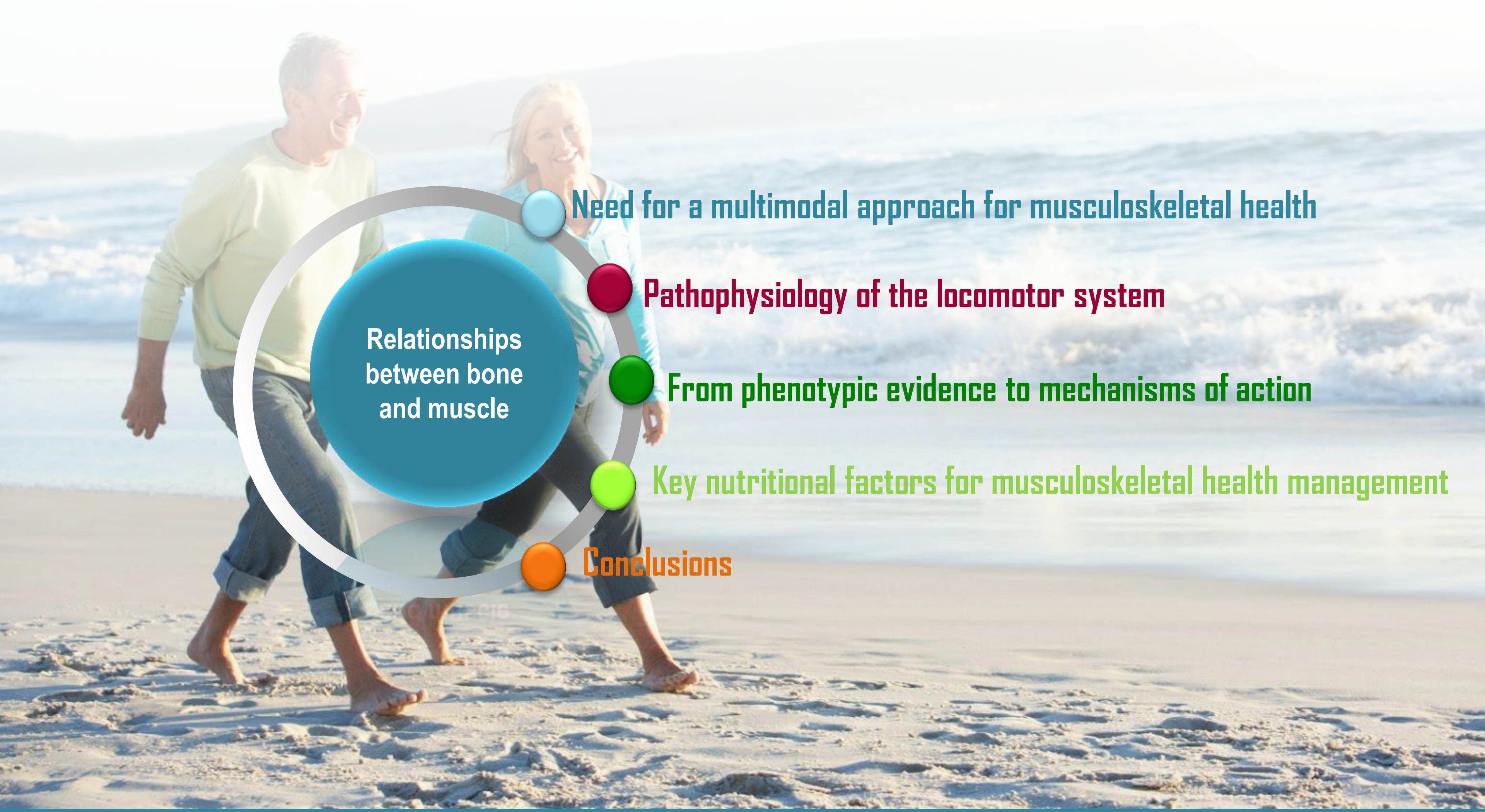
CERIN SYMPOSIUM

Osteosarcopenia: cross-talking between muscle and bone

Malaga, Saturday 16th April 2016

Relationships between bone and muscle the mechanical framework for movement



Need for a multimodal approach

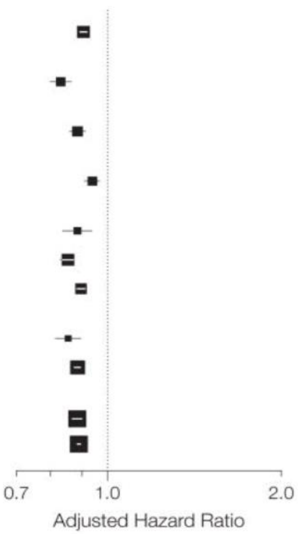
An evolution toward holism

- A shift toward a new holistic paradigm to take into account biological complexity
- A new perspective from «organ disease» to «system/function disease»

- Major role of the musculoskeletal system in the elderly : gait speed and survival

A 0.1 m/s ↘ in gait speed or a 1 SPPB point ↘ over 1 year significantly ↘ 5- and 10 year survival
(Perera, J Gerontol 2005)

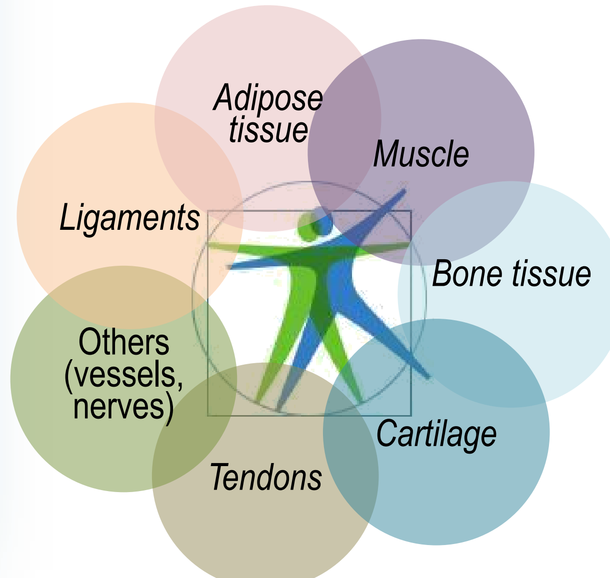
	No. of Deaths	Total Sample Size
Cardiovascular Health Study,[22] 1991	3851	5801
Established Populations for the Epidemiologies Study of the Elderly,[23] 1985	1955	2128
Health, Aging, and Body Composition Study,[11,12] 2009, 2005	848	3048
Hispanic Established Populations for Epidemiological Study of the Elderly,[13] 1999	972	1905
Invecciare in Chianti,[17] 2000	187	972
Osteoporotic Fractures in Men,[20] 2005	1073	5833
Third National Health and Nutrition Examination Study,[21] 2004	2837	3958
Predicting Elderly Performance,[28] 2003	293	491
Study of Osteoporotic Fractures,[26] 1990	5512	10349
Pooled (random effects)		
Pooled (shared frailty model)		



Age-Adjusted Hazard Ratio for Death per 0.1-m/s Higher Gait Speed

Multimodal approach
Formulate systems- level interpretation of biological phenomena

- Musculoskeletal system



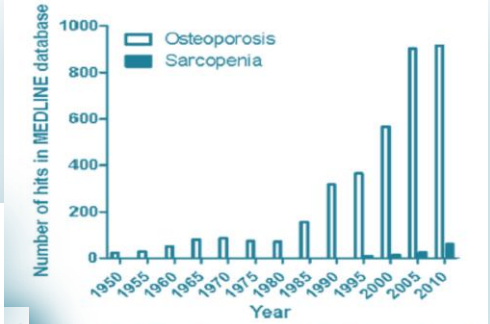
Mounting evidence of inter-organ cross talk → Functional decline, Disability

System biology based approaches represent a true challenge for human health

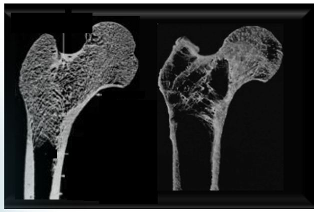
Need for a multimodal approach

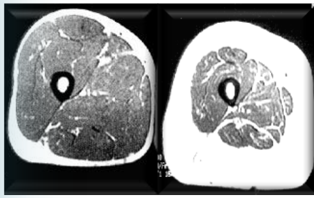
A recent awareness of the problem

- Musculoskeletal health



g. 2. Amount of hits in the MEDLINE database with the term “osteoporosis” (white rs) and “sarcopenia” (black bars). Both terms were entered as a single term in the EDLINE database search engine per year with 5-year intervals.





« Dysmobility syndrome »

Aging Clin Exp Res. 2015 Nov 12. [Epub ahead of print]

Osteosarcopenia is more than sarcopenia and osteopenia alone.

