Osteosarcopenia: understanding bone, muscle & fat interactions
G Duque

Joint IOF-ESCEO webinar
Osteosarcopenia: Understanding bone, muscle and fat interactions

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Chair of Medicine & Director of the Australian Institute for Musculoskeletal Science (AIMSS)
Melbourne Medical School and Western Health
Osteopenia → Osteoporosis → Fractures


Sarcopenia → Falls
Fractures

Falls
Osteosarcopenia

- Vitamin D deficiency
- Metabolic dysfunction
- Corticosteroid use
- Genetics
- Ageing
- Inflammation
- Inactivity
- Comorbidities
- Fat infiltration

↓ Muscle mass
↓ Muscle function (Sarcopenia)
↓ Bone mass (Osteopenia)

↓ Bone strength
↑ Risk of falls
↑ Frailty
↑ Mortality
↑ Disability

Kirk et al, Aging Med. 2019
Osteosarcopenia: A growing concept

Source: Pubmed
Pathophysiology
Osteosarcopenia: Muscle and bone interactions

Common mechanisms

Defective muscle leads to defective bone

Defective bone leads to defective muscle
Common mechanisms
Fat infiltration of muscle and bone
Duque G, BoneKey-Osteovision. 2008
Osteosarcopenia as a lipotoxic disease

Sfyri et al, J Biomed Sci. 2017

Duque et al, Curr Osteoporos Rep. 2018
Severe bone changes in a case of Hutchinson–Gilford syndrome

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Vicente Spinola Dias Neto a

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bDivision of Geriatric Medicine and Calcium Research Laboratory, Royal Victoria Hospital, 687, Pine Avenue West, Room H4-80, McGill University, Montreal, Canada H3A 1A1
Lamin A/C KO mice as a model of osteosarcopenia

Tong et al., Mech Ageing Dev. 2011
Hormones and common mechanisms of osteosarcopenia
Hormones and osteosarcopenia

Kaji. JBM. 2014
Vitamin D and osteosarcopenia

Low vitamin D → Falls → Fractures

Kawao et al. J Cell Biochem. 2015

Fig. 2. Vitamin D affects the linkage of muscle to bone.
IGF-I and osteosarcopenia

Kawao et al. J Cell Biochem. 2015
PTH and osteosarcopenia

Suriyaarachchi et al. Maturitas. 2018
Defective muscle leads to defective bone
Mechanical factors
Myokines

IGF-I, Myostatin, Osteoglycin, FAM5C, Irisin, Osteonectin, FGF2, IL-6, IL-7, IL-15, MMP-2

Hamrick MW. Exerc Sport Sci Rev. 2011

Kawao et al. J Cell Biochem. 2015
Defective bone leads to defective muscle
Osteokines


IGF-I, Sclerostin, Osteocalcin, MGF, VEGF, HGF

Kawao et al. J Cell Biochem. 2015
Osteosarcopenia: Genetics

<table>
<thead>
<tr>
<th>eBMD gene</th>
<th>Muscle-related trait</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHNAK</td>
<td>Gene expression in human skeletal muscle</td>
<td>Su, Ekman et al. 2015</td>
</tr>
<tr>
<td>AQP1</td>
<td>Gene expression in human skeletal muscle</td>
<td>Su, Ekman et al. 2015</td>
</tr>
<tr>
<td>ARHGA26</td>
<td>Positive/mouse skeletal muscle mass KO</td>
<td>Verbrugge, Schönfelder et al. 2018</td>
</tr>
<tr>
<td>BCKDHB</td>
<td>Gene expression in human skeletal muscle</td>
<td>Su, Ekman et al. 2015</td>
</tr>
<tr>
<td>DAAM2</td>
<td>Gene expression in human skeletal muscle</td>
<td>Su, Ekman et al. 2015</td>
</tr>
<tr>
<td>DLEU1</td>
<td>Gene expression in human skeletal muscle</td>
<td>Su, Ekman et al. 2015</td>
</tr>
<tr>
<td>GRB10</td>
<td>Negative/mouse skeletal muscle mass KO</td>
<td>Verbrugge, Schönfelder et al. 2018</td>
</tr>
<tr>
<td>HMGA2</td>
<td>Positive/mouse skeletal muscle mass KO</td>
<td>Verbrugge, Schönfelder et al. 2018</td>
</tr>
<tr>
<td>IGFBP2</td>
<td>Negative/mouse skeletal muscle mass overexpress</td>
<td>Verbrugge, Schönfelder et al. 2018</td>
</tr>
<tr>
<td>MMP9</td>
<td>Positive/mouse skeletal muscle mass overexpress</td>
<td>Verbrugge, Schönfelder et al. 2018</td>
</tr>
<tr>
<td>MPP7</td>
<td>Gene expression in human skeletal muscle</td>
<td>Su, Ekman et al. 2015</td>
</tr>
<tr>
<td>PPARD</td>
<td>Positive/mouse skeletal muscle mass overexpress</td>
<td>Verbrugge, Schönfelder et al. 2018</td>
</tr>
<tr>
<td>SMAD3</td>
<td>Positive/mouse skeletal muscle mass KO</td>
<td>Verbrugge, Schönfelder et al. 2018</td>
</tr>
<tr>
<td>SMAD7</td>
<td>Positive/mouse skeletal muscle mass KO</td>
<td>Verbrugge, Schönfelder et al. 2018</td>
</tr>
<tr>
<td>SOX6</td>
<td>Positive/mouse skeletal muscle mass KO</td>
<td>Verbrugge, Schönfelder et al. 2018</td>
</tr>
</tbody>
</table>

