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)

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
A recent awareness of the problem

- Musculoskeletal health

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

**Need for a multimodal approach**

- Dysmobility syndrome
- Osteosarcopenia (Bijlsma et al., *Ageing Res Rev* 2012)


Associations of fat and muscle masses with bone mineral in elderly men and women

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

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

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In older adults, muscle and bone provide evidence that a variety of growth factors and cytokines are actively secreted by muscle and bone, respectively. Numerous studies have demonstrated that these factors may have a direct effect on muscle and bone. For instance, muscle-derived myostatin, an known to have a direct effect on muscle mass, and several cytokines and growth factors have recently been identified as having a direct effect on bone. Furthermore, these findings further underscore the complex nature of muscle-bone interactions, and highlight the importance of understanding muscle biology and physiology in the understanding of bone growth, development and aging.
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)
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

<table>
<thead>
<tr>
<th></th>
<th>Partial $R^2$</th>
</tr>
</thead>
<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>

Adjustment 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 weight 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)
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...
Bone and muscle, similar temporal patterns

- In osteoporotic patients, the prevalence of sarcopenia is greater than that of osteoporosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence of sarcopenia</th>
<th>Definition</th>
<th>Mean interval between fracture and DXA assessment (days)</th>
<th>Mean age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hida et al.(^{30}) 2013</td>
<td>44.7% (M), 81.1% (F)</td>
<td>Japanese criterion</td>
<td>Immediately after fracture and before surgery</td>
<td>80.3 (M), 82.7 (F)</td>
</tr>
<tr>
<td>Di Monaco et al.(^{32}) 2012</td>
<td>95% (M), 64% (F)</td>
<td>New Mexico Elder Health Survey</td>
<td>20.9</td>
<td>79.7</td>
</tr>
<tr>
<td>Present study, 2015</td>
<td>73.6% (M), 67.7% (F)</td>
<td>AWGS definition</td>
<td>14.2</td>
<td>82</td>
</tr>
</tbody>
</table>

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

(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≤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

- Complication of sarcopenia: increased risk of fracture

<table>
<thead>
<tr>
<th>Test of physical performance</th>
<th>Number of fractures</th>
<th>Age-adjusted rate per 1000 person-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat chair stands</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>Narrow walk</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>Grip strength</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)
From phenotypic evidence to mechanisms of action

- Mesenchymal stem cells commitment into different lineages

... A common mesodermic origin

(Nielson et al., ASBMR 2009)
From phenotypic evidence to mechanisms of action

- 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

**OSTEOPOROSIS**

- Bone mass ↓
- Impaired microarchitecture ↓
- Biomechanical properties ↓

**SARCOPENIA**

- 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)

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

**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

\[ \text{Mechanotransduction involves osteocytes (and their cross-talk with the other cells)} \]

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

(Adapted from Gortazar et al., J Biol Chem 2013)
From phenotypic evidence to mechanisms of action

- Bone/muscle cross-talk

→ Physical exercise 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 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

**Molecular (signaling pathways)**
- Myokines
- Osteokines
- Cytokines
- Growth factors

**Cellular**
- Intercellular communications

**Organ**
- Mechanical and biochemical factors from physical activity

**Systemic**
- Nutritional, hormonal, genetic, nervous, mechanical factors
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
Nutritional management

- Osteo-sarcopenia, or malnutrition, same inevitable gear

Muscle wasting

Back pain

Osteopenia

Osteoarthritis

Risk of fall

Fracture risk

Sarcopenia

Emaciation

Anorexia

Asthenia

Undernutrition

Immune deficiency

Respiratory infections

Urinary infections

Mental disorders

Iatrogenic risks

Bedsores

Spiral of fragility

Spiral of malnutrition (M Ferry)

Bedridden

Loss of independence

Institutionalization

Death

Management of osteosarcopenia
Management of osteosarcopenia

• Malnutrition is associated with functional limitations

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

- 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

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)

NUTRITION

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

MUSCULOSKELETAL FRAGILITY

- (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**

- 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)
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