우리는 어떻게 근육을 유지하고 노쇠를 피할 수 있을까?

박 형 준
이화여자대학교 의학전문대학원 신경과학교실

How can we keep our muscle and avoid frailty?

Hyung Jun Park
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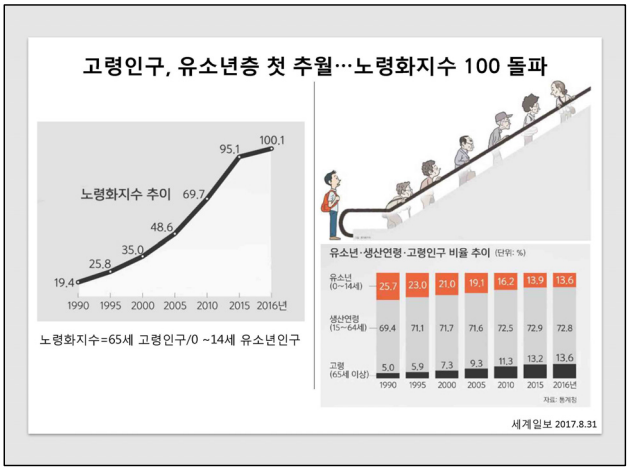
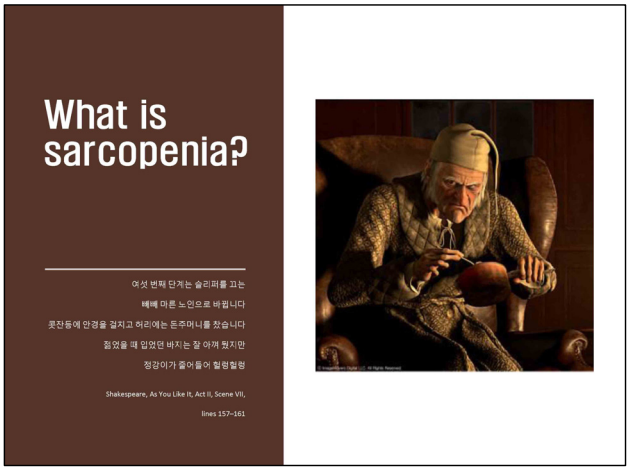




What is sarcopenia?

- Sarcopenia is associated with loss of type II muscle fibers.
- The direct effect of sarcopenia, on strength is illustrated by the dramatic age-associated decline by 30% in men and over 50% in women between the ages of 30 to 60 years.
- A clear decline in muscle mass, strength and power begin at approximately 35 years of age.
- Intramuscular lipid increases with age and increasing body fatness.

History of sarcopenia

Year	Event
1931	Critchley noted that muscle loss occurs with aging and is most noticeable in intrinsic hand and foot muscles
1988	Rosenberg described sarcopenia as a phenomenon whereby the age-related decline in lean body mass affects ambulation, mobility, energy intake, overall nutrient intake and status, independence, and breathing
1993	Evans and Campbell described age related loss of muscle mass
1998	Sarcopenia was defined as being 2SD below the mean muscle mass of younger persons (usually age 35 years)
2011	Definition of International Working Group on Sarcopenia (IWGS)
2013	Definition of European Working group on Sarcopenia in Older People (EWGSOP)

Prevalence of sarcopenia

- The prevalence in 60–70-year-olds is reported as 5–13%, while the prevalence ranges from 11 to 50% in people >80 years.
- Even with a conservative estimate of prevalence, sarcopenia affects >50 million people today.

Definition of sarcopenia

IWGS

- Low muscle mass
  - ✓The lean mass is less than 20%tile of values for healthy young adults
- Slow gait speed
  - ✓A measured gait speed less than 1.0 m/s

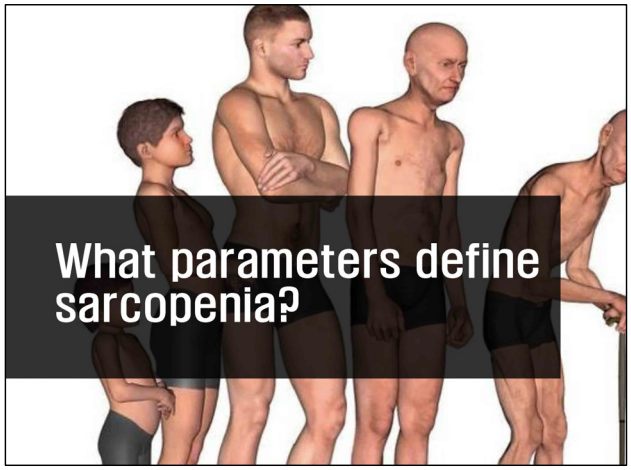
EWGSOP

- Criterion 1 plus (criterion 2 or 3)

