WEBINAR | Stronger Longer: Muscle Mass and Aging
Stronger, Longer
Muscle Mass & Aging

Nathan K. LeBrasseur, PT, PhD
Robert & Arlene Kogod Center on Aging
Department of Physical Medicine & Rehabilitation
Department of Physiology & Biomedical Engineering
Strength

Lasha Talakhadze
2016 Olympic Games
258 kg dead lift

Image: Fernando Frazão/Agência Brasil
Power

Venus Williams
2012 Wimbledon
114 mph serve
Endurance

Eliud Kipchoge
2019 London Marathon
2:02:37 (4:41/mile)
Beyond Superhumans: Why Muscle Matters

Physical Performance
- Powers movement
- Enables activity/function

Metabolism
- Primary sight of insulin-mediated glucose disposal
- Largest reservoir of glycogen in body
- Primary determinant of REE and driver of AEE (10x!)

Resilience
- Strength and mobility predict resistance to, and recovery, from stressors
- More muscle = better medical/surgical outcomes

Cross-talk
- An endocrine organ: “myokines”
- Communicates with liver, brain, pancreas, adipose tissue, bone....

Aversa et al., Bone, 2019
Image: Leslie Samuel, Interactive Biology
Threats to Skeletal Muscle Health

Aging (sarcopenia)
Chronic disease (cachexia)
Inactivity (disuse)
Congenital disease (degeneration)
Obesity (lipotoxicity)
Skeletal Muscle: An Early Casualty of Aging

Baltimore Longitudinal Study of Aging (Luigi Ferrucci)
1300 subjects, 5200 longitudinal observations

### Men
- Body Weight (kg)
- Lean Mass (kg)
- Fat Mass (kg)
- Waist Circ (cm)

### Women
- Body Weight (kg)
- Lean Mass (kg)
- Fat Mass (kg)
- Waist Circ (cm)
Sarcopenia - poverty (penia) of the flesh (sarx)
The Age-Related Loss of Skeletal Muscle Mass and Function

Aversa et al., Bone, 2019
Sarcopenia
The Age-Related Loss of Skeletal Muscle Mass and Function

Ferrucci et al., J of Gerontology, 2016
The Impact of Sarcopenia

Sarcopenia

Impaired strength, power, endurance

Limited function

Falls
Disability
Institutionalization
Death

$19B

Janssen, J Am Geriat Soc, 2004
Pharmacological “Growth Promoting” Strategies for Sarcopenia

- Growth factors: GH, IGF-1, mGF
- Androgens: testosterone, SARMs
- Nutrition: protein supplements, essential AAs (leucine), Vit D
- Orexigenic agents: dronabinol, megestrol acetate, ghrelin mimetics
- Anti-catabolics: ub-proteos inhibitors, myostatin/ActRII antag
- Anti-inflammatory: ACE-I, ARBs, TNFα blockers

Protein synthesis & muscle growth

Protein degradation & muscle atrophy
**Myostatin (GDF-8):** A highly conserved and powerful negative regulator of muscle mass

*New Engl J Med*, 2004

Myostatin Mutation Associated with Gross Muscle Hypertrophy in a Child

Markus Schuelke, M.D., Kathryn R. Wagner, M.D., Ph.D., Leslie E. Stolz, Ph.D., Christoph Hübner, M.D., Thomas Riebel, M.D., Wolfgang Kömen, M.D., Thomas Braun, M.D., Ph.D., James F. Tobin, Ph.D., and Se-Jun Lee, M.D., Ph.D.

