Altering lifestyle to improve nutritional status in older adults

Nutritional interventions to prevent and treat frailty

F. Landi (IT)
Nutritional interventions to prevent and treat frailty

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Frailty: An Emerging Public Health Priority

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Problem statement

- Frailty is a “a multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors” with an increased risk for adverse health outcomes;
- Physical frailty (PF) is a condition characterized by impairments in strength, gait, and balance;
- The PF phenotype presents overlaps with sarcopenia, “progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes”; 
- Sarcopenia may be considered both as the biological substrate for the development of PF and the pathway through which the negative health outcomes of frailty ensue.
Aging and muscle loss of muscle mass, strength and function

Original Study

Age-Related Variations of Muscle Mass, Strength, and Physical Performance in Community-Dwellers: Results From the Milan EXPO Survey

Francesco Landi MD, PhD*, Riccardo Calvani PhD, Matteo Tosato MD, PhD, Anna Maria Martone MD, Domenico Fusco MD, PhD, MD, Alex Sisto BA, Elena Ortolani MD, Giulia Savera BS, Sara Salini MD, Emanuele Marzetti MD, PhD

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Aging and muscle

Loss of muscle mass, strength and function
Aging and muscle

Loss of muscle mass, strength and function
Aging and muscle

Loss of muscle mass, strength and function
Sarcopenia as substrate of frailty

Sarcopenia as the Biological Substrate of Physical Frailty

Francesco Landi, MD, PhD,*, Riccardo Calvani, PhD,1, Matteo Cesari, MD, PhD,1, Matteo Tosato, MD, PhD, Anna Maria Martone, MD, Roberto Bernabei, MD, Graziano Onder, MD, PhD, Emanuele Marzetti, MD, PhD

http://dx.doi.org/10.1016/j.cger.2015.04.005
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Table 1
Conceptual framework of physical therapy and sarcopenia—resemblance to common conditions of advanced age

<table>
<thead>
<tr>
<th>Condition</th>
<th>Measurable Biological Substrate</th>
<th>Measurable Clinical Manifestations</th>
<th>Measurable Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>Myocardial dysfunction (echocardiography)</td>
<td>• Shortness of breath</td>
<td>6-min walking test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fatigue</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>Airways destructive changes (spirometry)</td>
<td>• Dyspnoea</td>
<td>6-min walking test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cough</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sputum</td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td>Arterial stenosis (Doppler echocardiography)</td>
<td>• Intermittent claudication</td>
<td>Treadmill walking distance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Numbness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ulcers</td>
<td></td>
</tr>
<tr>
<td>PF&amp;S</td>
<td>Reduced muscle mass (DXA)</td>
<td>• Slow walking speed</td>
<td>SPPB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Poor balance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Weakness</td>
<td></td>
</tr>
</tbody>
</table>
Under-nutrition, Sarcopenia and Frailty

Sarcopenia and frailty: From theoretical approach into clinical practice

F. Landi a,*, A. Cherubini b, M. Cesari c, R. Calvani a, M. Tosato a, A. Sisto a, A.M. Martone a, R. Bernabei a, E. Marzetti a

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Under-nutrition, Sarcopenia and Frailty

- Physical inactivity and decreased dietary intake
- Decreased protein synthesis and increased protein breakdown
- Infiltration of fat into muscle

Drivers of lean body mass loss

- Sedentary lifestyle
- Malnutrition/Anorexia: Low protein intake, ↓ vitamin D
- Age-related hormonal changes (↓ GH/IGF-1, testosterone, DHEAS, estrogens)
- Illness/Injury
- Oxidative stress
- Inflamm-aging
- ↑ myostatin
- ↓ alpha motor neurons

Physical frailty:
- Weakness
- Slow walking speed
- Balance impairment

Negative health outcomes (e.g., mobility disability)
Can sarcopenia/PF be prevented and/or treated?
Potential therapeutic strategies

**Testosterone**

**Growth Hormone**

**Ace-inhibitors**

**Estrogen**

**Statin**

**DHEA**

**Leptin**

**Essential fatty acids (Ω-3)**

**Antioxidants (Zn, Se)**

**Creatine**

**Cytokines inhibitors**

**Physical exercise**

**Myostatin inhibitors**

**Nutritional supplements**

**Protein - Vitamin D**
1.0 BACKGROUND

Anorexia of Aging: Risk Factors, Consequences, and Potential Treatments

Francesco Landi *, Riccardo Calvani, Matteo Tosato, Anna Maria Martone, Elena Ortolani, Giulia Savera, Alex Sisto and Emanuele Marzetti

Figure 3. Risk factors for anorexia of aging and negative outcomes.
1.0 BACKGROUND

Anorexia, physical function, and incident disability among the frail elderly population: Results from the iLSIRENTE Study

1.0 BACKGROUND

Figure 2. Anorexia of aging and risk of malnutrition.

