Evaluatie, preventie en behandeling van Sarcopenie

Ivan Bautmans

Frailty in Ageing research group

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Sarcopenia

Rosenberg J Nutr 1997

Age-related loss of muscle mass and muscle strength

Roubenoff R. J Gerontol 2003
T-score = $\frac{X_i - \text{mean}_{\text{young}}}{\text{SD}_{\text{young}}}$

- **Baumgartner ea. 1998**
  - New Mexico, USA
    - N-Hisp: 205M, 173F
  - Reference group
    - N-Hisp, 107M, 122F aged 18-40yrs
      - >80 yrs = ♂ 53%, ♀ 43%

- **Janssen ea. 2000**
  - NHANES III, USA
    - 2224M, 2278F aged ≥60yrs
  - Reference group
    - 3116M, 3298F aged 18-39yrs
    - Class 1: -1 ≥ T ≤ -2
      - >80 yrs = ♂ 43%, ♀ 61%
    - Class 2: T < -2
      - >80 yrs = ♂ 7%, ♀ 11%
Correction for weight or stature
### Table 1. Criteria for the diagnosis of sarcopenia

Diagnosis is based on documentation of criterion 1 plus (criterion 2 or criterion 3)

1. Low muscle mass
2. Low muscle strength
3. Low physical performance
Table 3. Reference values (in Kpa) for maximal grip strength

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Threshold value</td>
<td>Median</td>
</tr>
<tr>
<td>70-74 years</td>
<td>66 KPa</td>
<td>91 KPa</td>
</tr>
<tr>
<td>75-79 years</td>
<td>57 KPa</td>
<td>82 KPa</td>
</tr>
<tr>
<td>80-84 years</td>
<td>50 KPa</td>
<td>75 KPa</td>
</tr>
<tr>
<td>≥85 years</td>
<td>37 KPa</td>
<td>64 KPa</td>
</tr>
</tbody>
</table>

All reference values are valid for the dominant and non-dominant hand using the Martin Vigorimeter. The threshold value corresponds to the p=0.05 level. Adapted from Merkies et al. (60)

Lauretani ea. *J Appl Physiol* 2003
Fried ea. *J Gerontol* 2001
Bautmans ea. *Acta Clinica Belgica* 2009
"How often in the last week did you feel this way?"

(a) I felt that everything I did was an effort;
(b) I could not get going.

0 = rarely or none of the time (<1 day),
1 = some or a little of the time (1–2 days),
2 = a moderate amount of the time (3–4 days),
3 = most of the time.

Subjects answering “2” or “3” to either of these questions are categorized as frail by the exhaustion criterion.

Fried ea. JGerontol 2001
Fatigue resistance

• Based on max. grip strength

• Time (seconds) until grip strength ↓ to 50% Max

• Reliability
  – Inter-observer ICC(3,1)= 0.77 – 0.91
  – Intra-observer ICC(3,1)= 0.82 – 0.94
STRENGTH ENDURANCE

Grip Work = 0.75 x Grip strength x Fatigue resistance

= area under the curve

Grip strength (%max)

100%

75%

50%

0

FR

Time in seconds

N=291, age 20-93 yrs

Grip Work/kg Body mass

<table>
<thead>
<tr>
<th></th>
<th>Grip Work</th>
<th>Grip Work/kg Body mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Cutoff</td>
<td>3000 KPa*sec</td>
<td>2500 KPa*sec</td>
</tr>
<tr>
<td>AUC</td>
<td>86%</td>
<td>84%</td>
</tr>
<tr>
<td>Sens</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>Spec</td>
<td>70%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Muscle weakness & Fatigue

Underlying mechanisms
<table>
<thead>
<tr>
<th>Type</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous</td>
<td>↓ Anabolism</td>
</tr>
<tr>
<td></td>
<td>↓ Hormonal stimulation (Growth Hormone, IGF-1, Testosterone, Oestrogen)</td>
</tr>
<tr>
<td></td>
<td>Loss of motorneurones, denervation of muscle fibres</td>
</tr>
<tr>
<td></td>
<td>↑ non-contractile tissue in muscle</td>
</tr>
<tr>
<td>Exogenous</td>
<td>↓ Physical activity</td>
</tr>
<tr>
<td></td>
<td>Bed rest, immobilisation</td>
</tr>
<tr>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Endogenous</td>
<td>↑ Catabolism</td>
</tr>
<tr>
<td></td>
<td>↑ Basal inflammatory profile (IL-6, TNF-α)</td>
</tr>
<tr>
<td>Exogenous</td>
<td>Stress-induced inflammation: Life events, Depression</td>
</tr>
<tr>
<td></td>
<td>Disease</td>
</tr>
</tbody>
</table>

Bautmans et al. *Acta Clinica Belgica*, 2009; 64-4
Increase of 0.016 pg/mL per year in healthy subjects

**Basal inflammatory profile**

- ↑IL-6, TNF-α, ...
- Muscle weakness
- Muscle atrophy

*Cesari ea* *J Gerontol* 2004

**Figure 1.** Correlation of interleukin-6 and donor age.
Figure 1. Plasma levels of tumor necrosis factor-receptor 1 (TNF-r1) and interleukin (IL)-6 (mean ± SE) by age (n = 1,411).

