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NEPS Laboratory Mission:

- The NEPS Laboratory conducts studies aimed at the identification, evaluation, and understanding of nutritional and physical activity interventions that possess anabolic properties in skeletal muscle and have the potential to prevent or reverse impaired motor performance and/or physical dysfunction in older adults.
<table>
<thead>
<tr>
<th>Research Project</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower extremity muscle power and function in the elderly</td>
<td>NIH/NIA</td>
</tr>
<tr>
<td>Lifestyle Interventions for the Elderly (LIFE)</td>
<td>NIH/NIA</td>
</tr>
<tr>
<td>Efficacy of whey protein supplementation on resistance exercise-induced changes in muscle strength, fat free mass, and function in mobility-limited older adults</td>
<td>National Dairy Council</td>
</tr>
<tr>
<td>Ancillary Study to “Efficacy of whey protein supplementation”</td>
<td>Kraft Global Foods</td>
</tr>
<tr>
<td>A Translational approach to function promoting anabolic therapies (Boston Claude Pepper Older Americans Independence Center)</td>
<td>NIH/NIA</td>
</tr>
<tr>
<td>Metabolic markers to develop assays and optimize warfighter fitness</td>
<td>U.S. Special Operations Command (U.S. Department of Defense)</td>
</tr>
<tr>
<td>Effect of amino acid supplementation on skeletal muscle protein turnover following endurance exercise</td>
<td>U.S. Department of Defense</td>
</tr>
<tr>
<td>Effects of potassium bicarbonate intake on skeletal muscle catabolism during short term energy restriction</td>
<td>Unilever</td>
</tr>
<tr>
<td>Mechanism of skeletal muscle anabolism in response to progressive resistance exercise in older men and women.</td>
<td>NIH/NIA</td>
</tr>
<tr>
<td>Age-related changes intracellular signaling in skeletal muscle</td>
<td>NIH/NIA</td>
</tr>
<tr>
<td>Intramyocellular lipid effects on anabolic signaling in aging skeletal muscle</td>
<td>USDA/ARS</td>
</tr>
<tr>
<td>Vitality, Independence, and Vigor in Elders Studies (1 and 2)</td>
<td>Nestec</td>
</tr>
</tbody>
</table>
Goals of Presentation:

- Current methods for measurement of muscle mass in clinical trials
- Current consensus definition of sarcopenia
- Recognize the importance of muscle performance
- Muscle strength vs. power
- Neuromuscular factors related to muscle performance
- Age-related changes in muscle anabolic capacity
Demographic change in the U.S.

Number of people age 65 and over, by age group, selected years 1900-2000 and projected 2010-2050

Note: Data for 2010-2050 are projections of the population.
Reference population: These data refer to the resident population.
Source: U.S. Census Bureau, Decennial Census and Projections.
Skeletal (Voluntary) Muscle

- Largest single organ in the body
- 45% of body mass
- Primary locomotor organ
- Significant reserve of energy (amino acids stored as protein)
Body Composition

Male
70 kg

Female
57 kg

Kilograms

Fat Mass
Other
Muscle Mass

FFM
Methodological Considerations for Assessment of Muscle Mass* in Clinical Trials

• Accuracy
• Precision
• Sensitivity to change
• Accessibility at clinical centers (e.g.: multi-center trials)

* There is a lack of a true gold standard
## Assessment of Muscle Mass

<table>
<thead>
<tr>
<th></th>
<th>DXA</th>
<th>C-T</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Based on</strong></td>
<td><strong>Based on attenuation of bone mineral free lean tissue</strong></td>
<td>Measures direct physical property of muscle (e.g.: CSA)</td>
<td>Similar principles of measurement</td>
</tr>
<tr>
<td><strong>Precision</strong></td>
<td><strong>Precision 1-4%</strong></td>
<td><strong>Precision 1-3%</strong></td>
<td><strong>Precision 1-3%</strong></td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
<td><strong>Radiation (1 mrem; 3 days background)</strong></td>
<td><strong>Density of muscle area (association with intramyocellular lipid) and subcutaneous and intra-muscular adipose tissue deposition</strong></td>
<td><strong>Agreement with C-T (r=0.97-0.99; SEE 5-10%)</strong></td>
</tr>
<tr>
<td><strong>Machines</strong></td>
<td><strong>Machines are widely available</strong></td>
<td><strong>Radiation (15mrem)</strong></td>
<td><strong>No radiation exposure</strong></td>
</tr>
<tr>
<td><strong>Analytical differences</strong></td>
<td><strong>Analytical differences across manufacturers and models</strong></td>
<td><strong>Additional technical complications</strong></td>
<td><strong>Additional technical complications</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Additional capacity for multiple slice acquisition (3-d volume estimates)</strong></td>
<td><strong>Higher cost</strong></td>
</tr>
</tbody>
</table>
Percutaneous Needle Biopsy

- Invasive procedure (well-tolerated)
- Obtain muscle tissue for immuno-histochemical analysis of muscle phenotype (type I, IIa, and IIx fibers) and fiber size
- Additional measures for biomarker discovery (protein, gene expression, contractile properties)

Type I (A4.840 antibody)
Sarcopenia: “poverty of flesh”*

Age-associated decline in skeletal muscle mass

Appendicular fat free mass normalize to body size (FFM of arms plus legs/ht m²) 2 SD below normal values for young**

Residual method (adjusted for fat mass)***

Necessary for study enrollment criteria and indication for therapy(???)