Drey M[1], Sieber CC[2], Bertsch T[3], Bauer JM[4], Schmidmaier R[5]; FiAT intervention group.

PERSPECTIVE JBMR

Bone and Skeletal Muscle: Neighbors With Close Ties

Douglas J DiGirolamo,[1] Douglas P Kiel,[2] and Karyn A Esser[3]

Osteoporos Int (2013) 24:87–98

ORIGINAL ARTICLE

Sarcopenia and its relationship with bone mineral density in middle-aged and elderly European men

S. Verschueren · E. Gielen · T. W. O'Neill · S. R. Pye · J. E. Adams · K. A. Ward · F. C. Wu · P. Szulc · M. Laurent · F. Claessens · D. Vanderschueren · S. Boonen

Clinical Interventions in Aging — Dovepress

ORIGINAL RESEARCH

Muscular strength measurements indicate bone mineral density loss in postmenopausal women

Zhixiong Zhou[1,2], Lu Zheng[2], Dengyun Wei[3]

Background: The literature is inconsistent and inconclusive on the relationship between bone mineral density (BMD) and muscular strength in postmenopausal women.

Objective: To evaluate the relationship between isokinetically and isometrically determined

Maturitas. 2013 Jun;75(2):175-80. doi: 10.1016/j.maturitas.2013.03.016. Epub 2013 Apr 28.

Relationship between postmenopausal osteoporosis and the components of clinical sarcopenia.

Sjöblom S, Suuronen J, Rikkonen T, Honkanen R, Kröger H, Sirola J.

Osteoporos Int
DOI 10.1007/s00198-013-2427-1

OPINION PAPER

What's in a name revisited: should osteoporosis and sarcopenia be considered components of "dysmobility syndrome?"

N. Binkley · D. Krueger · B. Buehring

Reginster JY, Beaudart C, Buckinx F, Bruyère O. Osteoporosis and sarcopenia: two diseases or one? Curr Opin Clin Nutr Metab Care. 2016 Jan;19(1):31-6.

Associations of fat and muscle masses with bone mineral in elderly men and women[1–3]

Richard N Baumgartner, Patricia M Stauber, Kathleen M Koehler, Linda Romero, and Philip J Garry

PERSPECTIVE JBMR

Forum on Bone and Skeletal Muscle Interactions: Summary of the Proceedings of an ASBMR Workshop

Lynda F Bonewald,[1] Douglas P Kiel,[2] Thomas L Clemens,[3] Karyn Esser,[4] Eric S Orwoll,[5] Regis J O'Keefe,[6] and Roger A Fielding[7]

Ageing Research Reviews — ELSEVIER
journal homepage: www.elsevier.com/locate/arr

Review

Muscle and bone, two interconnected tissues

Camille Tagliaferri[a,b,c], Yohann Wittrant[a,b], Marie-Jeanne Davicco[a,b], Stéphane Walrand[a,b], Véronique Coxam[a,b,*]

Citation: BoneKEy Reports 1, Article number: 60 (2012) | doi:10.1038/bonekey.2012.60
© 2012 International Bone & Mineral Society All rights reserved 2047-6396/12
www.nature.com/bonekey

REVIEW

The skeletal muscle secretome: an emerging player in muscle–bone crosstalk

Mark W Hamrick

Department of Cellular Biology and Anatomy, Institute of Molecular Medicine and Genetics, Georgia Health Sciences University, Augusta, GA, USA.

In vitro and *in vivo* studies provide evidence that a variety of growth factors and cytokines are actively secreted by muscle tissue. Muscle can therefore function as an endocrine and paracrine organ. These peptides characterize the muscle secretome, and many muscle-derived factors such as insulin-like growth factor-1, basic fibroblast growth factor, interleukin-15, myostatin and secreted protein acidic and rich in cysteine (osteonectin) are also known to have significant effects on bone metabolism. The factors secreted by muscle may vary according to muscle activity, in that muscle contraction, muscle atrophy or traumatic muscle injury can alter the type and relative abundance of particular factors released from muscle cells. The molecular and cellular pathways by which muscle-derived factors affect different types of bone cells (for example, osteoblasts, osteoclasts and osteocytes) are, however, poorly understood. Nevertheless, these findings further underscore the complex nature of muscle–bone interactions, and highlight the importance of integrating muscle biology and physiology into our understanding of bone growth, development and aging.

BoneKEy Reports 1, Article number: 60 (2012) | doi:10.1038/bonekey.2012.60

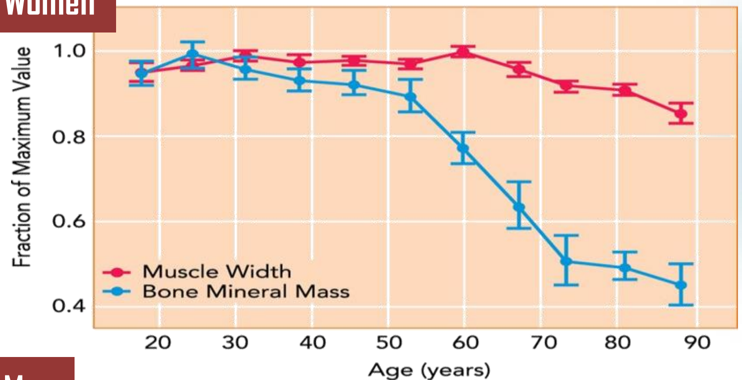
Patho-physiology

Bone and muscle, similar temporal patterns

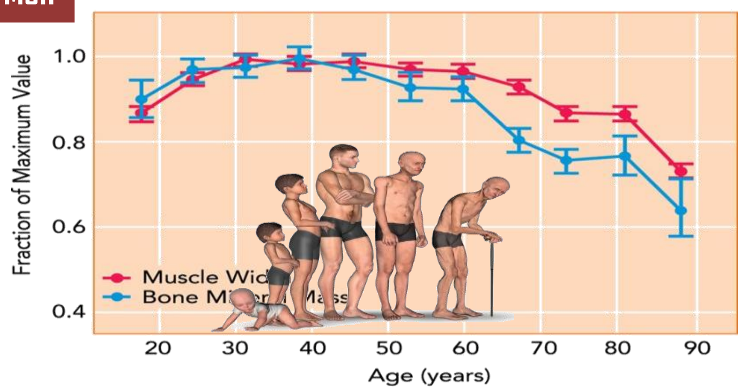
- A parallel chronological evolution throughout life

Aging-related changes in BMD of the radius and muscle width in the forearm

Women



Men



(Data were normalized to the peak value for bone and muscle across the lifespan)

(Novotny et al., Physiology 2015 ; adapted from Meema et al., Calcif Tissue Res 1973)

<u>After 50 y</u>

- **Muscle : mass ↘1-2% /y; strength loss 1.5-3% /y *(Lang et al., Osteoporosis Int 2010)***
- **Bone : loss 1-2% /y *(Riggs et al., J Bone Miner Res 2008)***

613 men and women across 11 different groups between the ages of 18–97 y

(Baumgartner et al., Am J Epidemiol 1998)

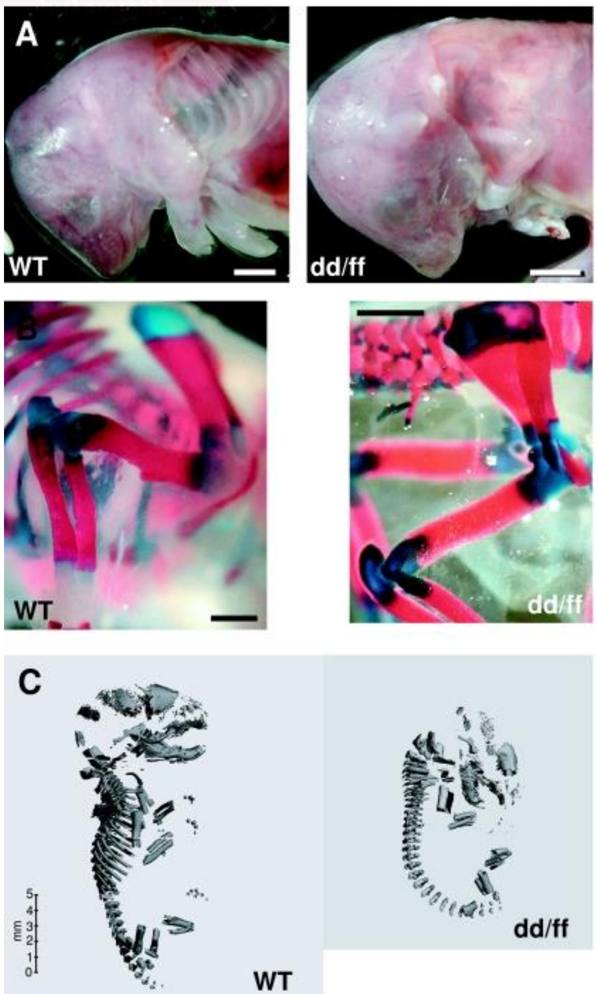
(Luna-Heredia et al., Clin Nutr 2005)