*Genome Research*, 1997;
*Scientific American*, 2004

*PLoS GENETICS*, 2007

*Neonate* 7 Months
Pharmacological Strategies to Inhibit Myostatin Signaling

Adapted from Brun & Rudnicki, Cell Metabolism, 2015
Targeting Myostatin: Preclinical Promise

• Increased **muscle mass and function** in mouse models of aging and disease
• Improved **body composition and metabolism** in models of obesity/diabetes
• Enhanced **resilience** in models of cancer
• Diminished **age- and disease-associated pathology** in other organs (i.e., bone, liver, heart, blood vessels)
• Marked excitement for translation!
Myostatin Therapies in Older Adults

Sarcopenic (low muscle mass, slow gait speed) older adults
Placebo vs. Bimagrumab (IV infusion): 1 or 2 (day 56) doses

Rooks et al., J of Am Geriatrics Soc, 2017
Myostatin Therapies in Older Adults

Older adults with a fall in past year
Placebo vs. LY2495655 (SQ injections): Every 4 wks x 5 weeks

Becker et al., Lancet Diabetes & Endo, 2015

Appendicular Lean Body Mass (kg)

4-step Stair Climb Minimum Time (s)

Fast Gait Speed (m/s)
Lost in Translation: Myostatin-based Therapies

• Short-term interventions exhibit moderate effects on muscle mass, but **limited effects on measures of function** (FDA)

• Some evidence that individuals who exhibit best response are **most affected** by sarcopenia. Challenging to recruit/retain in randomized clinical trials

• Agreement that pharmacological interventions are most effective when **combined with nutrition and exercise** programs. Challenging and expensive to design and run a RCT

• Future is, unfortunately, uncertain....
“Geroscience” Strategies for Sarcopenia and Age-related Functional Decline

The Biology of Aging

- **growth factors**
  - GH, IGF-1, mGF

- **androgens**
  - testosterone, SARMs

- **nutrition**
  - protein supplements
  - essential AAs (leucine)
  - Vit D

- **orexigenic agents**
  - dronabinol, megestrol acetate, ghrelin mimetics

- **anti-catabolics**
  - ub-proteos inhibitors
  - myostatin/ActRII antag

- **anti-inflammatory**
  - ACE-I, ARBs, TNFα blockers

- **protein synthesis & muscle growth**

- **protein degradation & muscle atrophy**
What is Aging?

Molecular & Cellular Damage
- DNA damage
- Telomere erosion
- Mitochondrial dysfunction
- Oxidative stress
- Protein aggregation
- Sterile inflammation
- Cellular senescence

Musculoskeletal
Metabolic
Cardiovascular
Neurodegen.
Hyperprolif.
Disability
Frailty
Functional decline

Interventions
- Metformin
- Rapamycin
- Senolytics
- …
What is Aging? Can We Intervene?

Molecular & Cellular Damage
- DNA damage ✓
- Telomere erosion ✓
- Mitochondrial dysfunction ✓
- Oxidative stress ✓
- Protein aggregation ✓
- Sterile inflammation ✓
- Cellular senescence ✓

Interventions
- Exercise
  Believe the hype!
  (and Dr. Joseph)
Geronscience
A New Era in Science and Medicine

• Targeting the biology of aging is a fundamentally different approach to optimizing human health

• Interventions targeting the effects of aging hold promise for extending human healthspan; delaying the onset of age-related conditions as a group

• Though early, there is significant promise that such interventions will positively affect skeletal muscle health and physical function
American Federation for Aging Research

Stronger, Longer: Muscle Mass and Aging.

Lyndon Joseph, PhD
Division of Geriatrics and Clinical Gerontology
National Institute on Aging

September 26, 2019
Hippocrates
(c. 460 B.C. - c. 370 B.C.)

• Even when all is known, the care of a man is not yet complete, because eating alone will not keep a man well; **he must also take exercise.** For food and exercise, while possessing opposite qualities, yet work together to produce health.
Percentage of people age 45+ who reported engaging in regular leisure-time physical activity (by age group, 1998-2009)

Source: CDC, National Center for Health Statistics, National Health Interview Survey 2007-2008
Sarcopenia: Age-associated loss in muscle mass and function

- Associated with weakness & poor physical function
  - Difficulty in rising from a chair
  - Problems with climbing stairs
  - Impaired gait/walking
  - Increased Falls
- Associated with lower survival
- Loss of independence
- Reduce quality of life
- Important for Skeletal Health
  - Osteoporosis
  - Vertebral compression fractures

Muscle quality affects performance: 
muscle size & composition are affected with age and mobility limitation
Mobility disability in the US in 2010

- About 23.9 million people living in the community had difficulty walking a quarter mile or 400m, including 13.1 million who could NOT perform the activity.

