Sarcopenia

경상대학교병원
호흡기알레르기내과
주선미

Sarcopenia

Sarx (flesh) + *penia* (loss)

\- Rosenberg, 1989 -

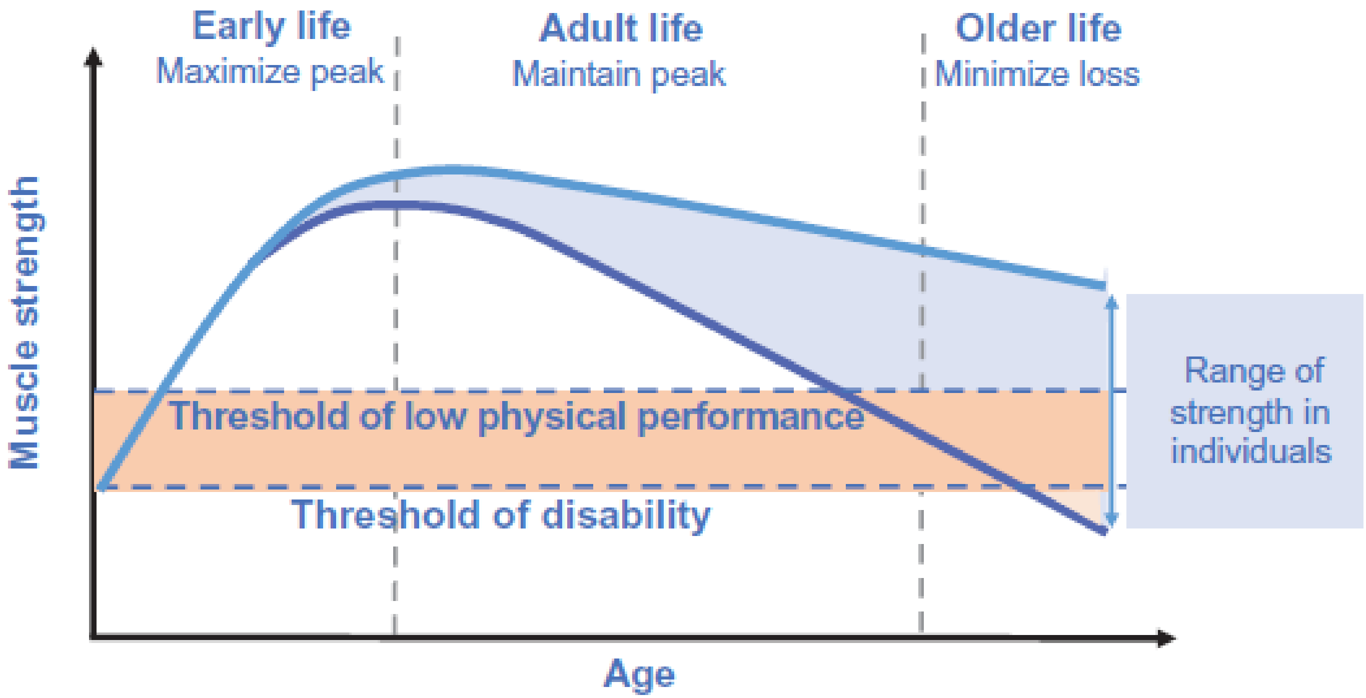
Age-related loss of skeletal muscle mass and function

Super-aged Society

Homo Hundred Era

Life expectancy
≒ Healthy life years + 10 years

Muscle strength and the life course



Cruz-Jentoft et al. *Age and Ageing* 2019; 48: 16–31

Factors contributing to sarcopenia

Disease

- Inflammatory conditions (organ failure, malignancy)
- Osteoarthritis
- Neurological disorders