Nutrients 2016 Jan 27;8(2).
2.0 PUTATIVE MECHANISMS OF PROTEIN ACTION ON MUSCLE CELLS

Overview of potential pathways whereby nutritional interventions may influence cellular events implicated in the regulation of muscle mass

Landi F. et al. The New Metabolic Treatments For Sarcopenia
2.0 PUTATIVE MECHANISMS OF PROTEIN ACTION ON MUSCLE CELLS

Protein Intake and Muscle Health in Old Age: From Biological Plausibility to Clinical Evidence

Francesco Landi *, Riccardo Calvani, Matteo Tosato, Anna Maria Martone, Elena Ortolani, Giulia Savera, Emanuela D’Angelo, Alex Sisto and Emanuele Marzetti

- Protein: the principal component of all muscles
- High quality protein to help support adults’ protein needs
- Most aging adults do not consume enough protein
- Inadequate levels reduce muscle reserves (immune function, increase skin fragility)
2.0 PUTATIVE MECHANISMS OF PROTEIN ACTION ON MUSCLE CELLS

Perspective: Protein: What Kind, How Much, When?
3.0 DIETARY PROTEIN REQUIREMENTS: HOW MUCH PROTEIN IS ENOUGH FOR OLDER ADULTS?

DIETARY PROTEIN INTAKE EVIDENCE: A prospective analysis including 2000+ elderly adults in the health, aging, and body composition (Health ABC) study

Protein is important in the maintenance and rebuilding of lean body mass in aging adults: participants in the top fifth of protein intake lost 40% less lean mass (LM) – Overall and appendicular – than did those in the bottom fifth of protein intake, a difference that is statistically significant ($p<0.01$).
3.0 DIETARY PROTEIN REQUIREMENTS: HOW MUCH PROTEIN IS ENOUGH FOR OLDER ADULTS?

Pre-hospital dietary intake correlates with muscle mass at the time of fracture in older hip-fractured patients

Riccardo Calvani¹, Anna Maria Martone¹, Emanuele Marzetti, Graziano Onder, Giulia Savera, Maria Lorenzi, Elisabetta Serafini, Roberto Bernabei and Francesco Landi *
**3.0 DIETARY PROTEIN REQUIREMENTS:**
**HOW MUCH PROTEIN IS ENOUGH FOR OLDER ADULTS?**

Lower quintiles of protein intake are associated with higher risk of frailty

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Protein Intake (% kcal)</th>
<th>Odds Ratio (with 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2</td>
<td>70.8 g/day</td>
<td>1.0</td>
</tr>
<tr>
<td>Q3</td>
<td>72.8 g/day</td>
<td>0.9</td>
</tr>
<tr>
<td>Q4</td>
<td>74.4 g/day</td>
<td>0.8</td>
</tr>
<tr>
<td>Q5</td>
<td>78.5 g/day</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Risk of frailty by quintile of protein intake (% kcal) (n = 24,417)

Increasing dietary protein intake, % of kcal
3.0 DIETARY PROTEIN REQUIREMENTS: HOW MUCH PROTEIN IS ENOUGH FOR OLDER ADULTS?

PROT-AGE summary

New recommendations call for higher protein intake (g per kg of bodyweight) in those aged >65 years:

- Minimum protein intake: 1.0-1.2 g/kg
- People with acute or chronic diseases: 1.2-1.5 g/kg
- People with severe illness or injury, or marked malnutrition: Up to 2.0 g/kg

*Caution needed among those with severe kidney disease (i.e. estimated Glomerular Filtration Rate <30mL/min/1.73m²), calculating their needs differently.
4.0 PROTEIN QUALITY: WHAT IS THE BEST PROTEIN SOURCE?
4.1 FAST VERSUS SLOW PROTEINS

• **No evidences** are available in terms of animal versus plant based protein. This issue is of interest considering that proteins are absorbed at different rates upon digestion.

