Skeletal Muscle and Aging: Going, Going, Gone

National Science Teachers Association
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20 yr → 80 yr

(http://www.sarcopenia.com/)
Conditions Leading to Muscle Wasting (Atrophy)

- Limb immobilization (casting)
- Microgravity
- Prolonged bed rest/hindlimb suspension
- Tumor bearing
- Fasting/malnutrition
- Burns
- Infection
- Denervation
- Sarcopenia
“No decline with age is more dramatic or potentially more functionally significant that the decline in lean body mass. Why have we not given it more attention? Perhaps it needs a name derived from the Greek. I’ll suggest *sarcopenia*.”

I. H. Rosenberg, 1989

William J. Evans
Sarcopenia

Sarcopenia is age-related loss of lean muscle mass
Loss of ~40% of muscle mass by 80 years of age
Loss of locomotion due to atrophy of type IIb fibers
Loss of capacity to withstand injuries and diseases

(http://www.sarcopenia.com/)
Sarcopenia

“sarx” – flesh

“penia” – loss or deficiency

**Class I**

A value of lean body mass 1 to 2 standard deviations below the average value calculated in healthy, young adults.

**Class II**

A value of lean body mass greater than 2 standard deviations below the average value calculated in healthy, young adults.
Sarcopenia

**Physical Consequences**
- Loss of muscle strength
- Decreased mobility and stability
- Increased risk of falls and injuries
- Decreased reserve of body proteins and energy
- Impaired metabolic adaptation and immunological response

**Fiscal Consequences**
- Annual cost of sarcopenia in U.S. = $18.5 billion
  - 35% of older adult population has moderate sarcopenia
  - 10% of older adult population has severe sarcopenia
  - $897 per sarcopenic individual
- Annual cost of osteoporotic fractures in U.S. = $16.3 billion
## Muscle Functional Characteristics

### Muscle Fiber Type

<table>
<thead>
<tr>
<th>Fast Twitch</th>
<th>Slow Twitch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative (Ila)</td>
<td>Highly oxidative</td>
</tr>
<tr>
<td>Glycolytic (IIb)</td>
<td>Slow shortening</td>
</tr>
<tr>
<td>Rapid shortening</td>
<td>Low power output</td>
</tr>
<tr>
<td>High power output</td>
<td>Fatigue resistant</td>
</tr>
<tr>
<td>Fatigable (Glycolytic)</td>
<td>Recruited in all stages of muscle contraction</td>
</tr>
<tr>
<td>Fatigue resistant (Oxidative)</td>
<td></td>
</tr>
<tr>
<td>Recruited in high intensity contractions</td>
<td></td>
</tr>
</tbody>
</table>
Muscle Functional Characteristics

**Characteristics that determine strength**
- Fiber cross-sectional area
- Fiber number
- Fiber type
- Ability to maximally recruit fibers
- Protein content

**Characteristics that change with age**
- Cross-sectional area decreased
- Fiber number decreased
- Fast twitch ‘converted’ to slow twitch
- Inability to activate all fibers
- “Defective” protein
Changes in Skeletal Muscle With Age

Strength is not lost uniformly:

- Across different muscles
- Across different types of movements
- Clinical observations: lower body strength declines faster than upper body
- Weightlifter data: relative disuse may be the reason for non-uniform strength loss across muscle groups

Fig. 3 - Relative decline with age of peak leg muscle strength. Data were acquired from concentric isokinetic (0.52 rad s⁻¹) knee extension tests performed on 654 men and women aged 20-93 years. Values are expressed relative to the highest (20-30 years) group. Adapted from Lindle et al. (4).
Changes in Skeletal Muscle With Age

Fig. 2 - Relative changes in muscle size parameters in humans. Data are summarized from whole vastus lateralis reported by Lexell et al. (18). The decline in total muscle cross-sectional area (CSA) appears to be due to both a reduction in total fiber number and atrophy of type II fibers. The proportion of fiber types was unchanged, but due to the reduced size of type II fibers, the proportion of the total area occupied by type II fibers also declined with aging.
Muscle Functional Characteristics

- Decreased # of fibers
- Decreased cross-sectional area of fiber
- Fiber type changes: decreased fast twitch to slow twitch ratio
- DNA damage: protein quality reduced

Total Muscle Force

Force/Cross-sectional Area
Sarcopenia

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Sarcopenia
Potential Age-Related Causes

- Motor unit remodeling
- Protein synthesis
- Hormonal changes
- Reactive oxygen species and antioxidants
- Inflammation and cytokines
- Mitochondrial mutations
- Protein degradation
- Physical activity
Sarcopenia

“The Vicious Cycle”

Sarcopenia

Inactivity
Sarcopenia

"The Vicious Cycle"

Sarcopenia

Inactivity
Sarcopenia

“The Vicious Cycle”

