La Sarcopenia
Definizione, Patogenesi e Trattamento

L’approccio Nutrizionale e Farmacologico

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19 Ottobre 2013
Aula Magna Nuovo Ospedale S. Anna
Cona, Ferrara
Why to identify Sarcopenia?

“Sarcopenia is becoming recognized as a major cause of disability and morbidity in the elderly population”.

Roubenoff and Hughes, 2000
Functional impairment according to skeletal muscle index

NHANES III (n = 2224 men older than 60 years)

- Normal SMI
- Pre-sarcopenia
- Sarcopenia

- Walking ¼ mile
- Climbing 10 stairs
- Lifting 5 Kg
- Kneeling
- Standing up from a chair

Janssen et al, 1998
Predictors of worsening disability during the follow-up period 5.5 years (160 subjects older 70)

- Basal Appendicular FFM
- Basal FM
- Age
- Basal BMI
- Meters (6 min walking test)
- Comorbidity (n of patologies)
- Gender
- Loss of appendicular FFM

OR 2.15 p<0.001

"Fantin et al, 2007"
Clinical Interventions in Aging

Aging skeletal muscle
↓
Alpha-motor neurons
↓
Type 2 muscle fibers
↓
Protein metabolism
↓
Sarcopenia
↓
Physical function
↓
Immunity
↓
Frailty
↓
Illness
↓
Disability
↓

Falls

Osteoporosis

Metabolic syndrome

Waters et al, 2010
### Sarcopenia and mortality risk in frail older persons aged 80 years and older: results from iISIRENTE study

197 subjects living in community
7- years follow up


<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hazard ratio (95% confidence interval)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sarcopenia</td>
<td>2.95 (1.44–6.04)</td>
<td>2.89 (1.40–5.96)</td>
<td>2.40 (1.07–5.42)</td>
<td>2.32 (1.01–5.43)</td>
</tr>
<tr>
<td>Age</td>
<td>1.15 (0.93–1.42)</td>
<td>1.08 (0.85–1.36)</td>
<td>1.12 (0.87–1.43)</td>
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<tr>
<td>Gender (female)</td>
<td>0.55 (0.29–1.03)</td>
<td>0.49 (0.25–0.99)</td>
<td>0.49 (0.23–1.04)</td>
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<tr>
<td>Education</td>
<td>0.87 (0.72–1.04)</td>
<td>0.87 (0.72–1.05)</td>
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<td>ADL impairment</td>
<td>1.91 (1.29–2.83)</td>
<td>1.75 (1.20–2.56)</td>
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<tr>
<td>Body mass index</td>
<td>0.92 (0.86–0.99)</td>
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<td>Hypertension</td>
<td></td>
<td>0.60 (0.26–1.35)</td>
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<td>Congestive heart failure</td>
<td></td>
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<td>6.71 (1.70–26.22)</td>
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<tr>
<td>COPD</td>
<td></td>
<td></td>
<td>1.46 (0.50–4.21)</td>
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<tr>
<td>Number of diseases</td>
<td></td>
<td></td>
<td>1.29 (0.92–1.80)</td>
<td></td>
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<tr>
<td>TNF-α</td>
<td></td>
<td>0.99 (0.85–1.15)</td>
<td></td>
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</tbody>
</table>

Model 1: adjusted for age, gender.
Model 2: adjusted for age, gender, education, ADL impairment, body mass index.
Model 3: adjusted for age, gender, education, ADL impairment, body mass index, hypertension, congestive heart failure, chronic obstructive pulmonary disease (COPD), number of diseases, TNF-α.

Age, education, ADL impairment, body mass index, number of diseases, TNF-α was treated as a continuous variable.
6-months hospital readmission

Gariballa and Alessa, 2013

432 hospitalized ill older patients with age higher than 65 years
<table>
<thead>
<tr>
<th>Bilions $</th>
<th>7.18</th>
<th>3.63</th>
<th>2.7</th>
<th>4.96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk disability%</td>
<td>1</td>
<td>3.48</td>
<td>4.6</td>
<td>1</td>
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</table>
Yearly costs, (US)

Osteoporotic fractures $16.3 billion

Sarcopenia $18.5 billion

Map of 1121 studies found by search of: osteoporosis
Only a handful of clinical trials are under way to treat sarcopenia