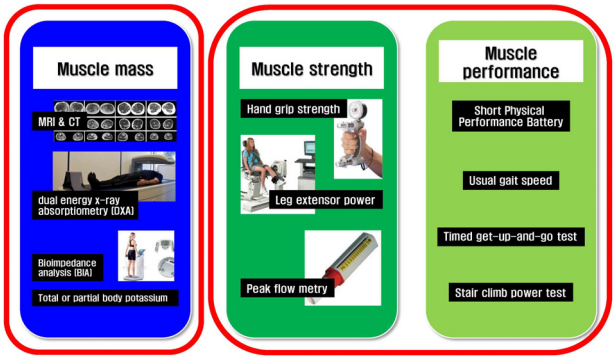
1. Low muscle mass
2. Low muscle strength
3. Low physical performance

EWGSOP conceptual stages of sarcopenia

Stage	Muscle mass	Muscle strength		Performance
Presarcopenia	↓			
Sarcopenia	↓	↓	Or	↓
Severe sarcopenia	↓	↓		↓



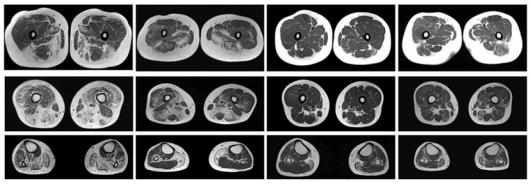
Parameters of Sarcopenia



Muscle Mass

MRI & CT

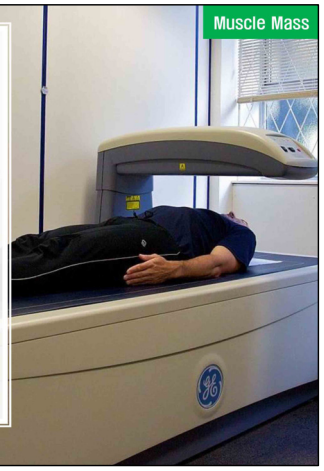
- CT and MRI are considered to be very precise imaging systems
  - ✓Gold standards for estimating muscle mass in research.
- Limitations
  - ✓High cost, limited access to equipment, and concerns about radiation exposure



Muscle Mass

Whole body dual energy x-ray absorptiometry (DXA)

- DXA is an attractive method both for research and for clinical use to distinguish fat, bone mineral and lean tissues.
- This whole-body scan exposes the patient to minimal radiation.
- The main drawback is that the equipment is not portable.



Muscle Mass

Bioimpedance analysis (BIA)

- The test is inexpensive, easy to use, readily reproducible and appropriate for both ambulatory and bedridden patients.
- BIA results under standard conditions have been found to correlate well with MRI predictions.
- BIA might be a good portable alternative to DXA.

Muscle Mass

Total or partial body potassium per fat-free soft tissue

- As skeletal muscle contains >50% of the total body potassium (TBK) pool, TBK is the classic method for estimation of skeletal muscle.
- Partial body potassium (PBK) of the arm has been proposed as a simpler alternative.
- PBK of the arm is safe and inexpensive.

Muscle Strength

Handgrip strength

- Isometric hand grip strength is strongly related with lower extremity muscle power, knee extension torque and calf cross-sectional muscle area.
- There is a linear relationship between baseline handgrip strength and incident disability for activities of daily living (ADL).

Muscle Strength

Knee flexion/extension

- Leg extensor power is measured with a commercially available power rig .
- Strength can be measured isometrically or isokinetically.
- These techniques are suitable for research studies, but their use in clinical practice is limited by the need for special equipment and training.

Muscle Strength

Peak expiratory flow

- In people without lung disorders, peak expiratory flow (PEF) is determined by the strength of respiratory muscles.
- PEF is a cheap, simple and widely accessible technique that has prognostic value.
- However, it cannot be recommended as an isolated measure.

Physical performance

Short Physical Performance Battery

- The SPPB can be used as a standard measure of physical performance both for research and in clinical practice.
- SPPB score is a summation of scores on three tests
  - ✓Balance
  - ✓Gait Speed
  - ✓Chair Stand

Physical performance

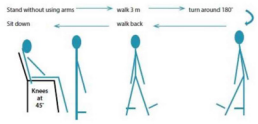
Usual gait speed

- Small changes in physiological capacity may have substantial effects on performance in frail adults, while large changes in capacity have little or no effect in healthy adults.
  - ➔ Timed usual gait provides a predictive value for the onset of disability.
- Gait speed is part of the SPPB, but it can also be used as a single parameter for clinical practice and research.

Physical performance

Timed get-up-and-go test

- TGUG requires the subject to stand up from a chair, walk a short distance, turn around, return and sit down again.
- It serves as an assessment of dynamic balance.



