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 for musculoskeletal health
- Pathophysiology of the locomotor system
- From phenotypic evidence to mechanisms of action
- Key nutritional factors for musculoskeletal health management
- Conclusions
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)

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

System biology based approaches represent a true challenge for human health
A recent awareness of the problem

• Musculoskeletal health

**Osteosarcopenia is more than sarcopenia and osteopenia alone.**


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


**What’s in a name revisited: should osteoporosis and sarcopenia be considered components of “dysmobility syndrome?”**

N, Binkley, D, Krueger, B, Buchring.

**Relationship between postmenopausal osteoporosis and the components of clinical sarcopenia.**


**Associations of fat and muscle masses with bone mineral in elderly men and women1,3**


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

Mark W, Hannah.
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

After 50 y
• 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

(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)

(Baumgartner et al., Am J Epidemiol 1998)
(Luna-Heredia et al., Clin Nutr 2005)
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)
During ageing, lean mass changes impact bone mass more efficiently than changes in fat composition.

MrOS study: Correlation with BMD changes

<table>
<thead>
<tr>
<th>Partial $R^2$</th>
<th></th>
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<tbody>
<tr>
<td>Baseline age</td>
<td>0.03</td>
</tr>
<tr>
<td>Weight change</td>
<td>0.07</td>
</tr>
<tr>
<td>Total body lean mass change</td>
<td>0.09</td>
</tr>
<tr>
<td>Total body fat mass change</td>
<td>0.04</td>
</tr>
</tbody>
</table>

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

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

From physiology to pathology…
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)
Conversely, sarcopenia is a risk factor for osteoporosis as well. The Finnish OSTPR-FPS study (590 postmenopausal women (mean age: 67.9y))
  - The risk of osteoporosis is 12.9X in sarcopenic women (p≤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)

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

A cohort of 17 891 subjects (3 ethnies: Afro-Americans, Caucasians, Chinese)
  - The risk of osteopenia/osteoporosis is 2X in sarcopenic subjects
  - Each SD ↑ of the «muscular score» leads to a 37% of osteopenia/osteoporosis risk

Presarcopenia and sarcopenia are associated with an abnormal BMD
### Test of physical performance

<table>
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<tr>
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<th>Number of fractures</th>
<th>Age-adjusted rate per 1000 person-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Repeat chair stands</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable (N = 135)</td>
<td>9</td>
<td>11.2 (2.1, 20.3)</td>
</tr>
<tr>
<td>Able (N = 5767)</td>
<td>68</td>
<td>2.3 (1.7, 2.8)</td>
</tr>
<tr>
<td><strong>Narrow walk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable (N = 471)</td>
<td>16</td>
<td>4.5 (1.2, 7.8)</td>
</tr>
<tr>
<td>Able (N = 5431)</td>
<td>61</td>
<td>2.3 (1.7, 2.9)</td>
</tr>
<tr>
<td><strong>Grip strength</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable (N = 95)</td>
<td>5</td>
<td>12.0 (1.0, 23.0)</td>
</tr>
<tr>
<td>Able (N = 5807)</td>
<td>72</td>
<td>2.3 (1.8, 2.9)</td>
</tr>
</tbody>
</table>

(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 and muscle, similar temporal patterns

- Complication of sarcopenia: increased risk of fracture

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

The components of clinical sarcopenia are strongly associated with osteoporosis.
Bone / muscle interactions

- Mesenchymal stem cells commitment into different lineages

Multipotent stem cell
- MyoD
- MEF2
- Sox
- Cbfa1
- Runx2
- PPARγ

Myoblast
Chondroblast
Osteoblast
Adipocyte
Fibroblast

... A common mesodermic origin

(Nielson et al., ASBMR 2009)
Bone / muscle interactions

- Many similarities between the two tissues

→ An unique systemic regulation and shared risk factors

**EXTRINSIC FACTORS**

- Innactivity Immobilisation
- Nutritional factors
- Medical treatments
- Lifestyle
- Vitamin D deficiency

- Bone mass
- Impaired microarchitecture
- Biomechanical properties

- Muscle mass
- Muscle strength
- Physical performances

**CONSTITUTIVE FACTOR**

- Genetic factors (VDR, AR, ER, ColA1 polymorphisms), epigenetic factors
- Hormonal deficiencies (somatotrope axis, steroid hormones, thyroid hormones, insulin)
- Insulin-resistance
- Co-morbidities (diabetes, obesity, Cushing syndrome, paralysis, cachexia, BOCD...)

**Metabolic dysregulations**

- Metabolic acidosis
- Low grade inflammation
- Oxidative stress
- Hormonal changes
- Lipotoxicity

(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 cross-talk

→ Mechanical stresses

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

• Skeletal responses selectively differ depending on the amplitude of the generated deformation (Frost’s mechanostat)
From phenotypic evidence to mechanisms of action
• Bone/muscle cross-talk

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

“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.”

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

Complex systems
- Mechanotransduction
- Paracrine/endocrine regulations

(Lebrasseur et al., J Bone Miner res 2012)
From phenotypic evidence to mechanisms of action

- Bone/muscle cross-talk

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

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

(Adapted from Gortazar et al., J Biol Chem 2013)
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
- Ins16, 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 cross-talk

→ Biochemical cross-talk is bi-directional

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)

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

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

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)

(Warning & Guise, Clin Cancer Res 2014)
(Kaji J Bone Metab 2014)
(Tagliaferri et al., Ageing Res Rev 2015)
(Schnyder & Handschin, Bone 2015)
From phenotypic evidence to mechanisms of action

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

Systemic

Organ

Cellular

Molecular (signaling pathways)

- Myokines
- Osteokines
- Cytokines
- Growth factors

Intercellular communications

Mechanical and biochemical factors from physical activity

Nutritional, hormonal, genetic, nervous, mechanical factors

Mechanical

Biochemical
Relationships between bone and muscle - the mechanical framework for movement

- Need for a multimodal approach for musculoskeletal health
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- Key nutritional factors for musculoskeletal health management
- Conclusions
Nutritional management

- Osteo-sarcopenia, or malnutrition, same inevitable gear

**Spiral of fragility**
- Back pain
- Osteopenia
- Osteoarthritis
- Risk of fall
- Fracture risk

**Spiral of malnutrition** (M Ferry)
- Undernutrition
  - Anorexia
  - Asthenia
- Sarcopenia
  - Emaciation
- Immune deficiency
- Respiratory infections
- Urinary infections
- Bedridden
- Loss of independence
- Institutionalization
- Death
- Mental disorders
- Iatrogenic risks
- Bedsores
Malnutrition is associated with functional limitations.

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

Management of osteosarcopenia

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

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
  - Lipids
- Micronutrients
  - Vitamin D
  - Others vitamins
  - Polyphenols
  - Minerals

NUTRITION

Whey proteins, leu, β-hydroxy β-methylbutyrate
Codfish proteins, arg, gly, tau lys, creatine
Hydrolyzed collagen,
N-3 fatty acids (EPA, DHA)

PHYSICAL ACTIVITY

(Mithal et al., Osteoporos Int 2013)
(Rizzoli et al., Maturitas 2014)
(Domingues-Faria et al., Ageing Res Rev 2016)
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Inflammaging
Inflammation
Lipotoxicity
Oxidative stress
Signalling pathways

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**Conclusion and perspectives**

- 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.

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(Tagliaferri et al., Ageing Res Rev 2015)
THANK YOU FOR YOUR ATTENTION

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