• The concept of “**fast**” protein (i.e. whey protein) versus “**slow**” protein (i.e. casein and animal protein) is of particular relevance taking into consideration the anabolic response following the ingestion of different foods and/or oral nutritional supplements.

~ 1.0–1.2 g/kg/day
4.1 FAST VERSUS SLOW PROTEINS

Special Article

Evidence-Based Recommendations for Optimal Dietary Protein Intake in Older People: A Position Paper From the PROT-AGE Study Group

Protein Quality and Specific Amino Acids

- The list of indispensable amino acids is qualitatively identical for young and old adults.
- There is no evidence that protein digestion and absorption capacities change significantly with aging.
- “Fast” proteins may have some benefits over “slow” proteins in muscle protein metabolism.
- Dietary enrichment with leucine or a mixture of branched-chain amino acids may help enhance muscle mass and muscle function, but further studies are needed to support specific recommendations.
4.2 ANIMAL VERSUS PLANT-DERIVED PROTEINS

The mean animal-derived protein intake:

- I tertile 17.7 g/day
- II tertile 27.3 g/day
- III tertile 39.1 g/day

Landi F et al. J Nutr Health Aging, 2017
5.0 PROTEIN DISTRIBUTION: WHEN IS IT BETTER TO CONSUME PROTEIN?

◆ A daily protein intake of 1.0-1.2 g/kg body weight per day has been recognized by the PROT-AGE Study Group as the minimum quantity necessary to preserve muscle health during aging.

◆ Nevertheless

➢ the timing of protein ingestion and
➢ the synergistic effect of protein intake with physical activity may also be critical to optimize muscle health.
5.1. PROTEIN TIMING

Daily protein distribution – typical?

A skewed daily protein distribution fails to maximize potential for muscle growth.
5.1. PROTEIN TIMING

Daily protein distribution – optimal

Repeated maximal stimulation of protein synthesis
→ increase / maintenance of muscle mass
5.2. PROTEIN INTAKE AND PHYSICAL EXERCISE

Original Study
Protein Supplementation Increases Muscle Mass Gain During Prolonged Resistance-Type Exercise Training in Frail Elderly People: A Randomized, Double-Blind, Placebo-Controlled Trial

Michael Tierland Msc, Marliou L. Dirks Msc, Nikita van der Zwalm Msc, Lex B. Verdijk PhD,*, Ordine van de Rest PhD, Lisette C.P.G.M. de Groot PhD, Luc J.C. van Loon PhD,**

Graphs showing changes in grip strength and body mass over time.
Aging is associated with a decreased sensitivity of muscle to the anabolic effect of amino acids.

A high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids in the elderly.

In conclusion, this study demonstrates for the first time in elderly humans that attenuated response of muscle protein synthesis following ingestion of small amounts of amino acids can be reversed by ingestion of extra leucine.
6.0. PROTEIN SUPPLEMENTATION: NEW EVIDENCE

Original Study

Effects of a Vitamin D and Leucine-Enriched Whey Protein Nutritional Supplement on Measures of Sarcopenia in Older Adults, the PROVIDE Study: A Randomized, Double-Blind, Placebo-Controlled Trial
Appendicular muscle mass (DXA, secondary)

The raw mean change from baseline to week 13 and standard error. The p-value represents the time x treatment interaction derived from a mixed model (MMRM) adjusting for age, sex, and baseline protein intake.

Change from baseline in appendicular muscle mass (kg)

Appendicular muscle mass

p = 0.044

Control (n=124)
Active (n=136)

Appendicular muscle mass (DXA, secondary)
6.0. PROTEIN SUPPLEMENTATION: NEW EVIDENCE

**p<0.001

**p=0.018

Chair-stand time (seconds)
Reduction from baseline

Control
Active

week 7
week 13

**p<0.001

PROTEIN SUPPLEMENTATION: NEW EVIDENCE

JAMDA 16 (2015) 740e747
HMB is an active metabolite of the amino acid leucine

- **HMB regulates protein in muscle cells**
  - Supports muscle protein synthesis and slows down muscle protein breakdown
  - Helps rebuild muscle mass lost naturally over time
  - Helps rebuild LBM to support muscle strength and functionality
Effects of HMB in non-exercising older adults

Objective:
Evaluate the effect of HMB on LBM and strength in older adults (with and without resistance training exercise)