Patho-
physiology

Bone and muscle, similar temporal patterns

- During growth

→The altered morphological features of dd/ff mice (lacking muscle) and the increased bone resorption show the role of muscle activity in bone shaping and the consequences of bone unloading



MyoD-/- , Myf5-/- mice (unloading *in utero model*)

→Lack of skeletal muscle, no active movement
→Abnormal innervation
→Shape of long bones profoundly different
→Less mineralization and shorter mineralized zones
↗Osteoclast number

(A) Images of pups after removal of the skin over the thorax. In dd/ff fetuses, the gaunt outline of the limb is striking because of the absence of the bulk of the leg musculature, and the characteristic appearance of the lung lobes is visible because of the absence of ribs
(B) Whole mount preparation of forelimbs for skeletal morphometry
(C) µCT 3D reconstruction of the skeletal architecture of wild type (WT) and mutant (dd/ff) mice

(Gomez et al., J Anat 2007)

Boys suffering from Duchenne muscular dystrophy or cerebral palsy have abnormal bones (osteopenia) and increased risk of fracture

(Larson & Henderson, Pediatr Orthop 2000)

(Shaw et al., Arch Dis Child 1994)

Bone and muscle, similar temporal patterns

- During ageing, lean mass changes impact bone mass more efficiently than changes in fat composition

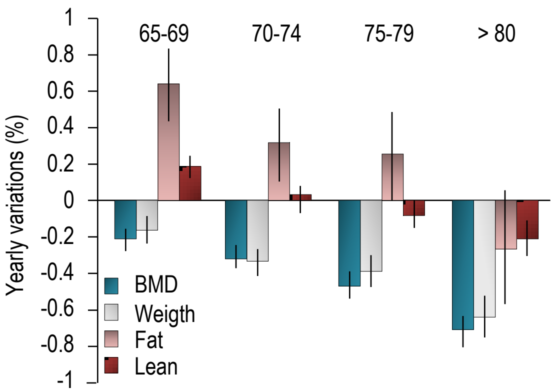
MrOS study: Correlation with BMD changes

	Partial R^2
Baseline age	0.03
Weight change	0.07
Total body lean mass change	0.09
Total body fat mass change	0.04

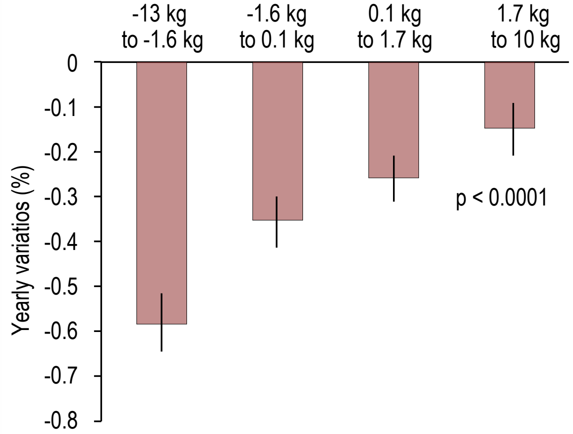
Ajustement for age, race and site

Measurements at baseline and repeated after 4.7 years on average, in 2487 men aged over 65 y

Change in hip BMD by quartile of change in weigth and body composition



Change in hip BMD by quartile of change in lean mass

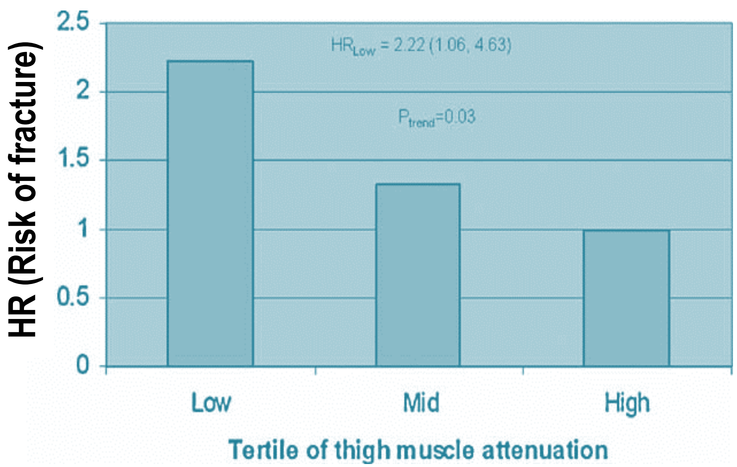


(Nielson et al., ASBMR 2009)
(Cruz-Jentoft et al., Age Ageing 2010)
(Ilich et al., Ageing Res Rev 2014)

Patho-physiology

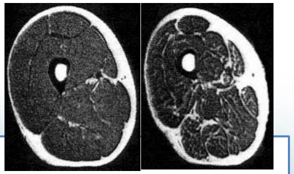
Bone and muscle, similar temporal patterns

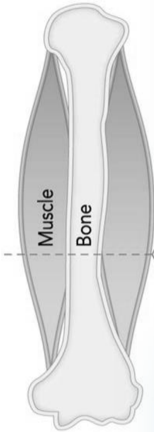
- Correlation between the skeleton and quantity but also quality of muscles



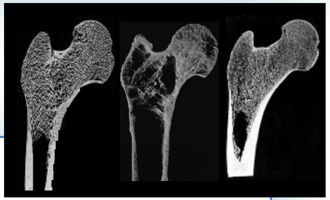
Muscle quality (thigh) predicts fracture risk regardless of the BMD

(Lang et al., J Bone Miner Res 2010)



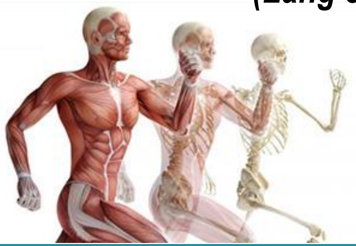


MUSCLE
- **Fatty infiltration (myosteatosis)**
- ↘ Fiber size
- Atrophy of fast-twitch fibers
- Loss of motoneurons
- Degradation of neuromuscular junction



BONE
- **Fatty infiltration of bone marrow**
- ↘Cellularity of periosteum
- ↘Osteocytes number
- ↘Periostal response to growth factors

(Novotny et al., Physiology 2015)



- **From physiology to pathology…**

Patho-physiology

Bone and muscle, similar temporal patterns

- In osteoporotic patients, the prevalence of sarcopenia is >

Osteoporosis → Sarcopenia

(Ho et al., Hong Kong Med J 2015)

	Hida et al,[30] 2013	Di Monaco et al,[32] 2012	Present study, 2015
Prevalence of sarcopenia	44.7% (M), 81.1% (F)	95% (M), 64% (F)	73.6% (M), 67.7% (F)
Definition	Japanese criterion	New Mexico Elder Health Survey	AWGS definition
Mean interval between fracture and DXA assessment (days)	Immediately after fracture and before surgery	20.9	14.2
Mean age (years)	80.3 (M), 82.7 (F)	79.7	82

Abbreviations: AWGS = Asian Working Group for Sarcopenia; DXA = dual-energy X-ray absorptiometry; F = female; M = male

The prevalence of presarcopenia (17%) and sarcopenia (58%) (European Working Group on Sarcopenia in Older People (EWGSOP) definition) **is higher in hip-fracture women (Italy)**
(Di Monaco et al., Aging Clin Exp Res 2015)

Patho-physiology

Bone and muscle, similar temporal patterns

•Conversely, sarcopenia is a risk factor for osteoporosis as well

Sarcopenia → Osteoporosis

(Sjöblom et al., Maturitas 2013)

The Finnish OSTPR-FPS study (590 postmenopausal women (mean age: 67.9y))

- **-The risk of osteoporosis is X12.9 in sarcopenic women** ($p \leq 0.01$, OR=12.9; 95% CI=3.1-53.5)
- **-The risk of falls during the preceding 12 months is 2.1X higher** ($p=0.021$, OR=2.1; 95% CI=1.1-3.9)
- **- The risk of fracture is 2.7X higher** ($p=0.05$, OR=2.732; 95% CI=1.4-5.5)

(Verschueren et al., Osteoporos Int 2013)

The European Male Ageing Study cohort (689 subjects with a mean age: 40-79y)