Aging

Malnutrition

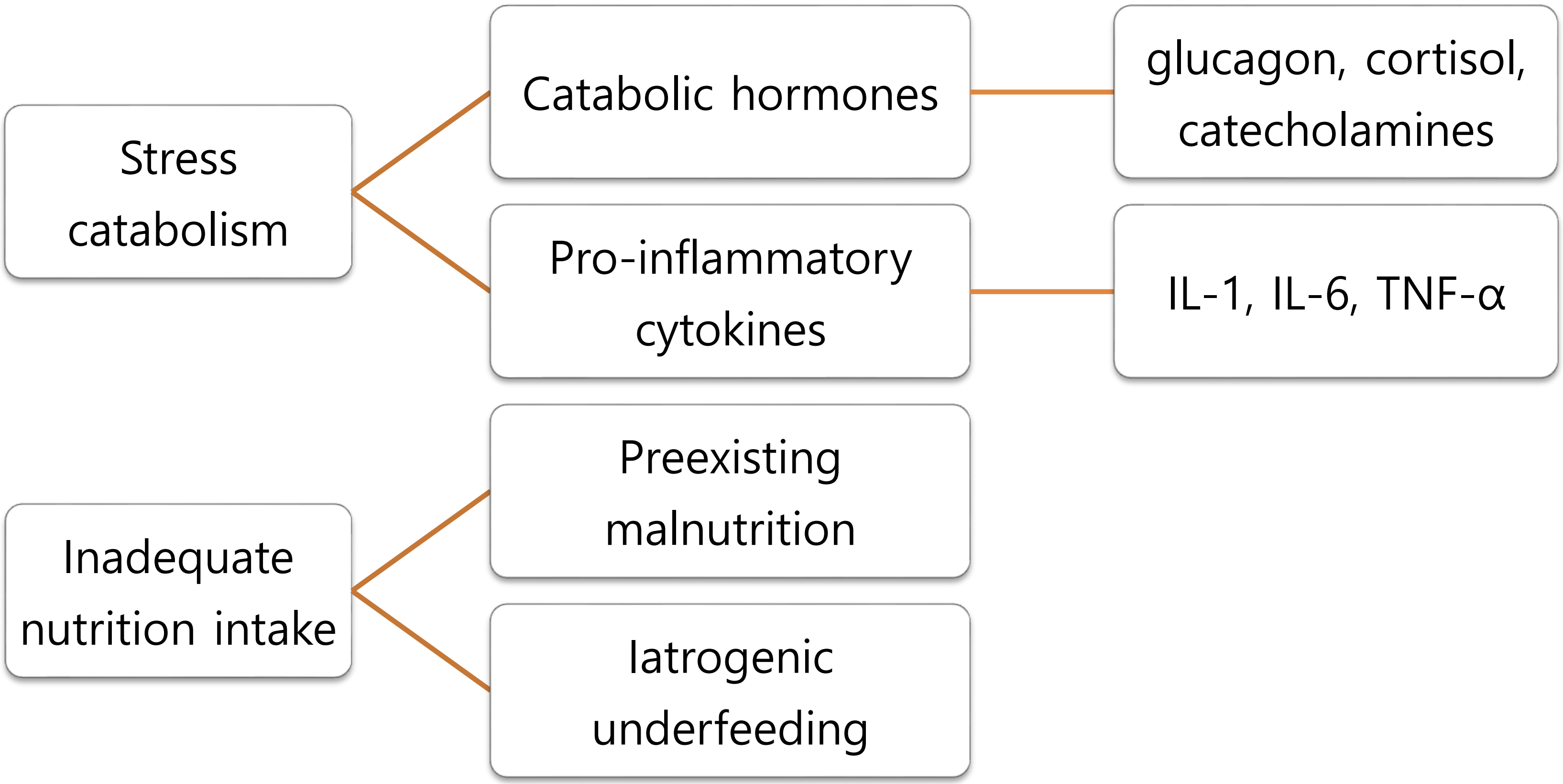
- Under-nutrition or malabsorption
- Medication-related anorexia
- Over-nutrition/obesity

Inactivity

- Sedentary behavior (limited mobility or bed rest)
- Physical inactivity

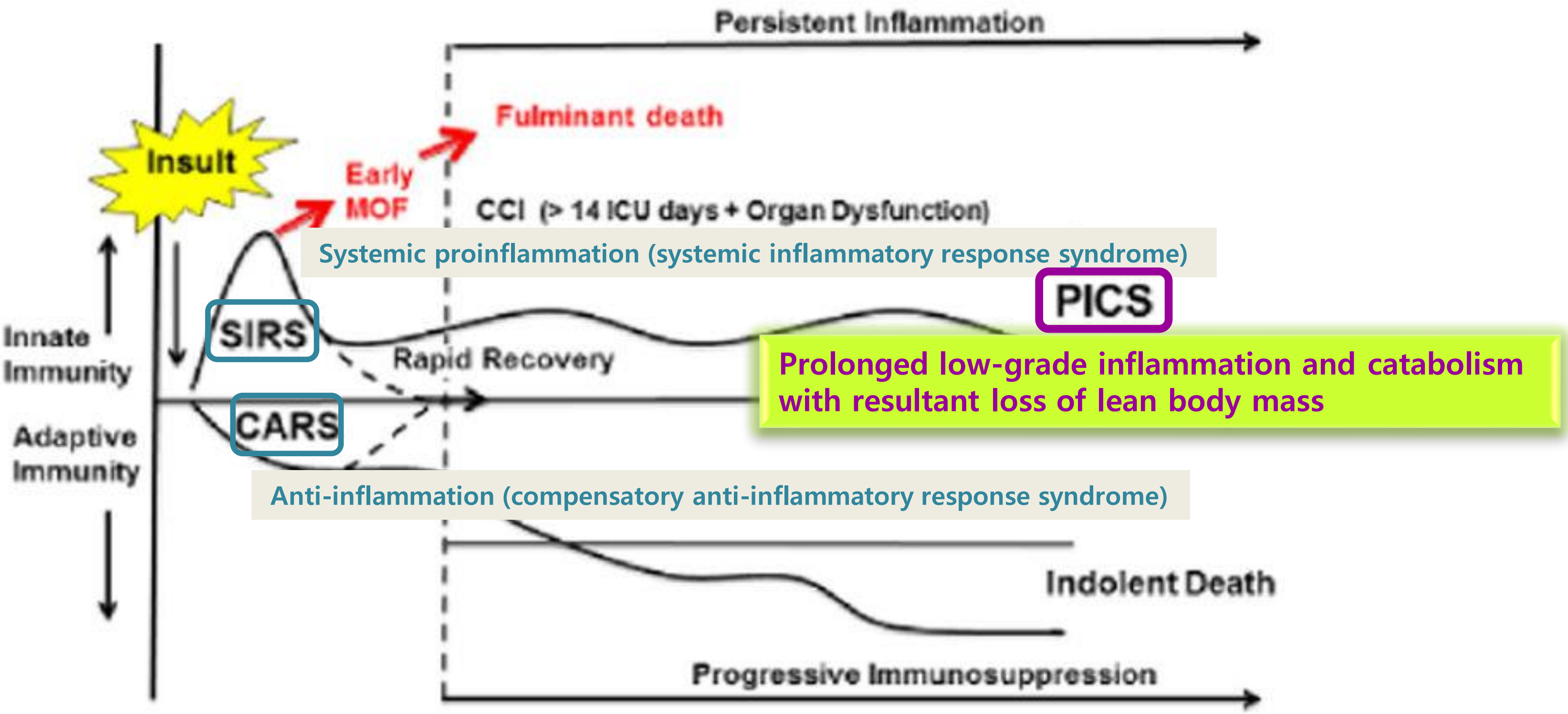
Cruz-Jentoft et al. *Age and Ageing* 2019; 48: 16–31