*eBMD* estimated bone mineral density, *KO* knock out.
Bivariate genome-wide association meta-analysis of pediatric musculoskeletal traits reveals pleiotropic effects at the SREBF1/TOM1L2 locus.

murine and human osteoblasts, as well as in human muscle tissue. This is the first bivariate GWAS meta-analysis to demonstrate genetic factors with pleiotropic effects on bone mineral density and lean mass.
Osteosarcopenia: A phenotype?
Table 1
Demographic and Clinical Characteristics of Participants (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>OS, n = 258</th>
<th>OP, n = 183</th>
<th>SP, n = 87</th>
<th>Nonsarcopenic/Nonosteopenic, n = 151</th>
<th>P'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>80.4 ± 7</td>
<td>78 ± 7</td>
<td>79.4 ± 7.2</td>
<td>77.4 ± 7</td>
<td>.001</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (17)</td>
<td>61 (33)</td>
<td>33 (38)</td>
<td>85 (56)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>213 (83)</td>
<td>122 (67)</td>
<td>54 (62)</td>
<td>66 (43)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMD, T-score, femoral neck</td>
<td>−2.31 ± 0.77</td>
<td>−2.05 ± 0.67</td>
<td>0.088 ± 0.85</td>
<td>0.14 ± 1.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Grip strength, kg</td>
<td>16.6 ± 5.9</td>
<td>21.8 ± 9.2</td>
<td>18.7 ± 6.2</td>
<td>27.2 ± 10.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gait velocity, cm/s</td>
<td>57.1 ± 15.2</td>
<td>87.6 ± 22.5</td>
<td>56.5 ± 16.2</td>
<td>90 ± 23.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>16 (6.2)</td>
<td>13 (7.1)</td>
<td>4 (4.5)</td>
<td>5 (2.8)</td>
<td>.11</td>
</tr>
<tr>
<td>Current drinker, n (%)</td>
<td>28 (11)</td>
<td>31 (17)</td>
<td>11 (12)</td>
<td>23 (15)</td>
<td>.14</td>
</tr>
<tr>
<td>On oral steroids, n (%)</td>
<td>21 (8)</td>
<td>10 (5)</td>
<td>6 (7)</td>
<td>7 (5)</td>
<td>.32</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2 ± 6.2</td>
<td>27.2 ± 6.4</td>
<td>29 ± 6.6</td>
<td>29.5 ± 5</td>
<td>.001</td>
</tr>
<tr>
<td>Been fractured, n (%)</td>
<td>102 (39)</td>
<td>81 (44)</td>
<td>26 (29)</td>
<td>33 (21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Menopause age</td>
<td>43 ± 7</td>
<td>45 ± 5</td>
<td>43 ± 5</td>
<td>44 ± 6</td>
<td>.23</td>
</tr>
<tr>
<td>Used HRT, n (% of female)</td>
<td>35 (24)</td>
<td>31 (25)</td>
<td>14 (25)</td>
<td>21 (31)</td>
<td>.99</td>
</tr>
<tr>
<td>HRT years</td>
<td>10.4 ± 10</td>
<td>7.8 ± 10</td>
<td>8.1 ± 7</td>
<td>11.2 ± 10</td>
<td>.59</td>
</tr>
<tr>
<td>Hematological results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D, nmol/L</td>
<td>63 ± 30</td>
<td>73.7 ± 74</td>
<td>64 ± 29</td>
<td>62 ± 29</td>
<td>.17</td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>66.3 ± 17</td>
<td>66.2 ± 18</td>
<td>63.3 ± 19</td>
<td>66.8 ± 16</td>
<td>.57</td>
</tr>
<tr>
<td>PTH, pmol/L</td>
<td>6.6 ± 5.6</td>
<td>6.7 ± 6.2</td>
<td>6.4 ± 4.3</td>
<td>5.7 ± 2.7</td>
<td>.42</td>
</tr>
</tbody>
</table>