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*Rosenberg, 1989
**Baumgartner 1998
***Newman 2007
## Prevalence (%) of Sarcopenia*

<table>
<thead>
<tr>
<th>Age group (yrs)</th>
<th>Males (n=205)</th>
<th>Females (n=173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>13.5</td>
<td>23.1</td>
</tr>
<tr>
<td>70 – 74</td>
<td>19.8</td>
<td>33.3</td>
</tr>
<tr>
<td>75 – 80</td>
<td>26.7</td>
<td>35.9</td>
</tr>
<tr>
<td>&gt;80</td>
<td>52.6</td>
<td>43.2</td>
</tr>
</tbody>
</table>

*New Mexico Elder Health Survey, Baumgartner et al. 1998*
## Association of sarcopenia with physical disability

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>&gt;3 disabilities</td>
<td>16</td>
<td>3.66</td>
</tr>
<tr>
<td>&gt; 1 balance abnormality</td>
<td>28</td>
<td>3.23</td>
</tr>
<tr>
<td>&gt;1 gait abnormality</td>
<td>25</td>
<td>1.87</td>
</tr>
</tbody>
</table>

*New Mexico Elder Health Survey, Baumgartner et al. 1998*
Cost of Sarcopenia to the Health Care System:

- In 2000 cost estimates of $18.5 billion.

- 1.5% of total health care expenditures.

- 10% reduction in sarcopenia would save $1.1 billion.

Sarcopenia: An Undiagnosed Condition in Older Adults.
Current Consensus Definition: Prevalence, Etiology, and Consequences

International Working Group on Sarcopenia

From the International Sarcopenia Consensus Conference Working Group Meeting*
Rome, Italy
November 18, 2009
Sarcopenia: Current consensus

“Sarcopenia is the age-associated loss of skeletal muscle mass and function. Sarcopenia is a complex syndrome that is associated with muscle mass loss alone or in conjunction with increased fat mass. The causes of sarcopenia are multi-factorial and can include disuse, changing endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies. While cachexia may be a component of sarcopenia, the two conditions are not the same.”

Gait speed < 1.0 m·s⁻¹; males = aLM/Ht² ≤ 7.23 kg/ m²
Females = aLM/Ht² ≤ 5.67 kg/ m²
Initial Patient Presentation to Evaluate for Sarcopenia

- Noted decline in function, strength, “health” status
- Self-reported mobility-related difficulty
- History of recurrent falls
- Recent unintentional weight loss (> 5%)
- Post-hospitalization
- Other chronic conditions (e.g., Type II diabetes, CHF, COPD, CKD, RA, and Cancer)
Targeting Sarcopenia

• Assess patient for reduced physical functioning (or weakness).

• Consider Sarcopenia in patients who are non-ambulatory or who cannot rise from a chair unassisted.

• Assess habitual gait speed over a 4 meter course.

• Patients with a habitual gait speed < 1.0 m/sec. should be considered for quantitative measurement of body composition by DXA.
Pathology: muscle mass (sarcopenia)

Impairment: muscle strength, power

Functional Limitation: gait speed, chair rise time

Disability: role limitations

Sarcopenia does not represent the entire spectrum of muscle pathophysiology with aging (quality and performance)

Nagi, 1965; Verbrugge & Jette, 1994
Disability model has been both useful and challenging in studying muscle performance and aging:

- Compartmentalizes various domains
- Strengthens the ability to assess interrelationships
- Addresses effects of treatment in an individual’s environment
- Relationships may be non-linear
- Overlap between various domains
Correlation of Total Muscle Area (cm sq) vs. Keiser Leg Extension 1 Repetition Maximum (1RM), 70% and 40% of 1 RM Peak Power.

1RM (R squared = 0.676)

40% of 1RM (R squared = 0.600)

70% 1RM (R squared = 0.579)
Strength-Mass Divergence

• Interventions that increase lean mass do not necessarily increase strength. Strength improvements precede improvements with exercise training.

• Voluntary weight loss leads to reduced skeletal muscle mass but not necessarily changes in strength.