Malnutrition in critically ill patients



LEE Zyet al. *Nutr Clin Pract* 2019;34(1):96-111

Persistent inflammation, immunosuppression, and catabolism syndrome (PICS) paradigm

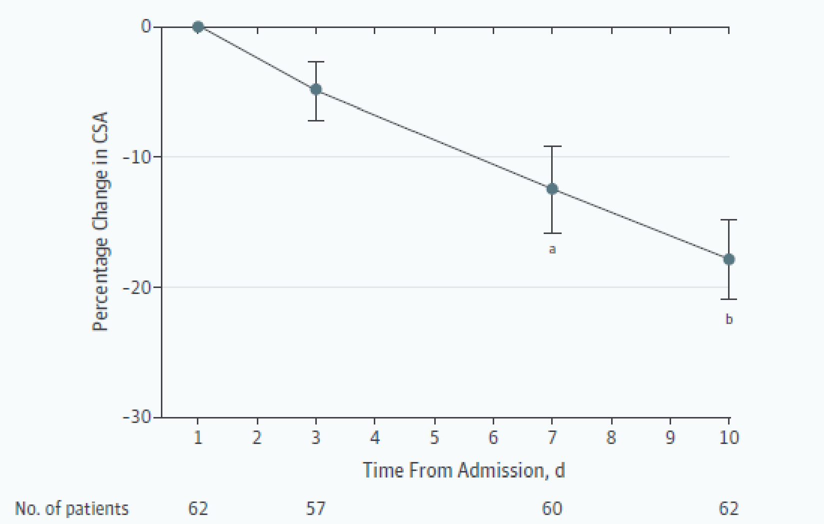


Moore FA et al. *Nutr Clin Pract.* 2017;32(1): 121S–127S

Acute skeletal muscle wasting in critical illness

- Prospective study, August 2009 - April 2011, England
- 63 patients, mean age 54.7 years, APACHE II score of 23.5
- > 48 hours of MV, >7 days in ICU

Change in *rectus femoris* cross-sectional area over 10 days



Summary data (dark circles) are expressed as means and 95% confidence intervals.