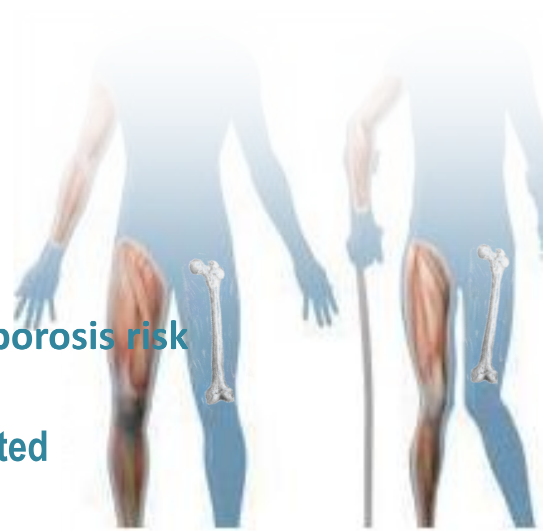
- **-Sarcopenia** (appendicular muscle <7.26 kg/m2) **is associated with a ↘ BMD**

(He et al., Osteoporos Int 2015)

A cohort of 17 891 subjects (3 ethnies: Afro-Americans, Caucasians, Chinese)

- **-The risk of osteopenia/osteoporosis is X2 in sarcopenic subjects**
- **-Each SD ↗ of the «muscular score» leads to a 37% of osteopenia/osteoporosis risk**

(Pereira et al., Arch Endocrinol Metab 2015) **Presarcopenia and sarcopenia are associated with an abnormal BMD**



Bone and muscle, similar temporal patterns

Patho-physiology

- Complication of sarcopenia: increased risk of fracture

Sarcopenia → Osteoporosis

(Cawthon et al., J Bone Min Res 2008)

Test of physical performance	*Number of fractures*	*Age-adjusted rate per 1000 person-years (95% CI)*
Repeat chair stands		
Unable (N = 135)	9	11.2 (2.1, 20.3)
Able (N = 5767)	68	2.3 (1.7, 2.8)
Narrow walk		
Unable (N = 471)	16	4.5 (1.2, 7.8)
Able (N = 5431)	61	2.3 (1.7, 2.9)
Grip strength		
Unable (N = 95)	5	12.0 (1.0, 23.0)
Able (N = 5807)	72	2.3 (1.8, 2.9)

The components of clinical sarcopenia are strongly associated with osteoporosis

(Vellas et al., Rev Méd Interne 2000)

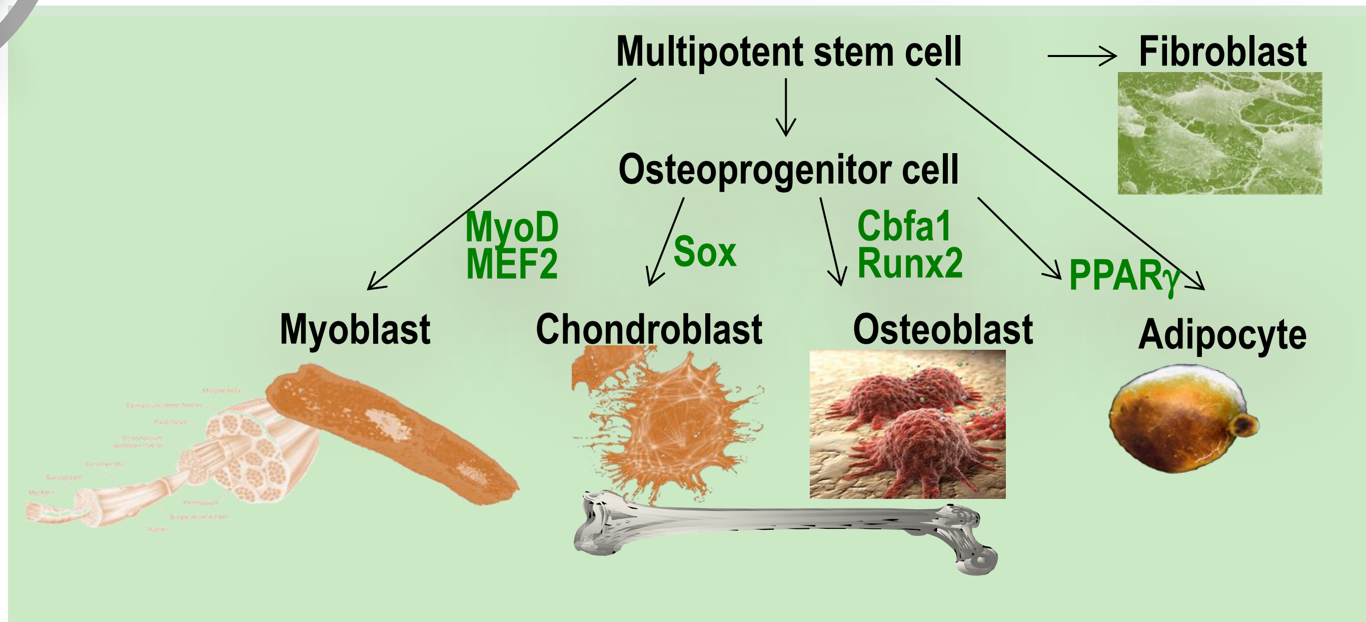
In sarcopenic women: 29 falls/ 1000 persons *vs* 13 falls/1000 in non sarcopenic volunteers

Joint American and British Geriatric Society guidelines for the prevention of falls in older people describe muscle weakness as the single biggest intrinsic risk factor for falling (RR 4.4) *(Rose Anne et al., J Am Geriatr Soc, 2001 ; Sayer et al., Am J Epidemiol, 2006)*

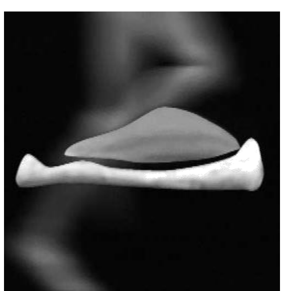
Bone / muscle interactions

From phenotypic evidence to mechanisms of action

- Mesenchymal stem cells commitment into different lineages



… A common mesodermic origin



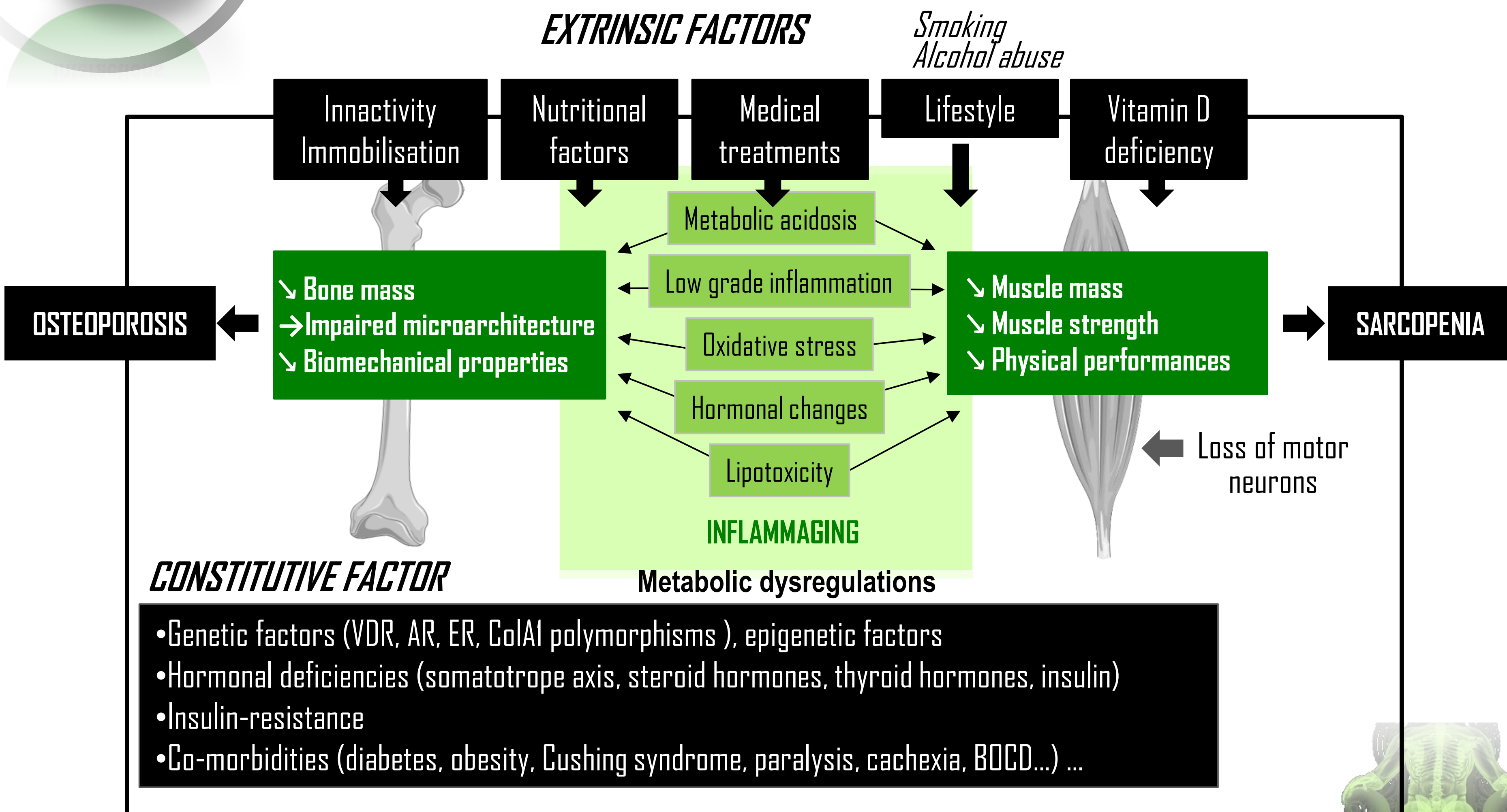
(Nielson et al., ASBMR 2009)