• Correlations between change in lean mass and change in strength in older adults is weak.

From: Anne Newman 2010
Health-ABC: Change in strength and lean mass

Goodpaster et al. 2006
Muscle Performance

**Strength**
- Maximum capacity to generate force or tension
- Related to muscle cross-sectional area, intrinsic force generating ability of the muscle fiber, and the ability of the nervous system to recruit motor units
- Typically measured as the isometric MVC or dynamic 1 repetition maximum (1 RM)

**Power**
- Maximum rate of work (force x distance/time) performance
- Peak power is related to force production and the velocity at which force can be generated
- Measured using isokinetic dynamometer, Bassey Rig, or pneumatic resistance equipment
Strength

- Resistance = 875 N
- Work = 91 J
- Velocity = 16 cm.s\(^{-1}\)
- Power = 65 Watts
Power

- Resistance = 875 N
- Work = 90 J
- Velocity = 70 cm.s\(^{-1}\)
- Power = 242 Watts
Relationship of Lower Extremity Power and Strength with Functional Performance

Demographics:
- N = 101
- Age (yrs) = 80.8 (0.4)
- Ht (cm) = 161.6 (0.9)
- Wt (N) = 711.3 (17.2)

Outcome Measures:
- LP 1RM
- LP Peak Power (70% 1RM)
- 4 Meter Walk
- 400 M Walk

<table>
<thead>
<tr>
<th>Physical Performance</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>R²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 meter walk time (n=67)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg Strength</td>
<td>-0.08</td>
<td>0.05</td>
<td>0.05</td>
<td>0.08</td>
</tr>
<tr>
<td>Leg Power</td>
<td>-0.19</td>
<td>0.05</td>
<td>0.16</td>
<td>0.001</td>
</tr>
<tr>
<td>Habitual Gait (4 m) (n=101)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg Strength</td>
<td>-0.0003</td>
<td>0.000</td>
<td>0.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leg Power</td>
<td>-0.0006</td>
<td>0.000</td>
<td>0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Habitual Gait (400 m) (n=101)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg Strength</td>
<td>-0.0003</td>
<td>0.000</td>
<td>0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leg Power</td>
<td>-0.0006</td>
<td>0.000</td>
<td>0.26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Is Power the “Key” Impairment Measure?

• Peak power declines more rapidly with age than strength

• Declines in peak power are more closely associated with loss in functional performance and disability

• What determines the age-associated loss in lower extremity power?
Loss of Muscle Power

- What determines the age-associated loss in lower extremity power?
  - Muscle size
  - Neuromuscular control?
  - Intrinsic contractile properties?
Neuromuscular Activation:

- Process by which excitation of motor neurons leads to force production in a population of muscle fibers.

- Each motor neuron and its associated muscle fibers are called a motor unit, and the number and firing rate of recruited motor units are the major intrinsic determinant of muscular force (extrinsic factors such as muscle length and contraction velocity also influence force).

- Weakness may directly result from an impaired capacity of the nervous system to maximize motor unit recruitment and/or rate coding in agonist muscles (prime movers) or may be indirectly caused by poor intermuscular coordination or by excessive activation of antagonist muscles that oppose the agonist.
Short Physical Performance Battery (SPPB):

- Composite measure of physical functioning
- Time 6 meter walk
- Timed repeated chair rise (5 times)
- Standing balance
- 0-12 score
- Predicts
  - Disability (Guralnik et al)
  - 12-month rates of hospitalization, decline in health, decline in physical function
  - (Studenski et al)
  - Mortality (Rolland et al)
Nursing Home Admission Rates According to Performance Test Summary Score

Age and Sex Adjusted

Age vs. Muscle Power Cross-Sectional Investigation

- **Healthy middle-aged (aged 40-55 yrs) (n=31)**
  - No manifest disease
  - No prescribed medications
  - Scored ≥ 10 on the Short Physical Performance Battery (SPPB)

- **Healthy older adults (aged 70-85 yrs) (n = 28)**
  - No manifest disease
  - No prescribed medications
  - Scored ≥ 10 on the SPPB

- **Mobility-Limited Older adults (aged 70-85 yrs) (n = 34)**
  - had to demonstrate functional limitation as defined by a score ≤ 9 on the SPPB
  - 12 point summary scale characterizing balance, habitual gait and repeated chair-rise performance: highly predictive of subsequent disability
Table 1 – Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Middle-Aged</th>
<th>Healthy Older</th>
<th>Mobility-Limited Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>47.3 ± 5</td>
<td>74.1 ± 4*</td>
<td>77.7 ± 5*^</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>25.5 ± 3</td>
<td>25.8 ± 4</td>
<td>26.5 ± 3</td>
</tr>
<tr>
<td>Medical Diagnoses</td>
<td>-</td>
<td>-</td>
<td>2.3 ± 1.7</td>
</tr>
<tr>
<td>Number of Medications</td>
<td>-</td>
<td>-</td>
<td>2.9 ± 2.1</td>
</tr>
<tr>
<td>SPPB score</td>
<td>11.7 ± 0.5</td>
<td>11.0 ± 0.9</td>
<td>8.2 ± 1.1*^</td>
</tr>
</tbody>
</table>