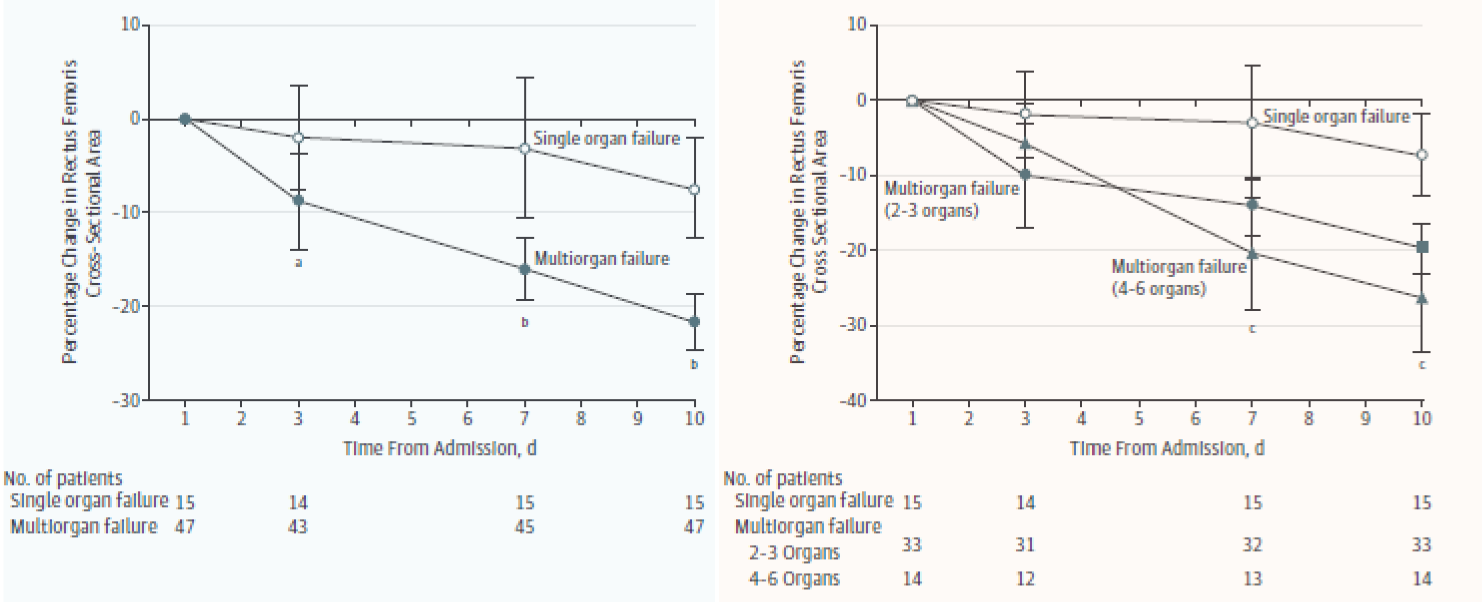
[a] P=.002 for change from day 1 to day 7 by repeated measures 2-way analysis of variance.

[b] P<.001 for change from day 1 to day 10.

Puthucheary ZA et al. *JAMA* 2013 16;310(15):1591-600.

Measurements of muscle wasting during critical illness by organ failure

Single *vs.* multi-organ failure | Single *vs.* multi-organ (2-3/4-6) failure



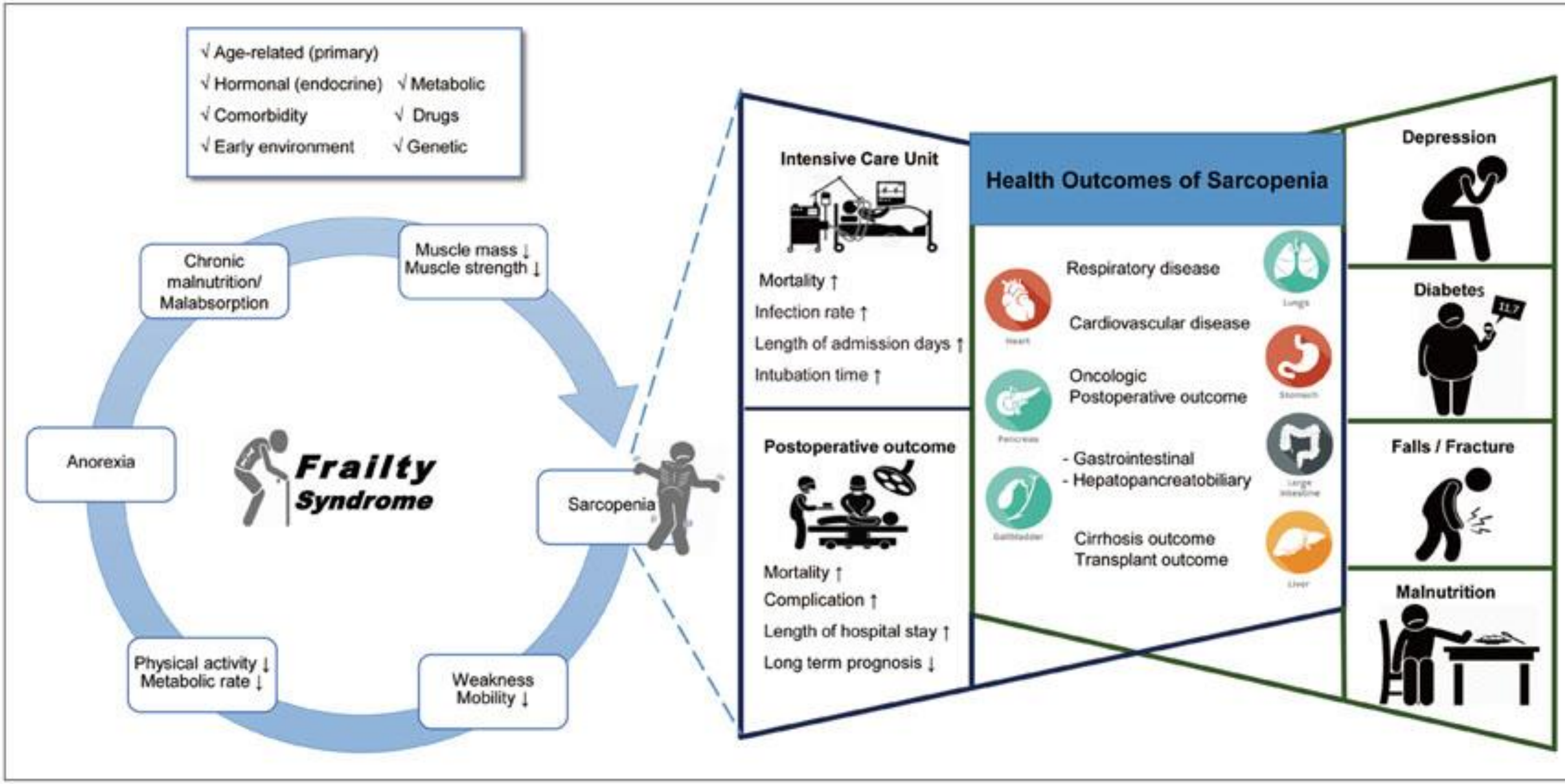
Data are expressed as means and 95% confidence intervals.