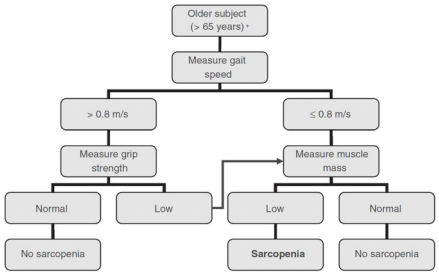
Stair climb power test

- The stair climb power test (SCPT) has been proposed as a clinically relevant measure of leg power impairment.
- SCPT results are consistent with more complex techniques for measuring leg power and performance.

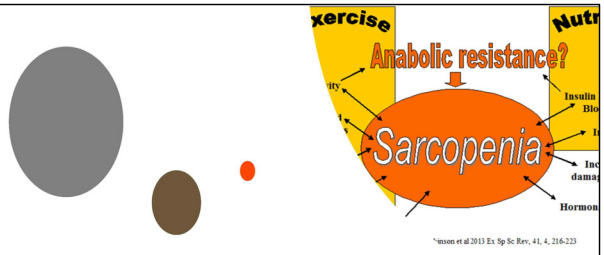
Cut-off points in IWGS

- **Muscle mass**
  - An appendicular fat lean mass/ ht2 (aLM/Ht2)
    - ✓≤ 7.23 kg/ m^2 in men
    - ✓≤ 5.67 kg/ m^2 in women
- **Muscle performance**
  - Assess gait speed over a 4 meter course
  - Gait speed <1.0m/s

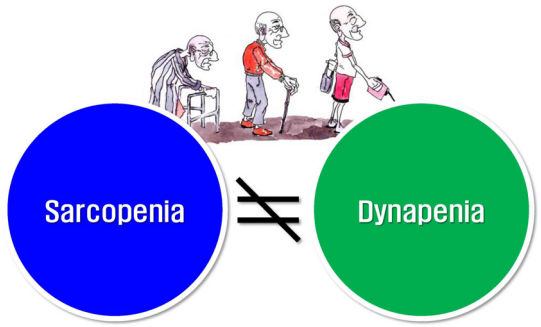
EWGSOP-suggested algorithm



* Comorbidity and individual circumstances that may explain each finding must be considered
+ This algorithm can also be applied to younger individuals at risk

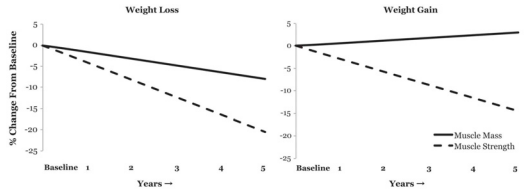


How does sarcopenia relate to nervous system?



Age-related muscle weakness = sarcopenia(muscle atrophy) + dynapenia(muscle power)

Dynapenia



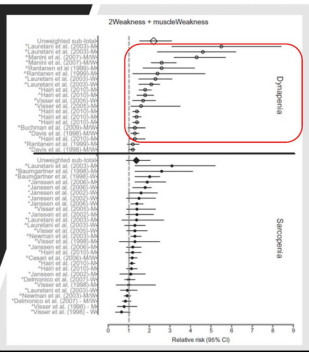
n=309 n=143

- Sarcopenia should be referred only as the age-related loss in muscle mass whilst the age-related loss in muscle strength should be isolated as a new condition called "dynapenia".

J Gerontol A Biol Sci Med Sci Med Sci 2012:28-40

Physical disability in older adults with dynapenia/sarcopenia

- The association between low muscle strength and poor physical performance or disability: 90% (18 out of 20 associations)
- The association with low muscle mass and disability: 35% (10 out of 28 associations)



Skeletal muscle mass/strength and mortality

- Muscle cross-sectional area of the calf was not associated with an increased risk of mortality

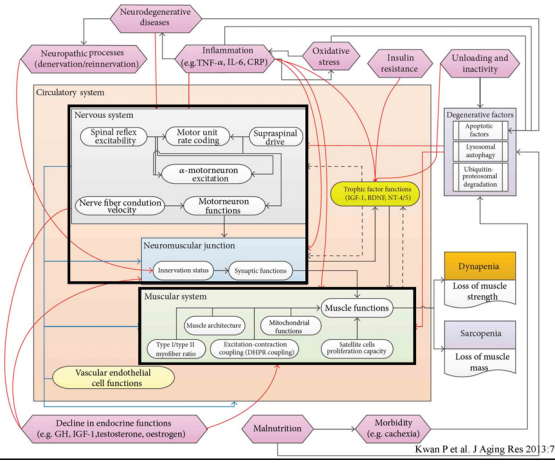
J Gerontol A Biol Sci Med Sci. 2009;64:377–384

- Whole leg-muscle mass and thigh cross-sectional area were not associated with risk of mortality.