Sarcopenia → Inactivity → Sarcopenia

Do we lose muscle mass and therefore become inactive because activity is more difficult? Or Do we become inactive with age and lose muscle mass as a result?
Protein Turnover

Synthesis vs Degradation

Steady State

Synthesis = Degradation
Muscle Protein Balance

- Physical Activity
- Protein Intake
- Protein Requirements
- Anabolic Hormones (GH, Testosterone, Estrogen)
- catabolic Cytokines (Interleukin 6)

Protein Synthesis : Protein Degradation

α-motor neurons and functional motor units
Pathways of Intracellular Protein Degradation

- Lysosomal Mechanisms (Cathepsins)
- The Calpain System
- Mitochondrial Proteases
- The Ubiquitin-Proteasome Pathway
Lysosomal Mechanisms

• Lysosomes digest “food” macromolecules into smaller subunits.

• The lysosome has hydrolytic enzymes to break down polymers into monomers.

• Subunits such as monosaccharides and amino acids are pumped across the lysosomal membrane into the cytoplasm.

• The lysosome is maintained at an acid pH to denature macromolecules, aiding hydrolysis.
The Calpain System

- Calcium-dependent neutral proteases
- Chimeras of a papain-like protease and a calmodulin-like calcium-binding protein
- Muscle-specific form is gene product responsible for limb girdle muscular dystrophy
- May degrade selected proteins during calcium-mediated signal transduction pathways
Pathways of Intracellular Protein Degradation

- Lysosomal Mechanisms (Cathepsins)
- The Calpain System
- Mitochondrial Proteases
- The Ubiquitin-Proteasome Pathway
The ubiquitin-proteasome pathway of intracellular protein degradation

Modification of proteins with ubiquitin

Degradation of ubiquitinated proteins
Topology of the proteasome’s catalytic sites

The proteasome’s multiple catalytic sites are located on β subunits and face the interior channel.
Proteolysis by the 26S proteasome

1) activation by gating
2) polyubiquitin chain binding
3) ATP hydrolysis
4) substrate unfolding
5) translocation of unfolded polypeptide chain
6) peptide bond hydrolysis
7) ubiquitin isopeptidase
Electron microscopy of proteasome-PA700 complexes

Proteasome

Proteasome -PA700
Sarcopenia and Ubiquitin-Proteasome Pathway

- Proteasome degrades >80% of cellular proteins
- Proteasome is the major player in a variety of atrophies
  - Myofibrillar proteins are proteasome substrates
- Proteasome degrades oxidized, damaged, & denatured proteins
Change in Lean Muscle Mass with Age

Muscle Mass to Body Mass Ratio
(Sprague-Dawley rats)

3 mo. 13 mo. 27 mo. 30 mo.
age (months)

% of body weight

Lateral Gastrocnemius
Medial Gastrocnemius

Muscle Mass to Body Mass Ratio
(F344BN rats)

4 mo. 12 mo. 32 mo.
age (months)

% of body weight

Lateral Gastrocnemius
Medial Gastrocnemius

Heart Mass to Body Mass Ratio
(Sprague-Dawley rats)

3 mo. 13 mo. 27 mo. 30 mo.
age (months)

% of body mass

Heart

Muscle mass (g) X 100 = % Body mass
Body mass (g)
Endogenous Expression of Proteasomal Subunits

TBP1- 
P45- 
S4- 
P31- 
Actin- 

PA 28 alpha-
PA 28 beta-

Subunit Z-
MCP 236-
MCP 76-
Actin-

Ubiquitin-

Tib. Anterior Liver
Proteasome Activity

Proteasome Activity in Muscle (Sprague-Dawley rats)

Proteasome Activity in Heart (Sprague-Dawley Rats)
Sarcopenia at the Cellular Level (Sprague-Dawley Rats)

ATPase (metachromatic stain)

S4
The ubiquitin-proteasome pathway of intracellular protein degradation

Modification of proteins with ubiquitin

- Ubiquitin
- E1
- E2\(_{(n)}\)
- ATP

Degradation of ubiquitinated proteins

- Proteasome
- Regulatory Proteins (PA700)
- ATP
- 26S Proteasome
Micro-array Analysis

“Atrogenes”

E3 Ubiquitin Ligases

MAFbx1
MuRF1
Exercise

• Strength Exercises
• Endurance Exercises
• Balance Exercises
• Stretching Exercises

National Institute on Aging
www.nia.nih.gov/exercisebook
American College of Sports Medicine
www.acsm.org
Indicators for Exercise and Diet Interventions

- Capacity of the muscle protein synthesis machinery is preserved until very old age (We can make muscle in old age)
- Significant gains in muscle mass (metabolic and strength benefits)
- Important gains in mobility and balance (improve quality of life and reduce risk of debilitating falls)

Protein Synthesis : Protein Degradation

Strength Training

Nutrition (Protein intake)
http://www.utsouthwestern.edu/stars