Study Design:
- Prospective, randomized, placebo-controlled trial
- Older adults (age≥ 65 y), n=27/group- 4 groups
- HMB at 3g/day vs. placebo (with or without progressive RT)
- 24-wks supplementation; Outcomes: lean mass and leg strength

Results: HMB increased lean mass and strength in non-exercising older adults

- HMB increased lean mass and strength in non-exercising older adults.
- Isokinetic Leg Extensor 60° (nM), change
- Control vs. HMB
- Baseline, 12 wks, 24 wks
- * p<0.05, Change from baseline by paired t-test
Original Study

Impacts of High-Protein Oral Nutritional Supplements Among Malnourished Men and Women with Sarcopenia: A Multicenter, Randomized, Double-Blinded, Controlled Trial

Joel T. Cramer PhD a,*, Alfonso J. Cruz-Jentoft MD, PhD b, Francesco Landi MD, PhD c, Mary Hickson PhD, RD d, Mauro Zamboni MD e, Suzette L. Pereira PhD f, Deborah S. Hustead PhD f, Vikkie A. Mustad PhD f

Cramer et al. JAMDA 2016
6.0. PROTEIN SUPPLEMENTATION: NEW EVIDENCE

Results - Leg Strength (Nm), Change from Baseline at 12 weeks

### Leg Strength Change from Baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Leg Strength, Nm, change from baseline</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>(-3.9, 11)</td>
<td></td>
</tr>
<tr>
<td>Severe Sarcopenia</td>
<td>(-5.12, -2.12)</td>
<td></td>
</tr>
<tr>
<td>Sarcopenia</td>
<td>(-1.10, -2.10)</td>
<td>0.0505</td>
</tr>
<tr>
<td>Sarcopenia Normal Gait</td>
<td>(*, *)</td>
<td></td>
</tr>
<tr>
<td>Sarcopenia Normal Grip</td>
<td>(*, #)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

* P<0.05 vs baseline
† P<0.01 vs baseline
# P<0.001 vs baseline

Cramer et al. JAMDA 2016
SPRINTT: an answer
SPRINTT: an answer

Identification of a target population with Sarcopenia and Frailty status

The identification of \textbf{physically frail/sarcopenic older persons} will rely on 3 key elements:

1. Target \textit{organ deterioration} (i.e., low muscle mass as measured by DXA = sarcopenia)

2. Clinical \textit{signs and symptoms of physical frailty} (i.e., weakness, slow walking speed and poor balance) objectively measured through the SPPB and corresponding to a summary score between 3 and 9

3. Ability to complete the 400-m walk test at usual pace within 15 minutes (no mobility disability)
Evaluation and validation of a new methodology

**Physical activity intervention**: structured exercise and PA, and will resemble the protocol already used in the LIFE study.

**Nutritional assessment and dietary intervention**: personalised dietary recommendations and eventual oral nutritional supplements of protein and/or vitamin D.

**Health technology intervention**: acquisition of information from the participant’s domicile (e.g., daily dietary and protein intake, daily physical activity, walk speed, falls or near-falls), implementation of home-based exercise training, remote nutritional counselling, reinforcement of intervention adherence.
SPRINTT: an answer

Definition of an experimental setting serving as template for regulatory purposes and pharmaceutical investigations

- 1,500 community-dwellers, aged 70+ years
- Low muscle mass (DXA, FNIH)
- SPPB 3-7 (n = 1,200) and 8-9 (n = 300)
- Able to walk 400 metres at usual pace in 15 minutes
- Two treatment arms: Multicomponent intervention (Exercise and Nutrition) versus Successful aging programme
7.0. TAKE HOME MESSAGE

Nutrition-muscle connection
Nutrition-muscle connection

The “Pachinko Model”

Calvani R, Landi F et al. 2013
7.0. TAKE HOME MESSAGE

**Sarcopenia**

- The consequences of sarcopenia warrant screening and treatment

**Physical Frailty**

**Proteins and Vitamin D**

- Adequate intake of proteins (≥1 g/kg/d) and vitamin D along with adequate physical activities may help prevent sarcopenia / PF

**Leucine + exercise**

- Leucine and HMB are of interest in the treatment, as well as physical activity (resistance training)

**Evidence Base Medicine**

- Better studies using clinically relevant outcomes (i.e., physical performance) are needed
Thank you for your attention and.....

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