J Gerontol A Biol Sci Med Sci. 2006;61:72–77

- Both grip and knee extensor muscle strength was highly associated with mortality, despite accounting for muscle mass

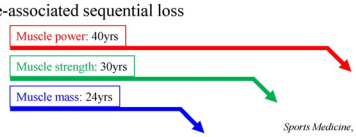
J Gerontol A Biol Sci Med Sci. 2006;61:72–77



Kwan P et al. J Aging Res 2013:791679

Muscular Factors

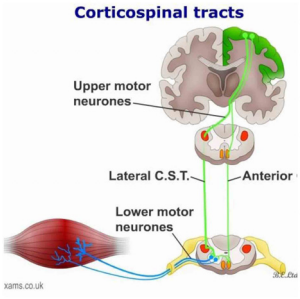
- Age-associated sequential loss



Sports Medicine, vol. 34, no. 12, pp. 809–824, 2004

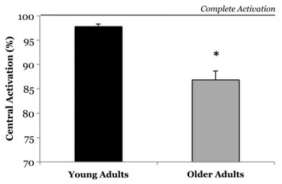
- **The molecular level**
  - ➔ reduction in Ca2+ release
- **The myocellular level**
  - ➔ reduction in the type I/II muscle fibers(type II dominance)
- **The cellular level**
  - ➔ reduction in cell density of the satellite cell population

Neural factors (1)

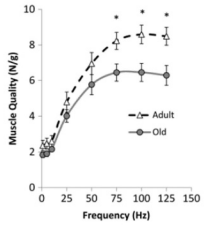


Frontal lobe
Basal ganglia
Spinal cord
Peripheral nerve & NMJ

Neural factors (2)



Older adults exhibit impairment in their nervous systems ability to fully activate the knee extensor muscles



Older animal skeletal muscle exhibits a reduction in it's intrinsic force-generating capacity, particularly at high stimulation frequencies.

Peripheral Nerve Factors (1)

- **The cellular level**

1. Reduction in motor axon conduction velocity and the number of myelinated axons

NCVs: 30 to 40yrs

2. Reduction in the number of motor units and motor neurons specific to the type II muscle fibers.

3. Preferential denervation of type II muscle fibers occurs and these denervated fibers are then reinnervated by the axonal sprouting from slow motor neurons in a process called motor unit remodeling.

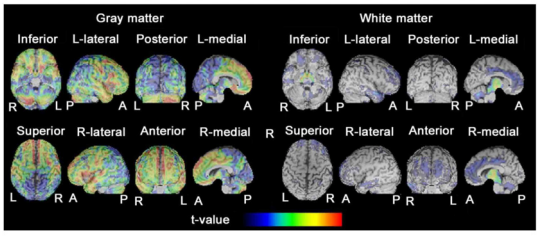
Peripheral Nerve Factors (2)

- **The molecular level**

1. Progressive denervation have disrupted the precise overlapping between the presynaptic nerve terminal and the postsynaptic AChR clusters at the NMJ.

2. Denervated muscles have elevated the expression of proapoptotic/atrophic factors including bax, caspase 3, 7, 8, and 10 along with a reduction in the trophic factor signals including TrkB signaling via BDNF and NT-4/5.

Brain factors
-Age-related atrophy in frontal cortex

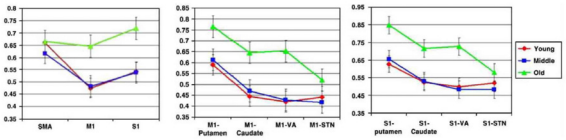


- Significant negative correlation of gray matter and white matter volume with advancing age in frontal cortex and brain stem

Aging Dis. 2013;29-37

Brain factors
-the cortico-basal ganglia circuitry

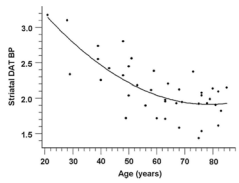
- Motor control relies on more widespread engagement of the prefrontal cortex and basal ganglia networks.
- Unfortunately, these systems are the most detrimentally affected by the aging process.



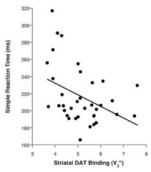
Increased connectivity of the cortico-basal ganglia circuit

Neuroimage 2011;194-203

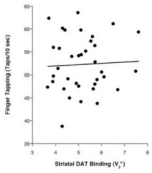
Brain factors
-Striatal dopaminergic degeneration



Association between striatal DAT activity and age
DAT BP: dopamine transporter binding potential