Bone / muscle interactions

From phenotypic evidence to mechanisms of action

•**Many similarities between the two tissues**

→ **An unique systemic regulation and shared risk factors**

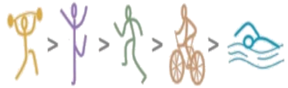


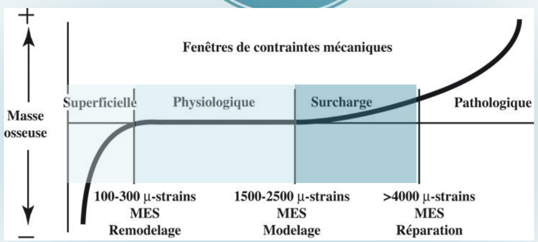
(Franchesci et al., Ann N Y Acad Sci 2000) (Inflammaging)
(Curtis et al., J Cell Physiol 2015) (Determinants of bone and muscle loss)

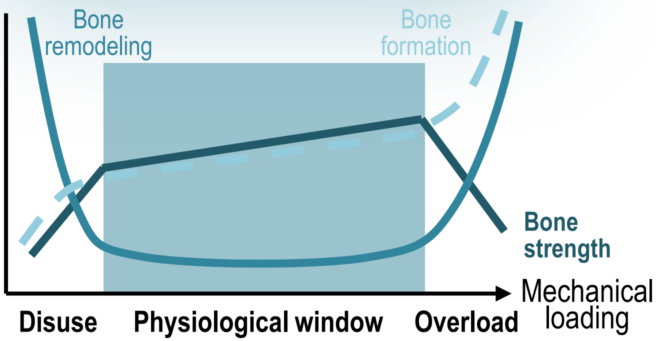
From phenotypic evidence to mechanisms of action

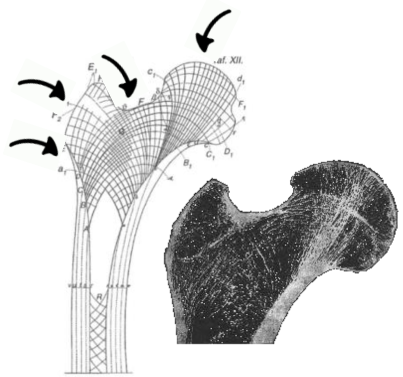
Bone / muscle interactions

•Bone/muscle cross-talk

→ Mechanical stresses 







von Meyer's Femur

•Bone adapts its shape and mass to the stresses it undergoes *(Wolff's law, 1892)*

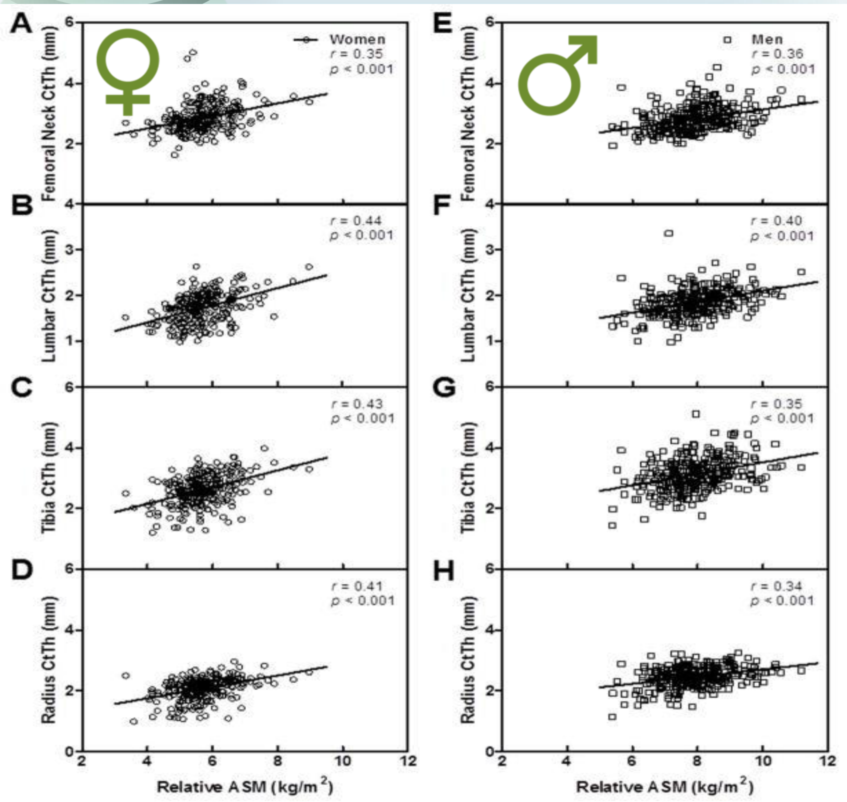
•Skeletal responses selectiveley differ depending on the amplitude of the generated deformation *(Frost's mechanostat)*

From phenotypic evidence to mechanisms of action

Bone / muscle interactions

- Bone/muscle cross-talk

→The « Mechanostat Theory » of Frost is not sufficient to explain the relationships between bones and muscles



Relation of relative appendicular skeletal muscle mass to CtTh at the femoral neck, lumbar spine vertebrae, tibia and radius

"Importantly, appendicular muscle mass correlates with bone cortical thickness *even at remote sites* and not just adjacent, mechanically loaded bone, suggesting additional paracrine or endocrine cross talk, by which bone and muscle coordinate their mass"

➧ **Complex systems**
- **-Mechanotransduction**
- **-Paracrine/endocrine regulations**

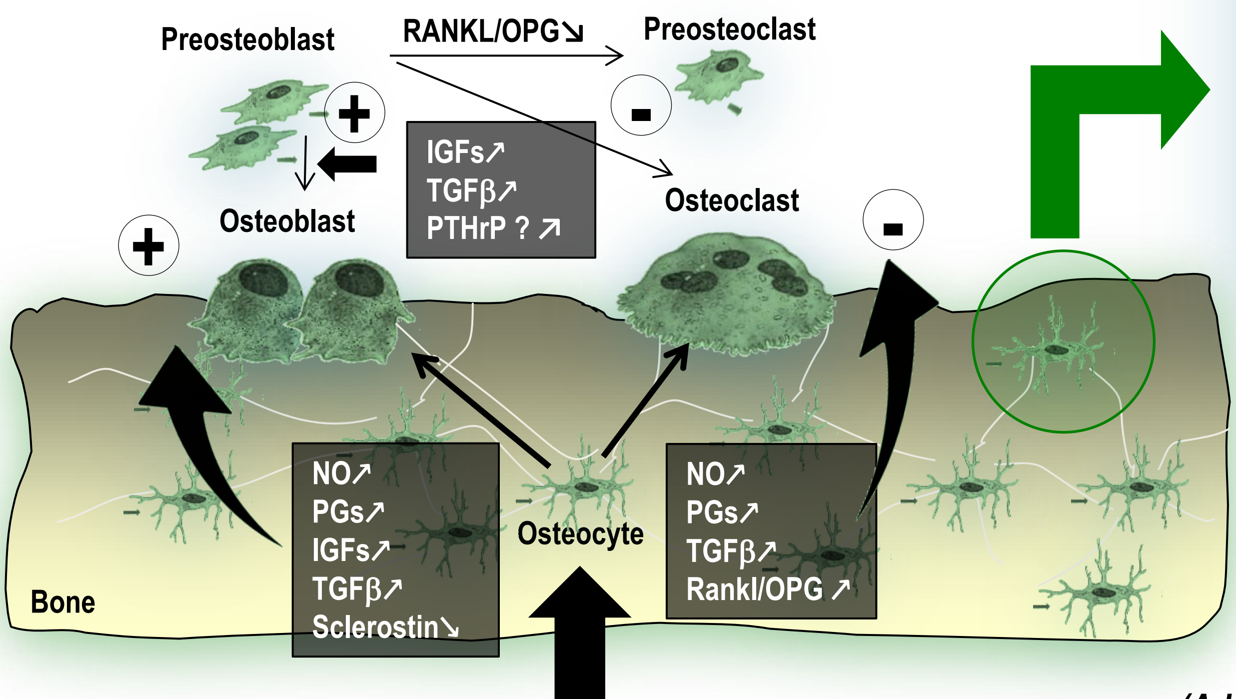
(Lebrasseur et al., J Bone Miner res 2012)