Map of 101 studies found by search of: sarcopenia
to maintain muscle mass

to reduce muscle mass loss or to regain

different aims
Nutrition and sarcopenia: evidence for an interaction

Potential interventions

- Physical activity (strength training)
- Increased protein?
- Inactivity
- Anabolic resistance
- Inflammation
- Acute, rapid wasting disorders (e.g., sepsis, AIDS-HIV wasting, cancer cachexia)
- Cronic conditions of muscle loss (e.g., renal failure, heart failure, COPD, rheumatoid arthritis)
- Vit D deficiency?
- Age-related sarcopenia
- Acidosis
- Acid buffering
- Anti-inflammatory
- Anti-oxidants & phase 2 protein inducers
- Oily fish (n-3PUFA)
- Fruit & vegetables
- Vitamin D

The healthy diet

Relative muscle loss

D. Joe Millward
Proceedings of the Nutrition Society (2012), 71, 566–575
Adjusted lean mass (LM) loss by quintile of energy-adjusted total protein intake. N= 2066

Protein intake: from 0.7 g/kg to 1.2 g/kg

Adjusted lean mass (LM) loss by quintile of energy-adjusted total protein intake and weight change status. N= 2066

Low protein intake means higher risk of Sarcopenia

Denise K Houston, 2008
Protein intake (g/d) by age

Protein intake (g/kg body weight) by age

NHANES 2003-2004

Fulgoni, 2008
Introito calorico e proteico in soggetti anziani di sesso femminile
Continuing Survey of Food Intakes by Individuals
(15000 soggetti, con età di 60, 70, 80 e oltre)

Wakimoto & Block, 2001
Istidina  Isoleucina  Leucina  Lisina  Metionina  Fenilalanina  Treonina  Triptofano  Valina

Non essenziali

Alanina  Acido  Aspartico  Asparagina  Acido  Glutammico  Serina

Conditionally Indispensable

Arginina  Cisteina  Glutamina  Glicina  Prolina  Tirosina
AA ramificati
30%
proteine muscolari
Mixed muscle fractional synthetic rate (FSR) in young and elderly before and after ingestion of 15 g of EAA
Amino Acid Supplementation Increases Lean Body Mass, Basal Muscle Protein Synthesis and IGF-1 Expression in Older Women

Anabolic response to EAA supplementation is maintained over time
The Role of Leucine in the Regulation of Protein Metabolism¹,²

Peter J. Garlick³

ABSTRACT: Studies both in vivo and in vitro have shown that leucine at a very high dose can stimulate muscle protein synthesis, an effect that is enhanced in vivo by insulin secreted in response to the leucine dose. High leucine can also inhibit protein degradation in skeletal muscle, as well as in liver. In contrast, at normal physiological levels, increasing leucine concentration by infusion stimulates muscle protein synthesis by enhancing its sensitivity to insulin. It is concluded that the role of leucine in vivo is to provide a signal that amino acids are available, which in combination with the signal of energy availability from insulin, stimulates muscle protein synthesis. J. Nutr. 135: 1553S–1556S, 2005.
### Aminoacidi essenziali in diete a vario contenuto calorico

<table>
<thead>
<tr>
<th>Dieta kcal</th>
<th>Valina</th>
<th>Isoleucina</th>
<th>Leucina</th>
<th>Lisina</th>
<th>Metionina</th>
<th>Fenilalanina</th>
<th>Treonina</th>
<th>Triptofano</th>
<th>Istidina</th>
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<tbody>
<tr>
<td>1500</td>
<td>2,84</td>
<td>2,47</td>
<td>4,25</td>
<td>4,171</td>
<td>1,19</td>
<td>2,40</td>
<td>2,47</td>
<td>0,59</td>
<td>1,51</td>
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<tr>
<td>1800</td>
<td>3,59</td>
<td>3,12</td>
<td>5,37</td>
<td>5,27</td>
<td>1,542</td>
<td>3,03</td>
<td>3,07</td>
<td>0,75</td>
<td>1,92</td>
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<tr>
<td>2000</td>
<td>3,73</td>
<td>3,24</td>
<td>5,57</td>
<td>5,50</td>
<td>1,622</td>
<td>3,14</td>
<td>3,19</td>
<td>0,77</td>
<td>2,00</td>
</tr>
</tbody>
</table>