Verbal stimuli

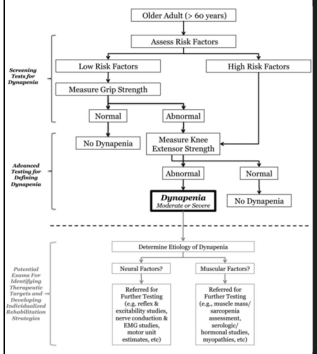


Finger tapping

Exp Brain Res 2008;185:391-8

Spinal cord factors

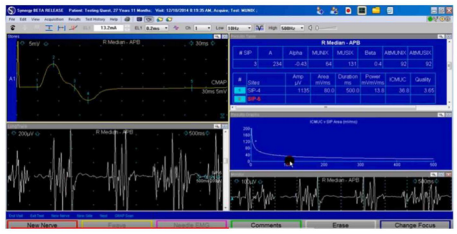
- The excitatory postsynaptic potentials in spinal motoneurons show a linear decline with age.
- Autopsy studies in humans have shown that the number and diameter of anterior horn motor neurons decline with increasing age.
- The conduction latencies in the spinal cord are slowing (Sensorium).
- Transcranial magnetic stimulation studies have shown reduced excitability of efferent corticospinal pathways in elderly (Motor).



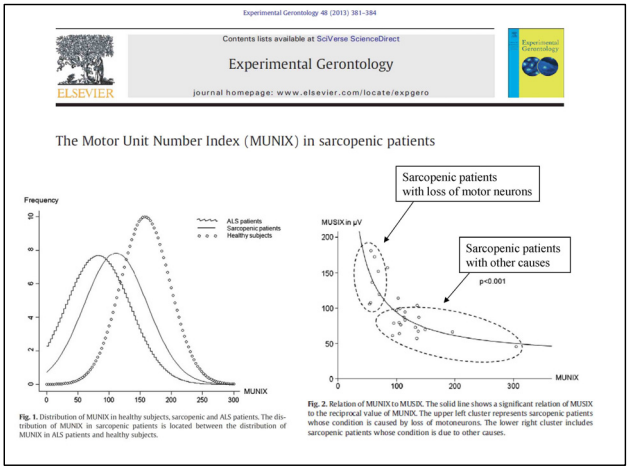
Algorithm to define dynapenia

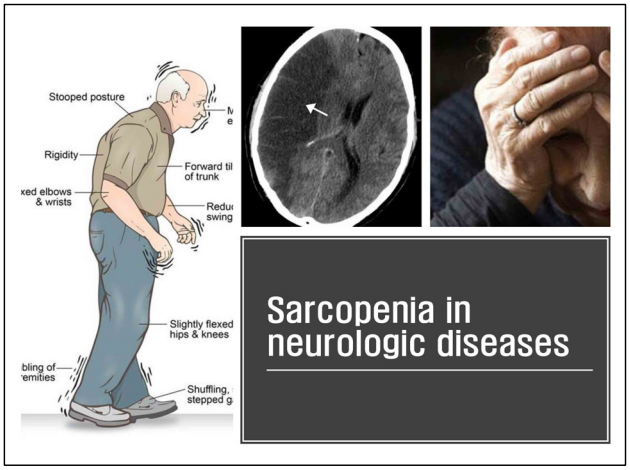
- Potential risk factors
  - ✓ low levels of physical activity
  - ✓ Malnutrition
  - ✓ Obesity
  - ✓ Osteoarthritis
  - ✓ vitamin D deficiency
  - ✓ Anemia
  - ✓ Osteoporosis
  - ✓ Cardiorespiratory diseases
  - ✓ Active cancer
  - ✓ Low cognitive function
  - ✓ Unexplained weight loss
  - ✓ History of falls
  - ✓ Self-reported muscle weakness
  - ✓ Mobility limitations
  - ✓ Fatigue
  - ✓ Exhaustion

Motor unit number index (MUNIX)

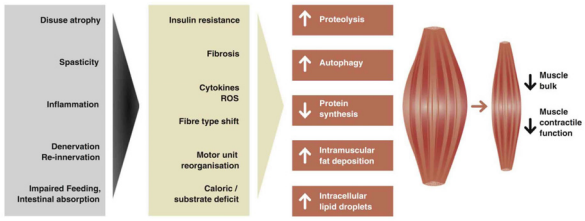


- MUNIX is a tool to obtain a parameter related to number of motor units.
- MUNIX uses a mathematical model based on the CMAP and the surface EMG interference pattern (SIP).
- MUSIX (Motor unit size index) = CMAP amplitude/MUNIX





Mechanism and pathways of muscle wasting in CNS diseases

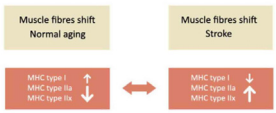


Stroke-related sarcopenia

- Rapid decline of the muscle mass, following an index incident;
- Structural muscle alterations
- Brain lesion determines the bilateral differences in physical and functional performance
- Muscle wasting is not age-depended
- Direct catabolic signal from the brain injury