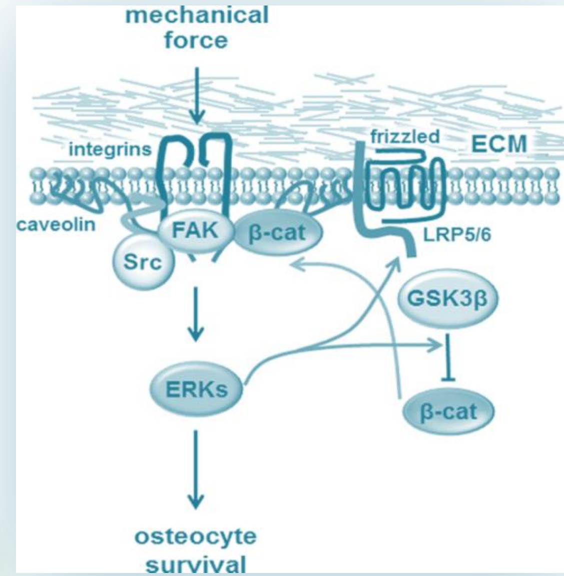
Bone / muscle interactions

From phenotypic evidence to mechanisms of action

- Bone/muscle cross-talk

→Mechanotransduction involves osteocytes (and their cross-talk with the other cells)





Caveolin-1/ERK and Wnt/β-catenin

(Adapted from Gortazar et al., J Biol Chem 2013)

Osteocytes transduce the loading mechanical signals and release signaling molecules to recruit OB or OC

Bone / muscle interactions

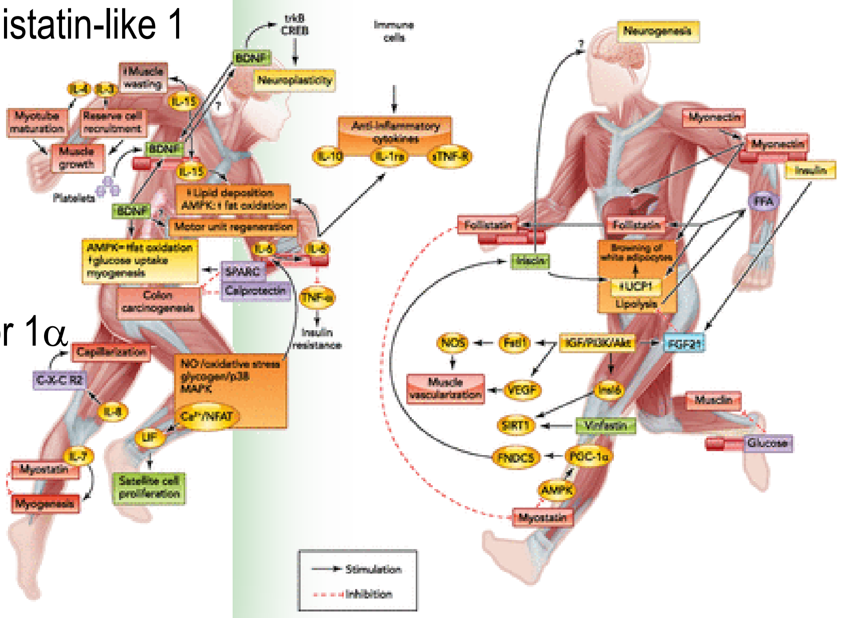
From phenotypic evidence to mechanisms of action

•Bone/muscle cross-talk

→Physical exercice and muscular secretome

Summary of the main myokines, their putative effects, and the molecular signals/pathways involved

•AMPK, AMP-activated protein kinase
•BDNF, brain-derived neurotrophic factor
•CREB, cAMP response-element-binding protein
•C-X-C R2, C-X-C receptor 2
•FFA, free-fatty acid
•FGF21, fibroblast growth factor 21
•Fndc5, fibronectin type III domain-containing 5 protein; Fstl1, follistatin-like 1
•IGF, insulin-like growth factor
•IL-1ra, IL-1 receptor antagonist
•Insl6, insulin-like 6
•LIF, leukemia inhibitory factor
•NO˙, nitric oxide; NOS, nitric oxide synthase
•PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α
•PI3K, phosphatidylinositol 3-kinase
•SIRT1, sirtuin 1
•SPARC, secreted protein acidic and rich in cysteine
•sTNF-R, soluble TNF receptors
•trkB, tropomyosin receptor kinase
•UCP1, uncoupling protein 1



(Fiuza-Luces et al., Physiol 2013)

From phenotypic evidence to mechanisms of action

Bone / muscle interactions

- Bone/muscle cross-talk

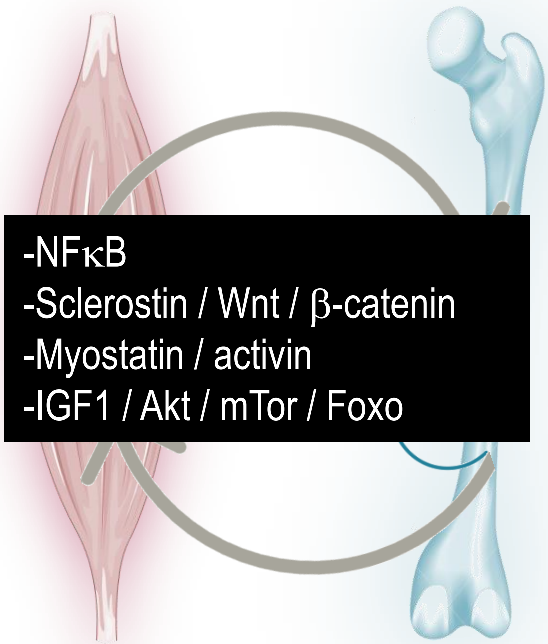
→Biochemical cross-talk is bi-directional

(Warning & Guise, Clin Cancer Res 2014)
(Kaji J Bone Metab 2014)
(Tagliaferri et al., Ageing Res Rev 2015)
(Schnyder & Handschin, Bone 2015)

Myokines
- -Myostatin (GDF8) (-)
- -Irisin (+ diff OB)
- -TGFβ
- -PGE2
- -IL6 (+/-), IL7 (-), IL8 (+/-)
- -IL15 (+/-)
- -IL11
- -Tm119 (-)
- -LIF (+)
- -CNTF (ciliary neurotrophic factor) (-)
- -Osteocrin (muscline)
- -Osteoglycin (+)
- -MEF2C (follistatine like 1)
- -MMP2 (+)
- -OPG/Rankl (+)

Chemokines
- -IL8
- -CXC ligand 1
- -CCL7

Growth factors
- -IGF1, IGF2 (+)
- -FGF2, 21 (+)
- -CTGF (connective tissue GF)



-NFκB
-Sclerostin / Wnt / β-catenin
-Myostatin / activin
-IGF1 / Akt / mTor / Foxo