Introito medio di Leucina negli USA: 6,1 g/die (da alimenti e/o supplementi) (1988-1994 NHANES III)
Hydroxy-β-Methylbutyrate: metabolita della Leucina

- **Essenziali**
  - Istitina
  - Isoleucina
  - **Leucina**
  - Lisina
  - Metionina
  - Fenilalanina
  - Treonina
  - Triptofano
  - Valina

- **Non essenziali**
  - Alanina
  - Acido
  - Aspartico
  - Asparagina
  - Acido
  - Glutammico
  - Serina

- **Conditionally Indispensable**
  - Arginina
  - Cisteina
  - Glutamina
  - Glicina
  - Prolina
  - Tirosina
**Studi in vitro: meccanismi d’azione**

In colture di miociti:
- aumenta sopravvivenza cellule muscolari satelliti ed inibisce apoptosi
  - Kornasio et al, 2009

Nei ratti inoculati con epatoma aumenta fosforilazione mTOR a livello del muscolo gastrocnemio prevenendo:
- perdita di peso
- decremento massa gastrocnemio
  - Aversa et al 2011

Inibizione caspasi 8 e 3
Change in Muscle Strength During HMB Supplementation

- 41 healthy young adults (19-29 years), untrained
- 2 protein levels: 117 g/day (control) or 175 g/day
  - Diet was controlled, nutrient powder in a shake
- 3 HMB supplementation doses randomized and blinded within each protein group
  - 0, 1.5, or 3.0 g/day Mixed in orange juice
- Weight training for 1.5 hours 3 days/week for 3 weeks

Data from control and high protein groups were pooled because there was no difference in HMB results
- Overall muscle strength increased at 3 weeks
  - 8% in control group
  - 13% in 1.5 g HMB group
  - 18% in 3.0 g HMB group

Change in Urinary 3-Methylhistidin (3-MH) Excretion During HMB Supplementation

- 3-MH is a muscle-specific amino acid
  - Formed during breakdown of muscle proteins (actin and myosin)
  - Excreted unchanged in urine

- Total muscle breakdown per day increased from 3% at baseline to
  - 6% at week 3 in control group
  - 5.5% at week 3 in 1.5 g HMB group
  - 4.5% at week 3 in 3.0 g HMB group

\[ a \rho < .04 \]
\[ b \rho < .001 \]

Randomized, double-blind study:
31 adults (men, 15; women, 16) 70 years of age
Received 3 g/day HMB or placebo for 8 weeks
Participants underwent an exercise program 5 day/week
diet not controlled
Double-blind study in old women (76.7 years)
2 g HMB (n 23) vs placebo (n 27)
12 weeks: no exercise

Flakol et al, 2004
Body composition data for elderly men and women

Baier S et al., 2009

12 months double-blinded study

127 elderly adults

Received:
2 to 3 g HMB + 1.5 to 2.25 g lysine + 5 to 7.5 g arginine per day

or isocaloric, isonitrogenous placebo

No exercise component

Baier S et al., 2009
Nutrition and sarcopenia: evidence for an interaction

D. Joe Millward

Proceedings of the Nutrition Society (2012), 71, 566–575
Dietary omega-3 fatty acid supplementation increase the rate of muscle protein synthesis in older adults: a randomized controlled trial

16 anziani randomizzati a ricevere omega 3 (4 g) o corn oil (4 g) per 8 sett In condizioni basali e dopo clamp iperinsulinemico e iperaminoacidemico.
Nutrition and sarcopenia: evidence for an interaction

Potential interventions

- Physical activity (strength training)
- Increased protein?
- Oily fish (n-3PUFA)
- Fruit & vegetables
- Vitamin D

Relative muscle loss

- Inactivity
- Anabolic resistance
- Anti-inflammatory
- Inflammation
- Acidosis
- Vit D deficiency?
- Age-related sarcopenia
- Chronic conditions of muscle loss (e.g. renal failure, heart failure, COPD, rheumatoid arthritis)

Acute, rapid wasting disorders (e.g. sepsis, AIDS-HIV wasting, cancer cachexia)

D. Joe Millward

Proceedings of the Nutrition Society (2012), 71, 566–575
The Minos study: 845 men aged 45-85 years