BMI: body mass index; SPPB: Short Physical Performance Battery

* = significant difference vs. Healthy Middle-Aged; ^ = significant difference vs. Healthy Older
Isokinetic Leg Power
## Mid-Thigh C-T

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Middle Age</th>
<th>Healthy Older</th>
<th>Mobility Limited Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Thigh CSA, cm²</td>
<td>194.9 ± 32</td>
<td>178.6 ± 26</td>
<td>179.2 ± 47</td>
</tr>
<tr>
<td>Total Muscle CSA, cm²</td>
<td>123.2 ± 28</td>
<td>114.9 ± 26</td>
<td>95.4 ± 23*^</td>
</tr>
<tr>
<td>Normal Density Muscle CSA, cm²</td>
<td>101.3 ± 25</td>
<td>89.5 ± 23</td>
<td>71.8 ± 20*^</td>
</tr>
<tr>
<td>Low Density Muscle CSA, cm²</td>
<td>22.0 ± 9</td>
<td>25.4 ± 9</td>
<td>24.6 ± 8</td>
</tr>
<tr>
<td>Intermuscular Atipose Tissue CSA, cm²</td>
<td>2.8 ± 1.8</td>
<td>3.5 ± 2.4</td>
<td>4.2 ± 1.8*</td>
</tr>
</tbody>
</table>

CSA: cross sectional area

* = significant difference vs. Healthy Middle-Aged; ^ = significant difference vs. Healthy Older
Isokinetic Leg Power

**Absolute power**

**Specific power**
(per muscle CSA)
Specific Leg Strength (double leg press)
Surface Electromyography

Agonists

Antagonists
Rate of Activation and Physical Functioning

- Raw EMG was filtered, rectified, and smoothed
- EMG was normalized to peak magnitude from a failed 1RM attempt (maximal voluntary contraction, MVC)
- EMG from each trial was aligned in time to the instant of movement onset
- All trials were averaged (red line)
  - Average was fit using linear regression to yield an index of activation rate (slope)
  - Time delay between muscle “ON” and movement was measured

Movement Begins
Results: Activation Measures

- Both time delay (top) and rate of activation (bottom) were significantly lower in the mobility-limited older group relative to the healthy groups.

- These findings indicate that the mobility-limited group has impaired ability to rapidly activate the muscle.

* MH > OML (p<.05)
† OH > OML (p<.05)
Muscle Performance Measures

• Consistent with the activation outcome measures, both movement acceleration (top) and peak muscle power (bottom) were significantly impaired in the mobility-limited older group.

* MH > OML (p<.05)
† OH > OML (p<.05)
• Across groups, activation rate was strongly related to initial acceleration and peak power

• Attenuated rate of neuromuscular activation likely contributes to low movement acceleration and impaired peak power in mobility-limited older adults
EMG rate and Physical Function

\[ \rho = .56 \]
Inverted Microscope and Single Fiber Attached...
Specific force of single skeletal muscle fibers in young & older men (cross sectional data).

- Sample size
  (young men = 7; older men = 12)

- Fiber type: myosin heavy chain isoform by SDS-PAGE

From: Frontera et al., Am. J. Physiol. Cell Physiol. 2000; 279:C611; * young>old; # IIA>I
Single Fiber Function

Type I Peak Force (Po)  \( p = 0.52 \)

![Bar chart for Type I Peak Force](chart1)

Type IIa Peak Force (Po)  \( p = 0.61 \)

![Bar chart for Type IIa Peak Force](chart2)
Specific force of single skeletal muscle fibers: longitudinal data 1996-2006

- Sample size
  n=12 older men and women (mean age T1: 71.1 ± 5.4 yrs; T2: 80.0 ± 5.3 yrs)

- Fiber type: myosin heavy chain isoform by SDS-PAGE

From Fielding et al., 2007
Sarcopenia is not the sole pathological change in neuromuscular function with aging.

Impairments in power may be a key modulators of function and disability.

Pathology

Impairment

Functional Limitation

Disability
Conclusions

- Muscle power is a critical determinant of function in older adults.
- Deficits in components of neuromuscular activation are related to decreased muscle power.
- Assessment of muscle quality may uncover other potentially important targets to improve physical functioning in older adults.
- Therapeutic agents may be able to improve physical functioning in older patients without affecting skeletal muscle mass but improving muscle performance.
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