Matrix Proteins
- -Osteonectin
- -Decorin
- -Cadherins
- -Cathepsins
- -Collagen

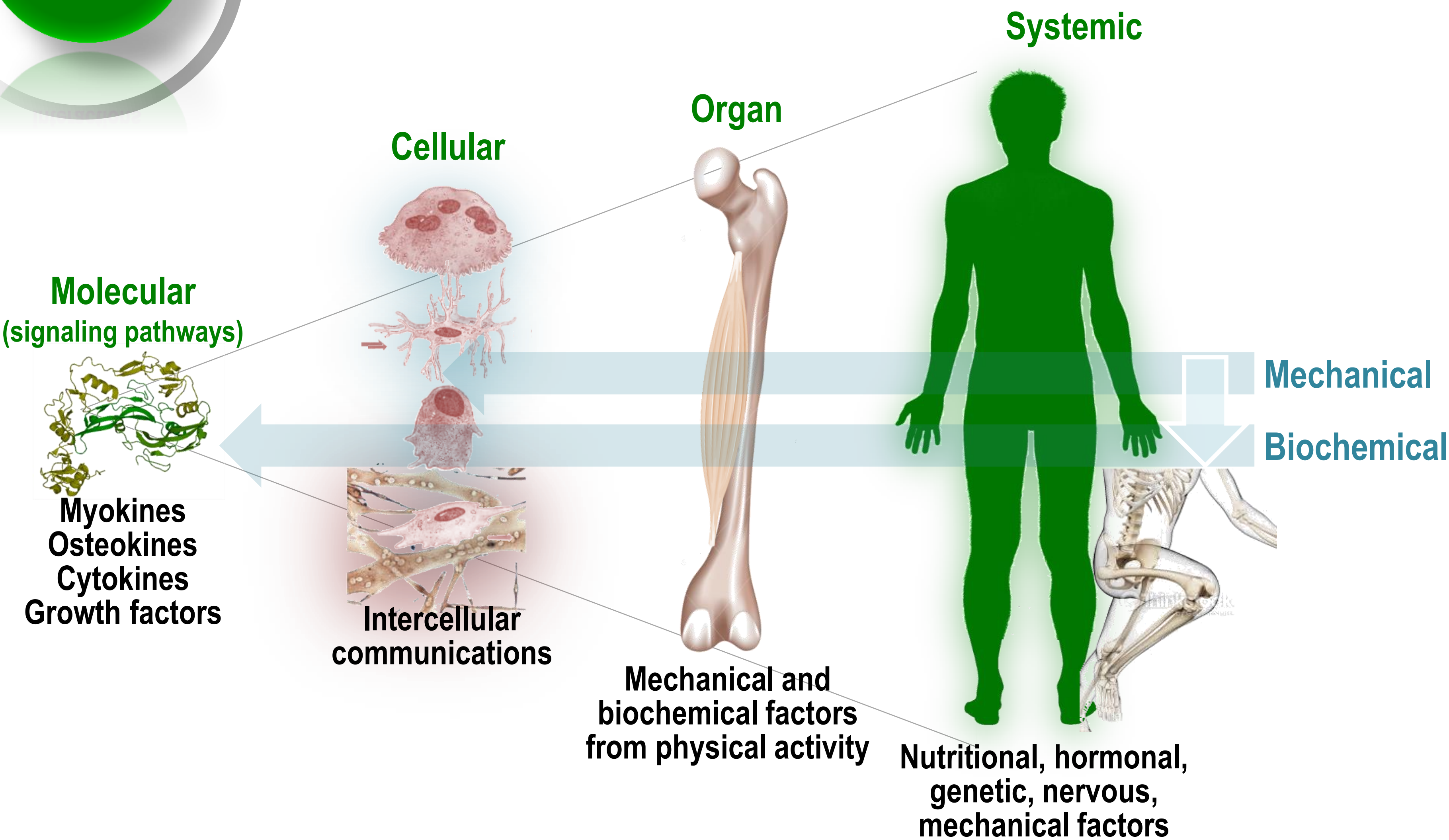
Osteokines
- -Osteocalcin (+)
- -Sclerostin (-)
- -OPG/RankL (+)
- -IHH (+)
- -Connexin 43 (+)
- -BMP2, 4 (+)
- -PGE (+ ; PGE2-)
- -Activin A (-)
- -Follistatin (+)
- -Wnt3 (+)

Growth factors
- -IGF1, IGF2 (+)
- -TGFβ (+/-)
- -VEGF (+)
- -FGF23 (?)
- -MGF (mechano growth factor)

Bone / muscle interactions

From phenotypic evidence to mechanisms of action

- A cross-talk on several organizational levels: a complex interplay of mechanical endocrine and paracrine signals



Relationships between bone and muscle the mechanical framework for movement

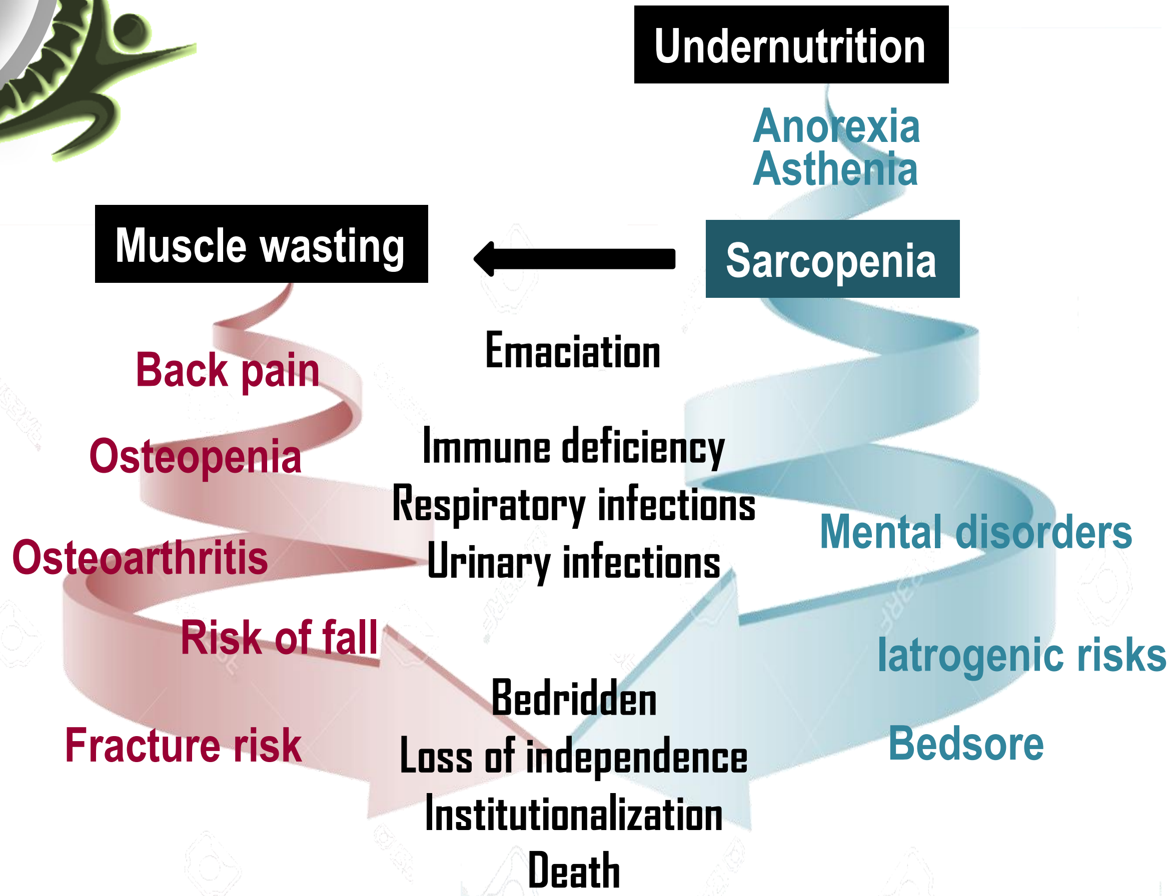
Relationships between bone and muscle

- Need for a multimodal approach for musculoskeletal health
- Pathophysiology of the locomotor system
- From phenotypic evidence to mechanisms of action
- **Key nutritional factors for musculoskeletal health management**
- Conclusions