Szulc et al, 2004
• Ipovitaminosis D associata ad atrofia fibre di tipo II
• Livelli Vitamina D associati a forza muscolare
• Supplemantazione Vitamina D aumenta forza muscolare e sembra ridurre il rischio di caduta
• Bassi livelli di vitamina D associati ad aumentato rischio di miopatia da statina
Nutrition and sarcopenia: evidence for an interaction

D. Joe Millward

Proceedings of the Nutrition Society (2012), 71, 566–575
Adherence to Mediterranean diet and decline in walking speed over 8 years in community-dwelling older adults

H-ABC study
2225 well functioning participants older than 70 years

Conclusion—Walking speed over 8 years was faster among those with higher MedDiet adherence at baseline. The differences remained significant over 8y, suggesting a long-term effect of diet on mobility performance with aging.
Sarcopenia in the aging high-fat fed rat: a pilot study for modeling sarcopenic obesity in rodents

L. Cornelius Bollheimer ·

Male rats
CD 25% fat
HFD 45% fat
Isocaloric
Starting 2
months
Sarcopenia in the aging high-fat fed rat: a pilot study for modeling sarcopenic obesity in rodents

L. Cornelius Bollheimer


Vastus lateralis biopsies at 24 months

At 12 months in HFD rats:
- Plasma insulin 3-fold higher
- Plasma leptin 1.6-fold higher
- Plasma adiponectin 20% lower
Sarcopenia nutritional recommendations

Metabolic efficiency in older persons is decreasing, requiring a higher protein intake: a 15%-38% of older men and 27%-41% of old women ingest less than the RDA for protein (B)

A trial of balanced amino-acid supplementation (leucine enriched?) alone and with exercise is recommended (B)

Vitamin D should be measured in all sarcopenic subjects (A)

A. A minimum single randomized-placebo controlled trial or meta-analysis. B. Small trials

J Morley, 2010
New concepts about protein for the Dietary Guidelines

• Protein is a critical part of the adult diet
• Protein needs are proportional to body weight; NOT energy intake
• Adult protein utilization is a function of intake at individual meals
  • Most adults benefit from protein intakes above the minimum RDA (1-1.2g/kg/die)

Layman DK, 2009

Acceptable Macronutrient Distribution Ranges (AMDR) is more relevant to normal dietary intake than RDA

Wolfe et al, 2008
Protein distribution at meals. A) Ingestion of 90 grams of protein, distributed evenly at 3 meals. B) Ingestion of 90 grams of proteins unevenly distributed throughout the day. Stimulating muscle protein synthesis to a maximal extent during the meals shown in Figure 1A is more likely to provide a greater 24 hour protein anabolic response than the unequal protein distribution in Figure 1B.

Nutrition & Metabolism

Donald K Layman, 2009
Drugs for Sarcopenia Treatment

Myostatin Inhibitors:

- antibody
- recepteror decoy
- activity inhibitors
Fig. 2. A fullblood Belgian Blue bull showing the double muscling phenotype.
The aging myostatin null phenotype:

Weights of muscles type I, type II and mixed 50-150 % greater in Mstn-

Liver, kidney, spleen weights lower in Mstn-

Jackson et al 2012
A myostatin inhibitor (propeptide-Fc) increases muscle mass and muscle fiber size in aged mice but does not increase bone density or bone strength. 

Myostatin propeptide prevents the binding of myostatin to its receptor.

Arounleut et al, 2013
A myostatin inhibitor (propeptide-Fc) increases muscle mass and muscle fiber size in aged mice but does not increase bone density or bone strength.

Male mice 22-m old:
20mg/kg myostatin propeptide (PRO) body weight i.p. for 25 days vs vehicle (VEH)

Arounleut et al, 2013
Arounleut et al, 2013

EDL Change in Gene Expression with Myostatin Propeptide Treatment

Fold Change Increase (PRO vs VEH)

VEH       PRO

MURF1
MAFbx
GAPDH

Femur Change in Gene Expression with Myostatin Propeptide Treatment

Fold Change Increase (PRO vs VEH)

Runx2   BMP-2   Osx
A Phase I/II trial of MYO-029 in Adult Subjects with Muscular Dystrophy

percentage change in muscle fiber diameter before and after treatment.