[a] P=.03 for change from day 1 to day 3 in multiorgan failure vs single organ failure.

[b] P<.001 for change from day 1 to day 7 and day 1 to day 10 in multiorgan failure vs single organ failure.

[c] P<.001 for difference between failure of 2-3 organs and 4-6 organs from day 1 to day 7 and day 10.

Puthucheary ZA et al. *JAMA* 2013 16;310(15):1591-600.



Koeun Lee el atl. *Korean J Radiol*. 2019;20(2):205-217

2018 operational definition of sarcopenia

European Working Group on Sarcopenia in Older People (EWGSOP2)

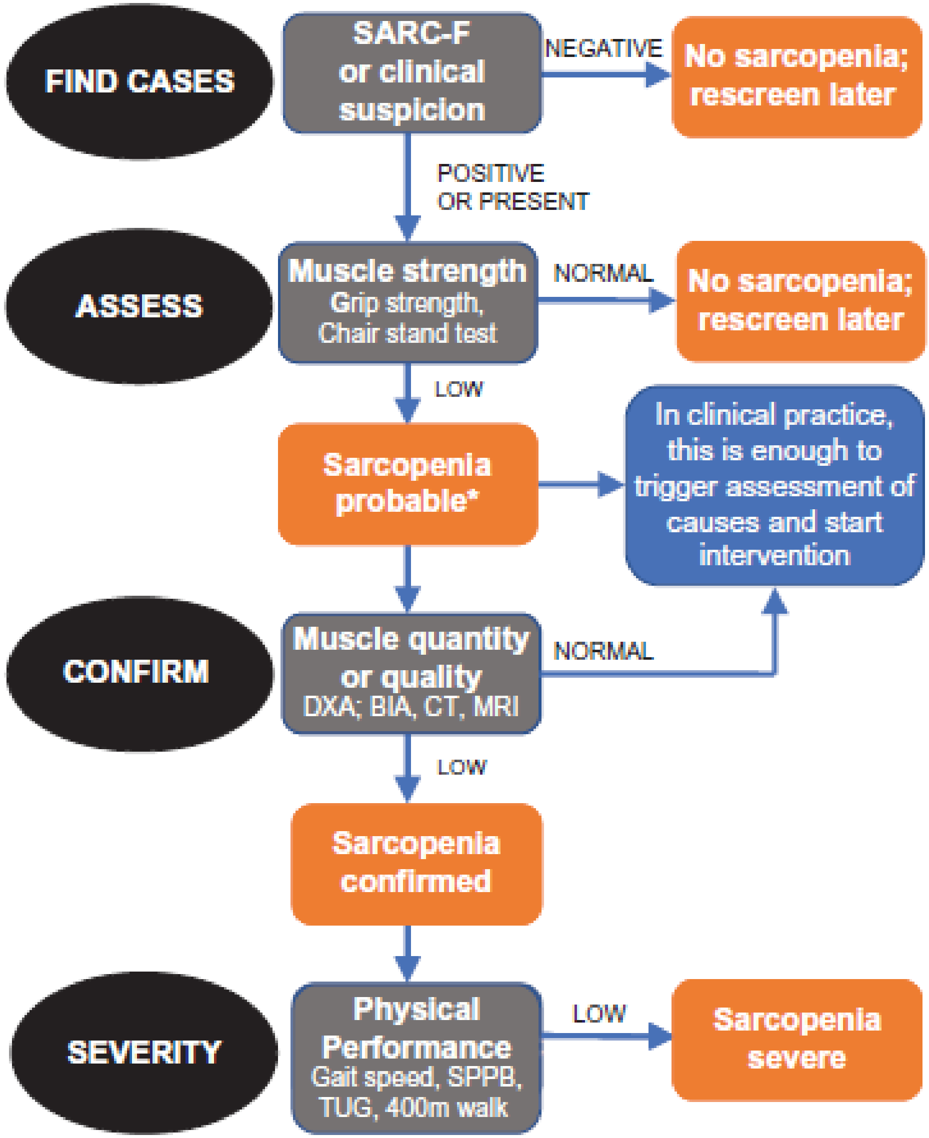
- **Low muscle strength**

➕ **Low muscle quantity** or **quality**

➕ **Low physical performance**

Cruz-Jentoft et al. *Age and Ageing* 2019; 48: 16–31

EWGSOP2 algorithm