Management of osteosarcopenia

Nutritional management

- Osteo-sarcopenia, or malnutrition, same inevitable gear

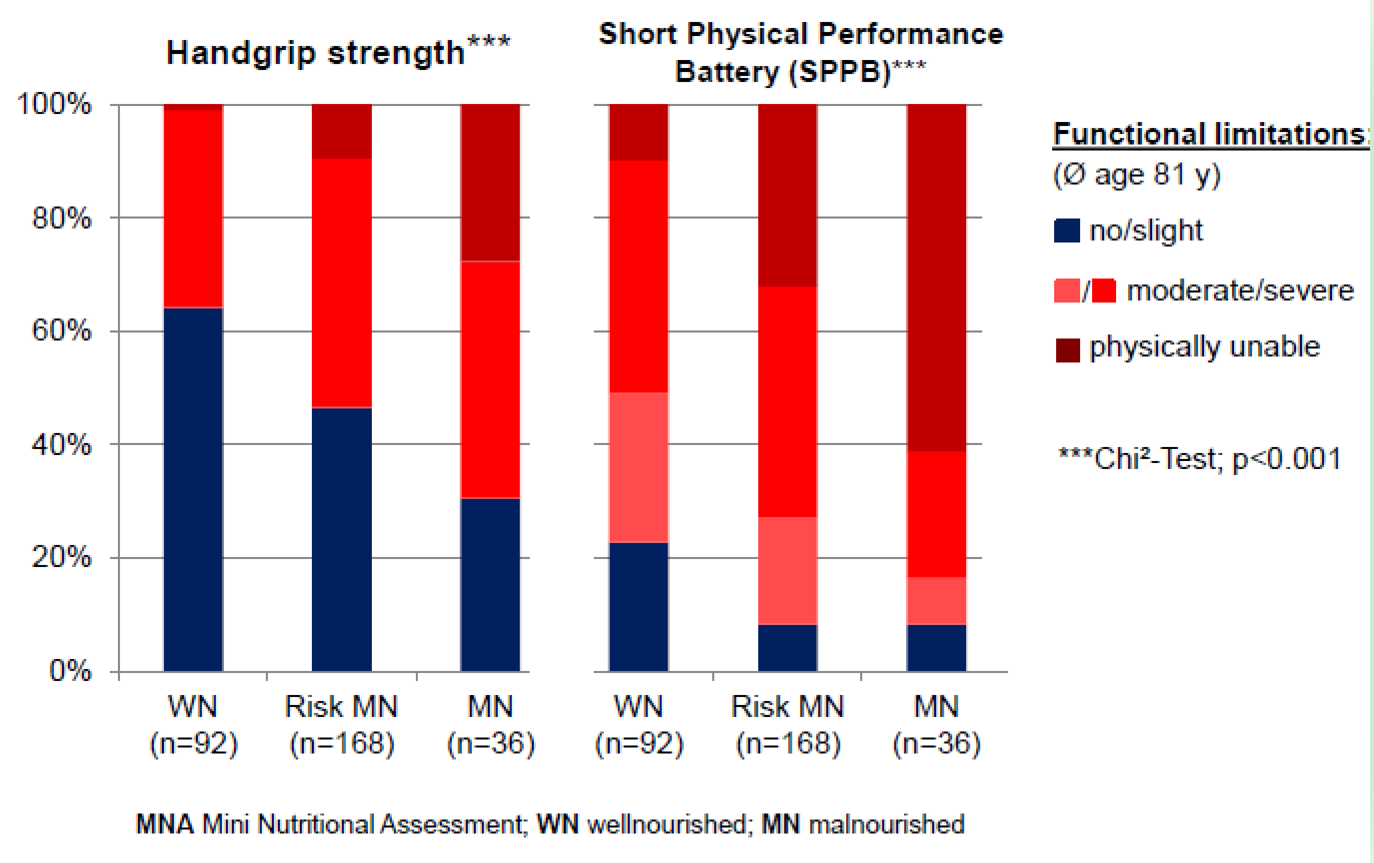


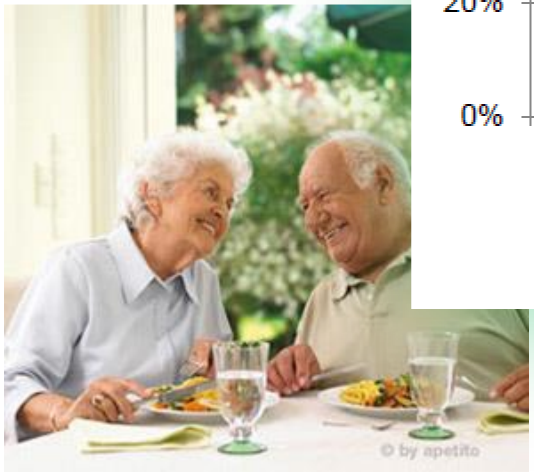
Spiral of fragility Spiral of malnutrition *(M Ferry)*

Nutritional management

Management of osteosarcopenia

- Malnutrition is associated with functional limitations





(Kiesswetter et al., J Nutr health Ageing 2013)

Management of osteosarcopenia

Nutritional management

- Muscle-bone unit: an unique preventive/therapeutic target

NUTRITION

1) Meet the need in constitutive nutrients

- Proteins
- Calcium *(Vitamin D)*

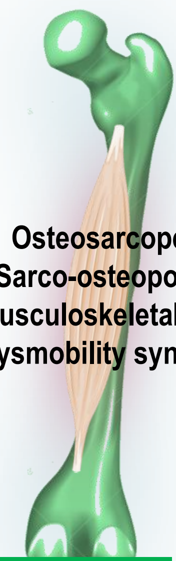
2) Avoid loss of bone/muscle components

- Limit metabolic acidosis

3) Provide nutrients endowed with specific biological properties

- Macronutrients
  - Proteins — *Whey proteins, leu, β-hydroxy β-methylbutyrate; Codfish proteins, arg, gly, tau lys, creatine; Hydrolyzed collagen,...*
  - Lipids — *N-3 fatty acids (EPA, DHA)*
- Micronutrients
  - Vitamin D
  - Others vitamins — *B, C, E, carotenoids...*
  - Polyphenols
  - Minerals

Inflammaging
Inflammation
Lipotoxicity
Oxidative stress
Signalling pathways



Osteosarcopenia
Sarco-osteoporosis
Musculoskeletal frailty
Dysmobility syndrome

PHYSICAL ACTIVITY

(Mithal et al., Osteoporos Int 2013
(Rizzoli et al., Maturitas 2014)
(Domingues-Faria et al., Ageing Res Rev 2016)
(Cruz-Jentoft et al., Age Ageing 2014)

(Francesci et al., Ann NY Acad Sci, 2000)
(Cevenini et al., Clin Nutr 2013)

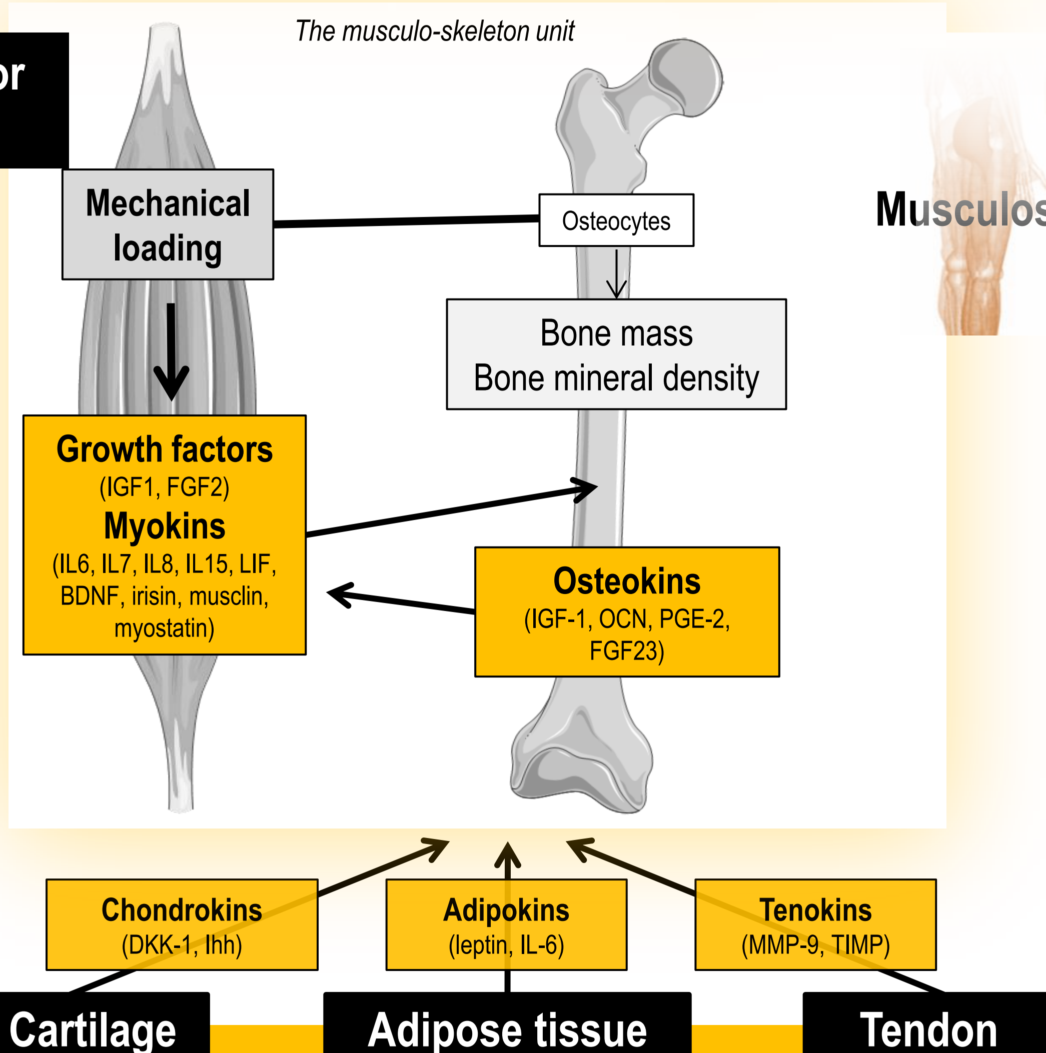
(Gielsen et al., Calcif Tissue Int 2012)
(Huo et al., J Am Med Dir Assoc 2015)
(Laurent et al., Mol Cell Endocrinol 2015)

Conclusion and perspectives

Conclusion

- The muscle-bone unit should be considered as a single therapeutic target
- Evolution towards more holistic strategy should be encouraged

There is a need for further studies



(Tagliaferri et al., Ageing Res Rev 2015)

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THANK YOU FOR YOUR ATTENTION

Osteosarcopenia: cross-talking between muscle and bone

Malaga, Saturday 16th April 2016

CERIN-EMF-GDP LUNCH SYMPOSIUM