Methods: This double-blind, placebo-controlled, multinational, randomized study included 116 subjects divided into sequential dose-escalation cohorts, each receiving MYO-029 or placebo (Cohort 1 at 1mg/kg; Cohort 2 at 3mg/kg; Cohort 3 at 10mg/kg; Cohort 4 at 30mg/kg). Safety and adverse events were assessed by reported signs and symptoms, as well as by physical examinations, laboratory results, echocardiograms, electrocardiograms, and in subjects with facioscapulohumeral dystrophy, funduscopic and audiometry examinations. Biological activity of MYO-029 was assessed through manual muscle testing, quantitative muscle testing, timed function tests, subject-reported outcomes, magnetic resonance imaging studies, dual-energy radiographic absorptionmetry studies, and muscle biopsy.

Wagner et al, 2008
Apoptosis in Skeletal Myocytes: A Potential Target for Interventions against Sarcopenia and Physical Frailty – A Mini-Review

<table>
<thead>
<tr>
<th>Behavioral interventions</th>
<th>Apoptotic signaling pathways</th>
<th>extrinsic</th>
<th>mitochondrial caspase-dependent</th>
<th>mitochondrial caspase-independent</th>
<th>sarcoplasmic reticulum pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>Resveratrol (CR mimic)</td>
<td></td>
<td>§</td>
<td></td>
<td></td>
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<tr>
<td>Exercise training</td>
<td>§</td>
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<table>
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<td>Enalapril</td>
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<td>Acetaminophen</td>
<td></td>
<td></td>
<td>§</td>
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<td>§</td>
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<tr>
<td>Antimyostatin antibody</td>
<td>§b</td>
<td>§b</td>
<td></td>
<td></td>
<td>§b</td>
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<tr>
<td>Q10 + creatine + ginseng</td>
<td>§a</td>
<td>§a</td>
<td></td>
<td>§a</td>
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<td>Testosteronec</td>
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</table>

Emanuele Marzetti\textsuperscript{a}  Riccardo Calvani\textsuperscript{b}  Roberto Bernabei\textsuperscript{b}  Christiaan Leeuwenburgh\textsuperscript{c}

Gerontology 2012;58:99–106
Drugs for Sarcopenia Treatment: Ancillary Effects

• Ace-Inhibitors ?

• Statin ?
641 Women Health and Aging Study
old disabled women without CHF
Follow-up 3 years
Effect of ACE INHIBITORS on skeletal muscle

Muscle fibers type effect
- Shift from type I to type II
  - Muscle fiber areas
  - Aerobic activity

Metabolic effects
- IGF-1 and IGFBP-3
- Insulin sensitivity
- Muscle loss
- Endothelial cell growth
- Skeletal muscle blood flow

Anti-inflammatory and nutritional effects
- IL-6, TNF-α
- Muscle loss
- Sympathetic activity
- Intestinal nutrient absorption
Effect of STATIN on skeletal muscle

- **Vascular effect**
  - ↓ Atherosclerosis
  - ↑ Perfusion
  - ↓ Muscle wasting

- **Metabolic effects**
  - ↑ Nitric oxide
  - ↑ Vascular endothelial growth factor

- **Anti-inflammatory effects**
  - ↓ C-reactive protein
  - ↓ Other inflammatory markers
<table>
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<tr>
<th>Potential Study End Point</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle mass</td>
<td>Readily measured and central to the condition of sarcopenia; relevant to expected actions of several potential interventions (see Table 1)</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>Easily measured; important component of physical function and correlates with clinical outcomes</td>
</tr>
<tr>
<td>Falls</td>
<td>Clinically important and of prognostic value</td>
</tr>
<tr>
<td>Fractures</td>
<td>Clinically important; accepted as regulatory endpoint in osteoporosis</td>
</tr>
<tr>
<td>Walking and other physical performance measures</td>
<td>Relevant to ambulatory function; treadmill assessments, walking speed and 6-minute walk accepted as regulatory endpoints for other indications</td>
</tr>
<tr>
<td>Patient-reported outcomes</td>
<td>Probably most relevant to patients’ ambulatory function and quality of life</td>
</tr>
</tbody>
</table>

Considerations in the Development of Drugs to Treat Sarcopenia

Eric P. Brass, MD, PhD, and Kathy E. Sietsema, MD

JAGS 59:530–535, 2011