Cruz-Jentoft et al. *Age and Ageing* 2019; 48: 16–31

한국형 근감소증 선별 질문지

항목	질문	점수
근력	무게 4.5kg (9개들이 배 한 박스)를 들어서 나르는 것이 얼마나 어려운가요?	전혀 어렵지 않다=0 조금 어렵다=1 매우 어렵다/할 수 없다=2
보행 보조	방안 한 쪽 끝에서 다른 쪽 끝까지 걷는 것이 얼마나 어려운가요?	전혀 어렵지 않다=0 좀 어렵다=1 매우 어렵다/보조기(지팡이 등)를 사용해야 가능/할 수 없다=2
의자에서 일어서기	의자(휠체어)에서 일어나 침대로, 혹은 침대에서 일어나 의자(휠체어)로 옮기는 것이 얼마나 어려운가요?	전혀 어렵지 않다=0 좀 어렵다=1 매우 어렵다/도움 없이는 할 수 없다=2
계단 오르기	10개의 계단을 쉬지 않고 오르는 것이 얼마나 어려운가요?	전혀 어렵지 않다=0 좀 어렵다=1 매우 어렵다/할 수 없다=2
낙상	지난 1년 동안 몇 번이나 넘어지셨나요?	전혀 없다=0 1~3회 =1 4회 이상 =2

*4점/10점 이상이면 근감소증 의심

S Kim et al, *Journal of the American Medical Directors*. 2018 Jan;19(1):40-45

EWGSOP2 Sarcopenia cut-off points

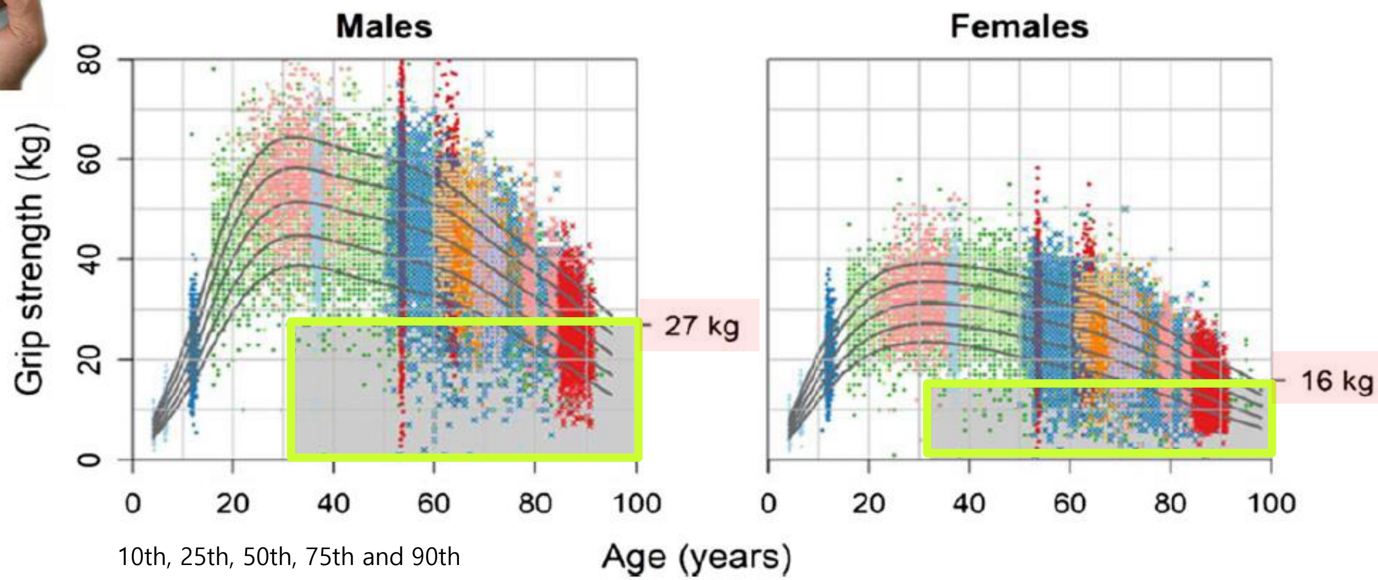
Table 3. EWGSOP2 sarcopenia cut-off points