- Among individuals aged 65 and older living in the community, about 15.2 million (39.4 percent) had difficulty with ambulatory activities, of which 11.2 million had sever difficulty.
High-intensity progressive strength training in frail, 90-yr-olds

- 48% improvement in gait speed
- 174% increase in strength

Fiatarone M., et al., JAMA, 1990
**Exercise/Physical Activity LIFE-Pilot SPPB score**

**INTERVENTION**
- Aerobic (walking)
- Strength (lower extremities)
- Balance
- Flexibility stretching
- Behavioral counseling

Means estimated from repeated measures ANCOVA adjusted for gender, field center and baseline values

Pahor et al J Gerontol 2006;61:1157
2-Year Follow-up of Life Pilot Participants

Walking Speed in m/sec (Mean ± SE)

Baseline  | 6-months  | 12-months  | 36-months
---|---|---|---
PA | SA | PA | SA | PA | SA | PA | SA

• 18% reduction in the risk of major mobility disability, defined as loss of ability to walk 400 m
• 28% reduction in the risk of persistent mobility disability

HR=0.82, 95%CI=0.69-0.98
p=0.03
Accelereometry (Moderate Intensity)

Physical activity

P<0.001

Health Education

Sample Size
Physical Activity
Health Education

Pahor et al JAMA 2014
Physical activity may reduce the likelihood of falling and sustaining a serious injury by improving gait, balance, and lower extremity strength

- randomized to physical activity experienced
  - 46% reduction in all serious fall injuries
  - 53% reduction in the rate of fall related fractures
  - 59% reduction in the rate of fall injuries leading to hospital admission
Effectiveness of several exercise modes on bone mass (BMD) during weight loss

Villareal et al. NEJM 2017
Effectiveness of several exercise modes on muscle mass/strength and functional status during weight loss

Villareal et al. NEJM 2017
Effects of Physical activity plus nutritional supplement on thigh muscle quality and intermuscular fat in older individuals (>70 y)

VIVE2 Study: Walking, Strength, balance, flexibility
Nutritional supplement- Whey protein (20g), vitamin D (800 IU), calcium, vitamins + minerals (150 kcal)

Englund et al J Gerontol 2018
Exercise and lifestyle changes substantially prevents the onset of diabetes compared to metformin alone or placebo.

Lifestyle goals:
- 7 percent weight loss
- at least 150 minutes of PA per week
Exercise and Lifestyle Influence on Diabetes Incidence

Source: Diabetes Prevention Program, 2001
Chronic Exercise on Body Fat Composition and Distribution in Women

Ryan et al. AJP 1996
Chronic Exercise on thigh Adipose Tissue distribution of with Obesity

Trained older woman

Sedentary older woman
Managing sedentary behavior to reduce the risk of adverse outcomes associated with increased sedentary time

- Predominant focus of clinical and public health research and guidelines
  **VERY LOW VOLUME**

- **HIGH VOLUME** with broad scope to displace sedentary time.

- **LIGHT ACTIVITY** 5 hr

- **MVPA** 11.3 min

- **SEDENTARY** 9.2 hr

- **VERY HIGH VOLUME** growing evidence of distinct cardio-metabolic risk.

Dempsey et al., Curr Diab Rep 2014
Exercise/physical activity remains the only treatment for improving physical function and preventing disability
Avoid taking < 5,000 steps/day and limit prolonged sitting bouts

Walk More
Take ≥ 7.500 steps/day

Exercise
Accumulate ≥ 3,000 steps/day at ≥ 100 steps/min

Sit Less

Tudor-Locke, Craig, Thyfault, & Spence, APNM, 2012