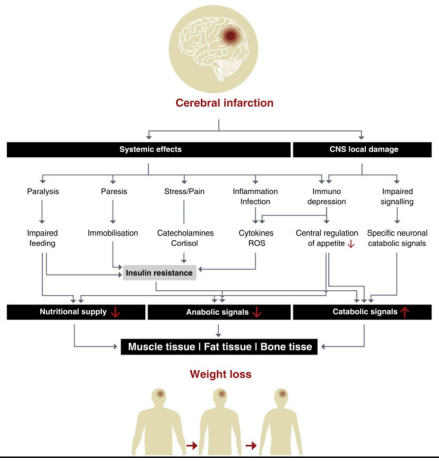
Muscle loss and muscle changes after stroke (1)

- After stroke, an up to 50% of patients suffer from some hemiparesis, and nearly 1/3 cannot walk without assistance.
- The paresis that frequently accompain a CNS lesion can lead to muscle abnormalities, due to different physiopathological mechanisms
  : denervation, disuse atrophy, spasticity, remodelling and myosteatosis
- Fiber-type shift in Stroke

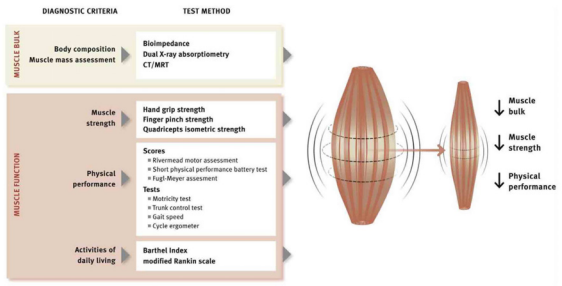


Muscle loss and muscle changes after stroke (2)

- Myosteatosis (the substitution of muscle tissue with intramuscular fat)
- The reduction of lean mass after stroke is a bit controversial.
- Spasticity
  - ✓ increased muscle atrophy and to the accumulation of intramuscular connective tissue (fibrosis)
- Disuse atrophy (immobilization, denervation, muscle unloading)
  - ✓ Decrease in muscle protein content, in fiber diameter
  - ✓ Reduced force production
  - ✓ Lack of fatigue resistance



Clinical tests in stroke-related sarcopenia

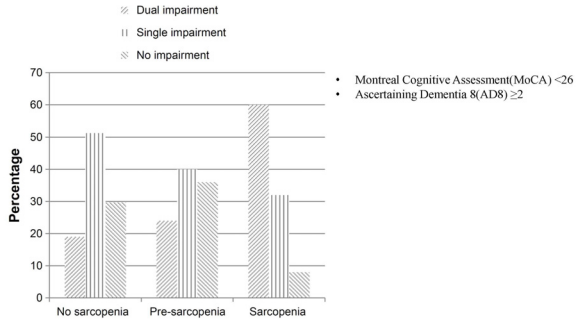


Muscle loss and muscle changes after spinal cord injury

- Spinal cord lesion leads to a reduction in slow-twitch fibers (type I) and an increase of fast-twitch fibers (type II).
- Fiber type shift is slow and progressive, and probably reaches a steady-state between 20 and 70 months after the SCI.
- Denervation atrophy
  - Results from injury to motoneurons in the spinal cord or to the motor nerves in the ventral roots.
- Myosteatosis
  - ✓ Afterr 8-10 years of denervation adipocytes can constitute up to 30% of the area in muscle biopsies.

Clinical Interventions in Aging
Dovepress
ORIGINAL RESEARCH

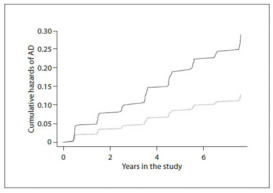
Sarcopenia and impairment in cognitive and physical performance



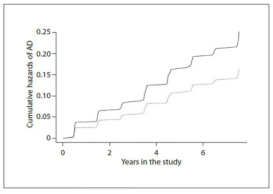
- Montreal Cognitive Assessment(MoCA) <26
- Ascertaining Dementia 8(AD8) ≥2

Original Paper
Neuro-epidemiology
Neuroepidemiology 2007;29:66–73
DOI: 10.1159/000109498
Published online: October 8, 2007

Grip Strength and the Risk of Incident Alzheimer's Disease



Solid line: baseline grip strength of 31 lb (10th ‰)
Dotted line: baseline grip strength of 86 lb (90th ‰)



Solid line: annual rate of change in grip strength = –4.9 lb/year (10th ‰)
Dotted line: annual rate of change in grip strength = 1.2 lb/year (90th ‰)

ELSEVIER
JAMDA
journal homepage: www.jamda.com

Original Study

Sarcopenia and Dynapenia in Patients With Parkinsonism

Michela Barichella MD[a], Giovanna Pinelli MD, PhD[a,b], Laura Iorio MD[a], Erica Cassani MD[a], Angela Valentino BioD[a], Chiara Pusani RD[a], Valentina Ferri MD[a], Carlotta Bolliri BioD[a], Marianna Pasqua BioD[a], Gianni Pezzoli MD[a], Giuseppe Frazzitta MD[b], Emanuele Cereda MD, PhD[c,*]