N=79, age= 80 years, 5 years follow-up

Figure 2 Percentage change in handgrip strength over 5 years among those with and without periodontitis at baseline ($p = 0.015$). Values are adjusted for gender, height, weight, number of chronic conditions and physical activity. Means with standard errors are shown.
BED REST

N=680, non-disabled, aged >70 yrs, 18 months follow-up

60% at least 1 episode bed rest!

Gill ea. J Gerontol 2004
### 11 healthy subjects, aged 67±5 yrs, 10 days bed rest

#### Table 2. Lower Extremity Muscle Performance and Aerobic Capacity

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-Bed Rest</th>
<th>Post-Bed Rest</th>
<th>% Change</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee extension (N = 11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-RM</td>
<td>–</td>
<td>–</td>
<td>–13.2 ± 3.5</td>
<td>.004</td>
</tr>
<tr>
<td>Isometric (N)</td>
<td>133.7 ± 15.1</td>
<td>117.6 ± 13.6</td>
<td>–11.2 ± 3.9</td>
<td>.017</td>
</tr>
<tr>
<td>Concentric 180° (N · m/s)</td>
<td>69.9 ± 8.1</td>
<td>60.1 ± 7.0</td>
<td>–13.5 ± 4.4</td>
<td>.011</td>
</tr>
<tr>
<td>Knee flexion (N = 11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isometric (N)</td>
<td>76.8 ± 10.0</td>
<td>68.1 ± 10.5</td>
<td>–14.2 ± 3.6</td>
<td>.003</td>
</tr>
<tr>
<td>Concentric 60° (N · m/s)</td>
<td>80.3 ± 8.8</td>
<td>71.6 ± 9.4</td>
<td>–11.8 ± 4.6</td>
<td>.03</td>
</tr>
<tr>
<td>Concentric 180° (N · m/s)</td>
<td>51.8 ± 7.7</td>
<td>46.6 ± 8.2</td>
<td>–13.2 ± 4.3</td>
<td>.01</td>
</tr>
<tr>
<td>Stair ascent power</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N · m/s) (N = 8)</td>
<td>403 ± 67</td>
<td>337 ± 48</td>
<td>–14.0 ± 4.1</td>
<td>.01</td>
</tr>
<tr>
<td>VO_{2max} (mL/kg/min) (N = 9)</td>
<td>22.7 ± 2.0</td>
<td>19.72 ± 1.7</td>
<td>–12.2 ± 4.5</td>
<td>.04</td>
</tr>
</tbody>
</table>

*Notes:* All values are mean ± standard error of the mean.  
1-RM = one repetition maximum; VO_{2max} = maximal oxygen uptake.
Fig. 5. Hypertrophy and atrophy signalling via Akt. Increases in RAS/RAF/MEK/ERK signalling results in an up regulation of cellular proliferation in response to IGF-I binding to its receptor. Activation of IRS-1/P13K/Akt1 pathway leads to an increase in hypertrophy via mTor and p70S6K up regulation. Akt activation inhibits FOXO binding to DNA preventing MAFbx and MuRF1 activity and subsequent protein breakdown. NF-κB activation occurs following the degradation of its associated inhibitory protein IκB, leading to the nuclear transport of NF-κB transcription factors and MAFbx and MuRF-1 activity, resulting in protein breakdown.
Fig. 6. The Ub–proteasome pathway which results in intracellular protein breakdown. Proteolysis is catalysed by the 26S proteasome which degrades ubiquitinated proteins into small peptides following the tagging of the whole protein via the ATP dependent activation of the E1 and E2 proteins. The ubiquitinated proteins are then presented to the proteasome for disassembly into their constituent peptides (Lecker et al., 1999, with permission).
Acute accelerating factors

• Serious systemic inflammation
  – Inflammatory conditions (e.g. infection, surgery)
Inflammatory Patients significantly weaker than Non-Inflammatory (p<0.05)

† Significant difference in evolution (p<0.05)

* Inflammatory Patients
† Non-inflammatory Patients

N=63, Age=70-98 yrs

Bautmans ea. J Gerontol 2005
Hospitalized geriatric patients with acute infection, N=43, aged 84 ± 6 years

Mets, Bautmans ea. Am J Geriatr Pharmacother 2004

* Evolution FR significantly different between 3 groups (p=0.021) and improvement celecoxib group significantly better than acetaminophen group (p<0.05) control group (p<0.05)
SURGERY
N=66, age 24-91 yrs, elective abdominal surgery

Bautmans ea. J Gerontology 2010
Figure 2 - Evolution of post-surgical muscle fatigue resistance according to age. Patients aged >75 years (N=20, dotted line) worsened significantly more and recovered significantly less rapidly for fatigue resistance at day 4 post-surgery compared to the younger (age<60 years: N=29, plain line; aged 60-75 years: N=29, semi-dotted line) patients (Repeated measures ANOVA, interaction between age and fatigue resistance p<0.05).