Huo et al. JAMDA. 2014
Osteosarcopenia: A continuum?
Osteosarcopenia: A dynamic syndrome?

- Falls & Fractures
- Osteosarcopenia
  - Social isolation
  - Fear of falling
  - Physical dependence
  - Malnutrition
  - Poor quality of life
- Frailty
  - Disability
  - Institutionalisation
- Robust individual
Clinical outcomes
Clinical outcomes in osteosarcopenia

Huo et al. JNHA 2015
Sepulveda-Loyola et al., JAMDA. 2019
Conclusions and Implications: Compared with the nonosteosarcopenic group, those with osteosarcopenia had greater impairment of physical performance and balance. The EWGSOP2 and FNIH criteria resulted in the strongest associations with physical performance and self-reported falls and fractures.
Osteosarcopenia in men

Scott et al. J Gerontol: Med Sci. 2018
Osteosarcopenia and anemia

EWGSOP 1

- Sarcopenic: 84 (15%)
- Anemic: 176 (31.5%)
- Osteopenic/porotic: 157 (28%)
- Total: 39 (7%)

EWGSOP 2

- Sarcopenic: 63 (11%)
- Anemic: 176 (31.5%)
- Osteopenic/porotic: 227 (41%)
- Total: 40 (7%)

Bani Hassan et al. Calc. Tissue Int. 2020
Osteosarcopenia and mortality

Pasco et al. J Cachexia Sarcopenia Muscle. 2017
How to Diagnose Osteosarcopenia? 
Imaging
- **Pharmacological:**
  - Growth hormone
  - Androgens
  - SARMs
  - Vitamin D
  - Activin signaling inhibitors

- **Non-pharmacological:**
  - Exercise
  - Protein supplementation

- **Future directions**
  - FAS Inhibitors
  - Myokines/Osteokines?
Non-pharmacological interventions
Vitamin D as an anabolic

Fig. 1. Potential vitamin D mediated mechanisms of bone-muscle cross-talk.

Guntun JE, et al, Bone muscle interactions and vitamin D, Bone (2015), http://dx.doi.org/10.1016/j.bone.2015.02.029
Kirk et al. J Cachexia Sarcopenia Muscle. 2020
Pharmacological interventions
Activin signalling inhibitors

Enrolment

365 patients assessed for eligibility

164 excluded
- 134 did not meet inclusion criteria
- 25 declined to participate
- 5 other reasons

201 randomly assigned

Allocation

99 assigned to placebo
- 98 received allocated intervention
- 1 did not receive allocated intervention

102 assigned to LY
- 102 received allocated intervention
- 0 did not receive allocated intervention

Follow-up

1 lost to follow-up
- 1 multiple phone calls and certified letter sent which was returned as undeliverable
- 12 discontinued intervention
er
- 6 adverse event
- 1 protocol violation
- 1 funder decision
- 1 staphylococcal sepsis
- 4 withdrawal by participant

0 lost to follow-up
- 20 discontinued intervention
- 9 adverse event
- 1 death
- 2 funder decision
- 1 diagnosis of non-Hodgkin lymphoma
- 1 protocol violation (only one hand tested for grip strength)
- 6 withdrawal by participant

Analysis

86 included in primary analysis
- 13 excluded from analysis
- 2 no DXA measurements
- 3 no baseline aLBM measurement
- 8 no post-baseline DXA measurement

84 included in primary analysis
- 18 excluded from analysis
- 3 no DXA measurements
- 2 no baseline aLBM measurement
- 13 no post-baseline DXA measurement