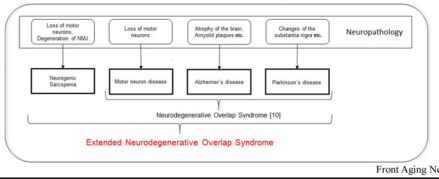
- Participants:
  - ✓ Consecutive patients (n = 364) aged 65 years or older, affected by parkinsonian syndromes
- Definition
  - ✓ Sarcopenia using the EWGSOP criteria.
  - ✓ Dynapenia as handgrip strength less than 30 kg in men and less than 20 kg in women.
- Results
  - ✓ GS could not be measured in 98 patients and was found to be reduced in 61.3% of those assessed.
  - ✓ Prevalence of sarcopenia and dynapenia was 6.6% and 75.5%, respectively.

Associations between Early Markers of Parkinson's Disease and Sarcopenia

TABLE 2 | Logistic regression with ESS as dependent variable. ESS: early stage sarcopenia

	Model 1		Model 2		Model 3	
	Odds ratio	*p*-value	Odds ratio	*p*-value	Odds ratio	*p*-value
UPDRS-III	2.609 [1.223; 5.563]	0.013	2.273 [1.046; 4.938]	0.038	2.309 [10.058; 5.037]	0.035
SN positive	0.871 [0.447; 1.698]	0.686	0.792 [0.395; 1.590]	0.512	0.795 [0.395; 1.600]	0.520
RBD	0.964 [0.384; 2.418]	0.938	0.969 [0.381; 2.464]	0.948	0.973 [0.382; 2.477]	0.954
Depression	1.040 [0.559; 1.933]	0.902	0.981 [0.511; 1.883]	0.955	0.986 [0.513; 1.894]	0.966
Hyposmia	0.734 [0.425; 1.266]	0.266	0.588 [0.328; 1.053]	0.074	0.608 [0.339; 1.092]	0.096
PS for prodromal PD	1.012 [0.984; 1.040]	0.397	1.000 [0.970; 1.030]	0.989	1.000 [0.970; 1.031]	0.997

UPDRS-III: Unified Parkinson's disease rating scale, SN: Substantia nigra, RBD: REM-sleep behaviour disorder, PS for prodromal PD: Probability score for prodromal PD. Model 1: unadjusted, Model 2: adjusted for age and gender, Model 3: adjusted for age, gender and physical activity.



Front Aging Neurosci. 2017; 9: 53.

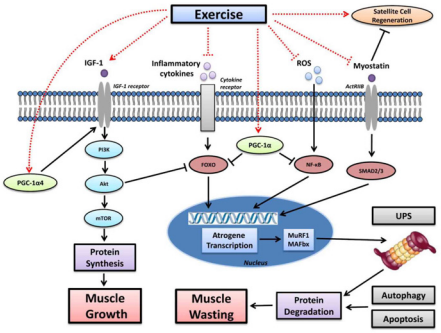
frontiers in AGING NEUROSCIENCE
ORIGINAL RESEARCH ARTICLE
published: 07 October 2014
doi: 10.3389/fnagi.2014.00274

Sarcopenia and sarcopenic obesity in patients with muscular dystrophy

- Participants:
  - ✓ 14 adult patients with different types of muscular dystrophy.
- Results
  - ✓ All patients were sarcopenic obese.
  - ✓ All were sarcopenic based on appendicular lean, fat and bone free, mass index (ALMI)
  - ✓ Skeletal muscle mass determined by DXA was markedly reduced in all patients
  - ✓ Muscle mass correlated with residual muscle strength determined by hand-held dynamometry, and physical performances determined by gait speed and respiratory function

Treatment of sarcopenia

The Effects of exercise in sarcopenia



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Review

Effectiveness of Nutritional Supplementation on Muscle Mass in Treatment of Sarcopenia in Old Age: A Systematic Review

Vincenzo Malafarina MD [a,*], Francisco Uriz-Otano MD [a], Raquel Iniesta PhD [c], Lucía Gil-Guerrero MD, PhD [b]

- 17 studies, with a total of 1287 patients, aged between 65 and 85 on average were included.
- An improvement in muscle mass was proven, whether measured with bioelectrical impedance analysis or dual energy x-ray absorptiometry, and an improvement in strength was also proven.
- Conclusion: Nutritional supplementation is effective in the treatment of sarcopenia in old age, and its positive effects increase when associated with physical exercise.

JAMDA 14 2013:10-17

Published in final edited form as:
J Am Med Dir Assoc. 2010 July ; 11(6): 391–396. doi:10.1016/j.jamda.2010.04.014.