Bautmans et al. J Gerontology 2010
Sarcopenia

Partly reversible
Cost of Sarcopenia USA 2000

<table>
<thead>
<tr>
<th>Group</th>
<th>Muscle Mass Range, kg/m²</th>
<th>Prevalence in Population, %</th>
<th>Relative Risk Disability</th>
<th>Population Attributable Risk for Disability, %*</th>
<th>Cost, billion $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal muscle</td>
<td>≥10.76</td>
<td>35.7</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Moderate sarcopenia</td>
<td>8.51–10.75</td>
<td>53.1</td>
<td>3.48</td>
<td>56.8</td>
<td>7.18</td>
</tr>
<tr>
<td>Severe sarcopenia</td>
<td>≤8.50</td>
<td>11.2</td>
<td>4.60</td>
<td>28.7</td>
<td>3.63</td>
</tr>
<tr>
<td>Older women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal muscle</td>
<td>≥6.76</td>
<td>68.7</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
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<td>Moderate sarcopenia</td>
<td>5.76–6.75</td>
<td>21.9</td>
<td>1.46</td>
<td>9.2</td>
<td>2.70</td>
</tr>
<tr>
<td>Severe sarcopenia</td>
<td>≤5.75</td>
<td>9.4</td>
<td>3.15</td>
<td>16.8</td>
<td>4.96</td>
</tr>
</tbody>
</table>

* [prevalence (RR – 1)]/[1+prevalence (RR – 1)].

Total 18.5 billion dollar!

10% reduction of sarcopenia = 1.1 billion dollar savings!
Countering Sarcopenia

Bennell ea. 2000

Bautmans ea. Gerontology 2005

Bautmans ea. BMC Geriatrics 2005

Strength training effective in elderly persons

• +30-170% strength in 6 weeks
• Even in oldest old (age >90 yrs)

Latham ea. *The Cochrane Library* 2003
Fig. 2. Forest plot of effect sizes and 95% confidence intervals for all 51 cohorts (32 studies) representing leg press, based on the random-effects meta-analysis results.
P<0.00001

Fig. 4. Signalling pathways involved in hypertrophy. Akt activation leads to the deactivation of FOXO, its release from the DNA strand and exit from the nucleus and binding with the 14-3-3 transport protein to prevent it from becoming active and rebinding to DNA, resulting in a blockade of proteolysis.
12 weeks strength training (85-97 j)

**FIGURE 2.** MRI images taken at the mid-thigh region of the male subject CC before (Pre) and after (Post) training (shown to the same scale). Quadriceps LCSA increased by 44% in this subject, who is represented by the triangle symbol with apex upwards in Figures 1, 5, and 6.

Fig. 1. Computer tomography images taken from the midthigh region of a female subject in the strength training (ST) group before and after training. The 2 images are shown at the same scale. Quadriceps muscle cross-sectional area of the operated side (op-leg) increased 32% in this subject; the nonoperated side (con-leg) did not change from pretraining to posttraining.
Non-frail elderly: Strength training in fitness

Frail elderly: supervised exercise + home-based program
Frail or ill Elderly


De situaties die gangrevalidatie behoeven worden als volgt gedefinieerd: "...rechthebbenden vanaf hun 65ste verjaardag, die al eens gevallen zijn met risico op herhaling, te objectiveren door de behandelend geneesheer en kinesitherapeut aan de hand van:
1) de "Timed up & go" test, met een score hoger dan 20 seconden;
2) een positief resultaat op ten minste één van twee volgende testen, die allebei moeten worden verricht:
   (01) - de "Tinetti" test, met een score kleiner dan 20/28;
   (02) - de "Timed chair stands" test, met een score hoger dan 14 seconden."

• → individually with Physical Therapist
Rehabilitation for older people in long-term care

Forster ea  Cochrane review 2010, Age&Ageing 2010

- 49 trials involving 3611 participants
- overall mean age = 82 yrs (69-89)
- 30 to 45-minute sessions, 3x per week
- physical rehabilitation
  - worthwhile and safe,
  - reducing disability,
  - few adverse events
- no recommendations for best intervention scheme
Organisation

• Supervised EXERCISE sessions
• Home-based EXERCISE program
• Frequency
  – Week 1&2 3 /week 6 sessions
  – Week 3&4 2 /week 4 sessions
  – Week 5-52 1 /week 48 sessions
  1 year 58 sessions
Bautmans ea. *Acta Clinica Belgica*, 2009; 64-4
Thank you.

ibautman@vub.ac.be

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