Table 4. Mean (SD) percent change from baseline to days 15, 29, and 57 in serum fat and bone biomarkers for the placebo and 1 mg/kg and 3 mg/kg ACE-031 groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study day</th>
<th>Placebo (n=12)</th>
<th>1 mg/kg (n=6)</th>
<th>3 mg/kg (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>15</td>
<td>-3.9 (22.8)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25.1 (26.1)</td>
<td>39.6 (27.6)&lt;sup&gt;*; †&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>13.7 (12.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19.4 (22.1)</td>
<td>51.3 (17.6)&lt;sup&gt;*; †&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>9.1 (17.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.1 (34.0)</td>
<td>35.1 (26.6)*</td>
</tr>
<tr>
<td>Leptin</td>
<td>15</td>
<td>-2.9 (44.0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-5.0 (30.7)</td>
<td>-24.1 (40.1)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>44.3 (50.4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28.8 (44.7)</td>
<td>-27.7 (24.1)&lt;sup&gt;*; †&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>9.0 (22.6)</td>
<td>38.6 (48.2)</td>
<td>10.1 (36.4)</td>
</tr>
<tr>
<td>BSAP</td>
<td>15</td>
<td>5.6 (4.0)*</td>
<td>14.1 (15.8)</td>
<td>22.7 (10.4)*</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>11.0 (10.3)*</td>
<td>33.6 (16.5)&lt;sup&gt;*; †&lt;/sup&gt;</td>
<td>33.9 (11.6)&lt;sup&gt;*; †&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>11.7 (10.6)*</td>
<td>16.3 (13.7)*</td>
<td>24.1 (14.3)*</td>
</tr>
<tr>
<td>CTX</td>
<td>15</td>
<td>8.9 (24.0)</td>
<td>-19.4 (9.3)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>-23.9 (35.1)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
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<td>10.0 (16.8)</td>
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</tr>
<tr>
<td></td>
<td>57</td>
<td>12.3 (21.9)</td>
<td>-4.5 (14.6)</td>
<td>-33.0 (13.1)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*P < 0.05 for the mean change from baseline.
†P < 0.05 for the comparison of mean change vs. placebo.
<sup>a</sup>n=4.

Denosumab and muscle

Bonnet et al. JCI. 2019
Dmab (n = 51) or ZOL (n = 28), combined with vitamin D supplementation

“Dmab displayed positive effects on balance, function, and fear of falling, which may underlie reductions in fall rates.”

Phu et al., JAGS. 2019
Table 7. Summary of the evidence regarding the effect of pharmacological agents on osteoporosis and sarcopenia related outcomes.

<table>
<thead>
<tr>
<th>Pharmacological agent</th>
<th>Osteoporosis</th>
<th>Sarcopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab</td>
<td>Meta-analysis of 4 RCTs, investigating the effect</td>
<td>Reduction in falls in the Denosumab treatment group of the FREEDOM Study. No evidence of effect on muscle function. Improves muscle strength and insulin sensitivity in osteoporotic humans.</td>
</tr>
<tr>
<td></td>
<td>of denosumab on BMD reported significant improvement in BMD at lumbar spine, hip, and radius.</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>Intramuscular testosterone increased lumbar spine bone density in men.</td>
<td>Testosterone in older men with decreased testosterone levels and muscle weakness can improve muscle mass, strength and physical performance.</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Meta-analysis of 7 RCTs and one extension trial</td>
<td>Low growth hormone levels with age contribute to decrease in lean body mass and increase adipose tissue.</td>
</tr>
<tr>
<td></td>
<td>concluded that growth hormone may not improve bone density but decrease fracture risk in women with age related bone loss.</td>
<td></td>
</tr>
<tr>
<td>Antimyostatin antibodies</td>
<td>Antimyostatin antibody in combination with resistance exercise improved bone health in rats.</td>
<td>(1) Antimyostatin antibodies increased muscle mass and strength in mice. (2) Antimyostatin antibodies increased lean mass and may improve functional measures of muscle power.</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; RCT, randomized controlled trial.
How to approach osteosarcopenia in clinical practice?

Kirk et al. J Cachexia Sarcopenia Muscle. 2020
Future Directions
Cerulenin
Inhibition of fatty acid synthase increases bone mass

Bermeo et al. Bone, 2019
Inhibition of fatty acid synthase improves muscle mass and strength

Bermeo et al. Bone, 2019

Bermeo et al. Submitted data
Osteosarcopenia: A geriatric giant

Geriatric Giants
- Instability
- Immobility
- Incontinence
- Intellectual impairment

Bernard Isaacs

Osteosarcopenia: A new geriatric syndrome

Ebrahim Bani Hassan, Gustavo Duque

AFP, 2018
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