Nutritional Recommendations for the Management of Sarcopenia

John E. Morley, MB, BCh, Jos
MD, David Cella, PhD, Nicolaa
H. Fearon, MD, Luigi Ferrucci,
Zadeh, MD, PhD, Herbert Loc
Maurizio Muscaritoli, MD, Piot
Filippo Rossi Fanelli, MD, Mo
W. Schuster, MD, Stefan D. Ar
Wasting Disease

- Aging is associated with a physiological anorexia, decreased protein and energy intake, and weight loss. This is associated with a decline in muscle mass and increased mortality.
- The metabolic efficiency in older persons is decreasing, requiring a higher protein intake for protein synthesis than in younger persons.
- This suggests that a balanced protein and energy supplement may be useful in preventing and reversing sarcopenia as part of a multimodal therapeutic approach. (A)
- Persons with obesity and sarcopenia have very poor outcomes. Appropriate dietary approaches for this group, other than aggressive resistance exercise, are unknown.
- As 15% to 38% of older men and 27% to 41 % of older women ingest less than the recommended daily allowance for protein it is suggested that protein intake be increased. (B)
- It is recommended that the total protein intake should be 1 to 1.5 g/kg/day. (B)
- It is suggested that a leucine-enriched balanced essential amino acid mix may be added to the diet. (B)
- A trial of balanced amino acid supplementation alone and with exercise in sarcopenia is recommended.
- Creatine may enhance the effects of exercise in sarcopenic patients. (A)
- Doses of 50,000 IU of vitamin D a week are safe. (A)
- Short-term resistance exercise improves strength and gait speed. (A)
- Aerobic exercise improves quality of life years (QALY) and is cost effective. (A)
- Epidemiology studies suggest positive effects of physical fitness on health.
- We recommend resistance and aerobic exercise for 20 to 30 minutes, 3 times a week. (A)

A = A minimum of a single randomized placebo-controlled trial or a meta-analysis; B = Small trials.

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Special Article

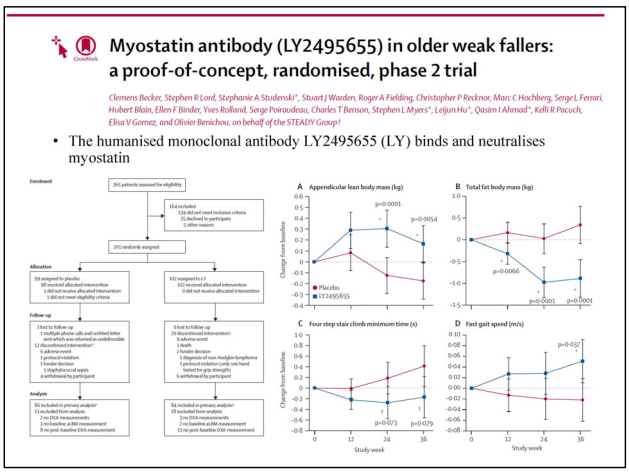
Evidence-Based Recommendations for Optimal Dietary Protein Intake in Older People: A Position Paper From the PROT-AGE Study Group

Jürgen Bauer MD [a,*], Gianni Biolo MD, PhD [b], Tommy Cederholm MD, PhD [c], Matteo Cesari MD, PhD [d], Alfonso J. Cruz-Jentoft MD [e], John E. Morley MB, BCh [f], Stuart Phillips PhD [g], Cornel Sieber MD, PhD [h], Peter Stehle MD, PhD [i], Daniel Teta MD, PhD [j], Renuka Visvanathan MBBS, PhD [k], Elena Volpi MD, PhD [l], Yves Boirie MD, PhD [m]

- Recommended protein intake for healthy older people

PROT-AGE recommendations for dietary protein intake in *healthy* older adults

- To maintain and regain muscle, older people need more dietary protein than do younger people; older people should consume an average daily intake in the range of 1.0 to 1.2 g/kg BW/d.
- The per-meal anabolic threshold of dietary protein/amino acid intake is higher in older individuals (ie, 25 to 30 g protein per meal, containing about 2.5 to 2.8 g leucine) in comparison with young adults.
- Protein source, timing of intake, and amino acid supplementation may be considered when making recommendations for dietary protein intake by older adults.
- More research studies with better methodologies are desired to fine tune protein needs in older adults.



Myostatin antibody (LY2495655) in older weak fallers: a proof-of-concept, randomised, phase 2 trial

Clemens Becker, Stephen R Lord, Stephanie A Studenski*, Stuart J Warden, Roger A Fielding, Christopher P Recknor, Marc C Hochberg, Serge L Ferrari, Hubert Blain, Ellen F Binder, Yves Rolland, Serge Poiraudeau, Charles T Benson, Stephen L Myers*, Leijun Hu*, Qasim I Ahmad*, Kelli R Pacuch, Elisa V Gomez, and Olivier Benichou, on behalf of the STEADY Group†

- The humanised monoclonal antibody LY2495655 (LY) binds and neutralises myostatin