Test	Cut-off points for men	Cut-off points for women	References
EWGSOP2 sarcopenia cut-off points for low strength by chair stand and grip strength			
Grip strength	<27 kg	<16 kg	Dodds (2014) [26]
Chair stand	>15 s for five rises		Cesari (2009) [67]
EWGSOP2 sarcopenia cut-off points for low muscle quantity			
ASM (Appendicular skeletal muscle mass)	<20 kg	<15 kg	Studenski (2014) [3]
ASM/height^2	<7.0 kg/m^2	<6.0 kg/m^2	Gould (2014) [125]
EWGSOP2 sarcopenia cut-off points for low performance			
Gait speed	≤0.8 m/s		Cruz-Jentoft (2010) [1] Studenski (2011) [84]
SPPB (Short physical performance battery) gait speed, balance test, and chair stand test	≤8 point score		Pavasini (2016) [90] Guralnik (1995) [126]
TUG (Timed-up-and-go test)	≥20 s		Bischoff (2003) [127]
400 m walk test	Non-completion or ≥6 min for completion		Newman (2006) [128]

Cruz-Jentoft et al. *Age and Ageing* 2019; 48: 16–31

Normative data for **grip strength** across the life course in men and women in the UK

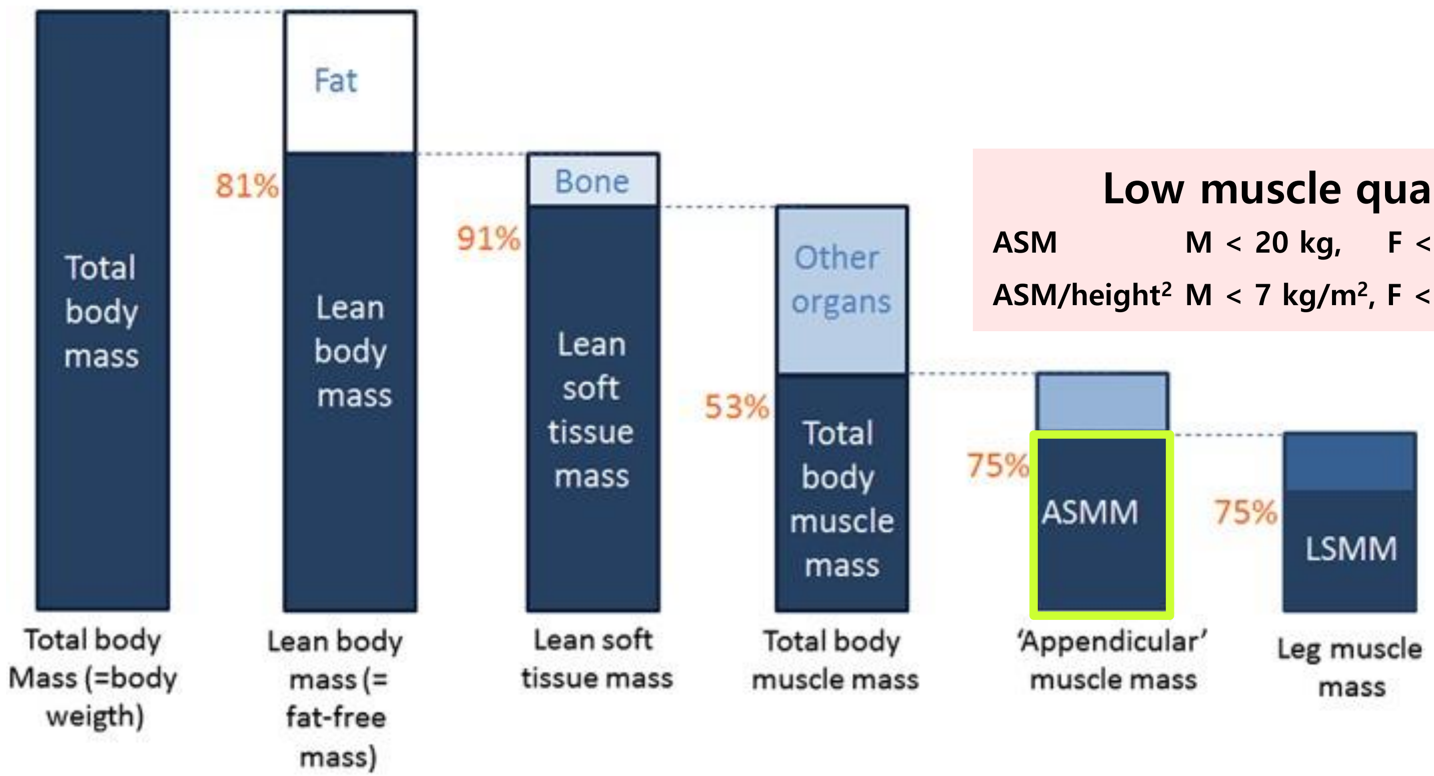
Low strength



10th, 25th, 50th, 75th and 90th

Dodds RM, et al. *PLoS One.* 2014;9:e113637

Body compartments

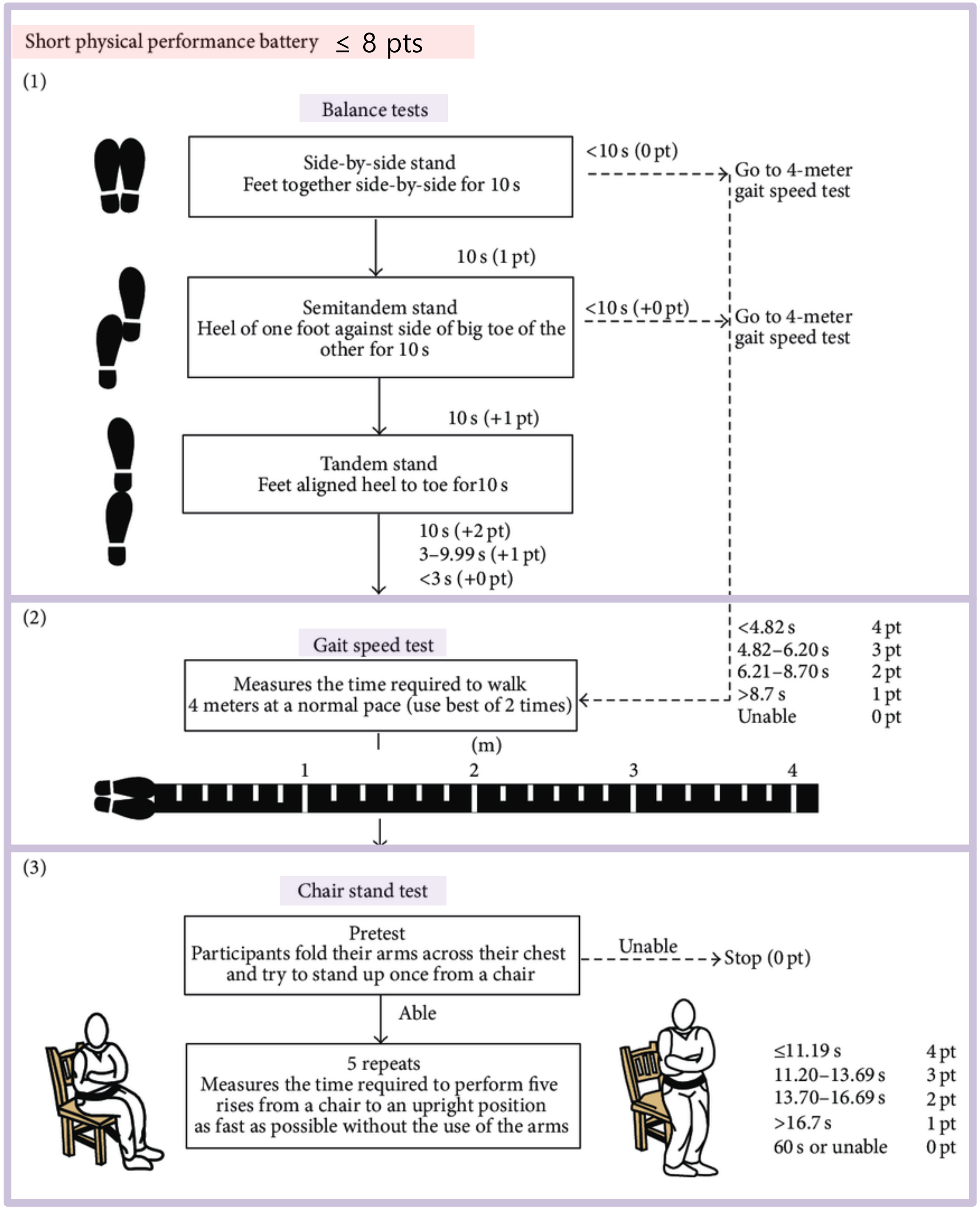


Low muscle quantity

ASM	**M < 20 kg, F < 15 kg**
ASM/height^2	**M < 7 kg/m^2, F < 6 (5.4) kg/m^2**

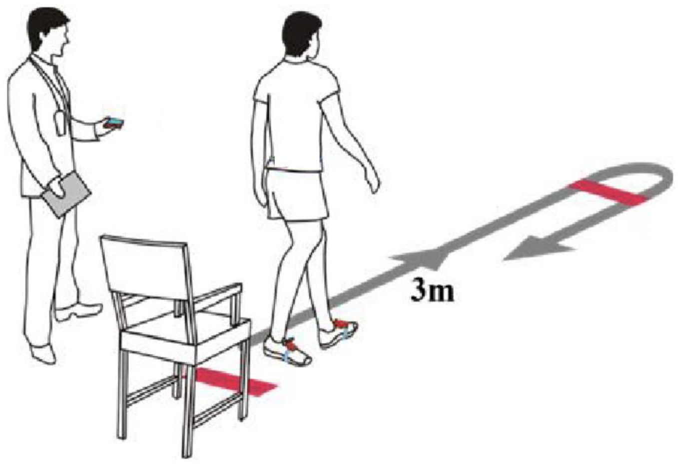
Buckins F et al. *J Cachexia Sarcopenia Muscle* 2018;9(2):269-278.

Low performance

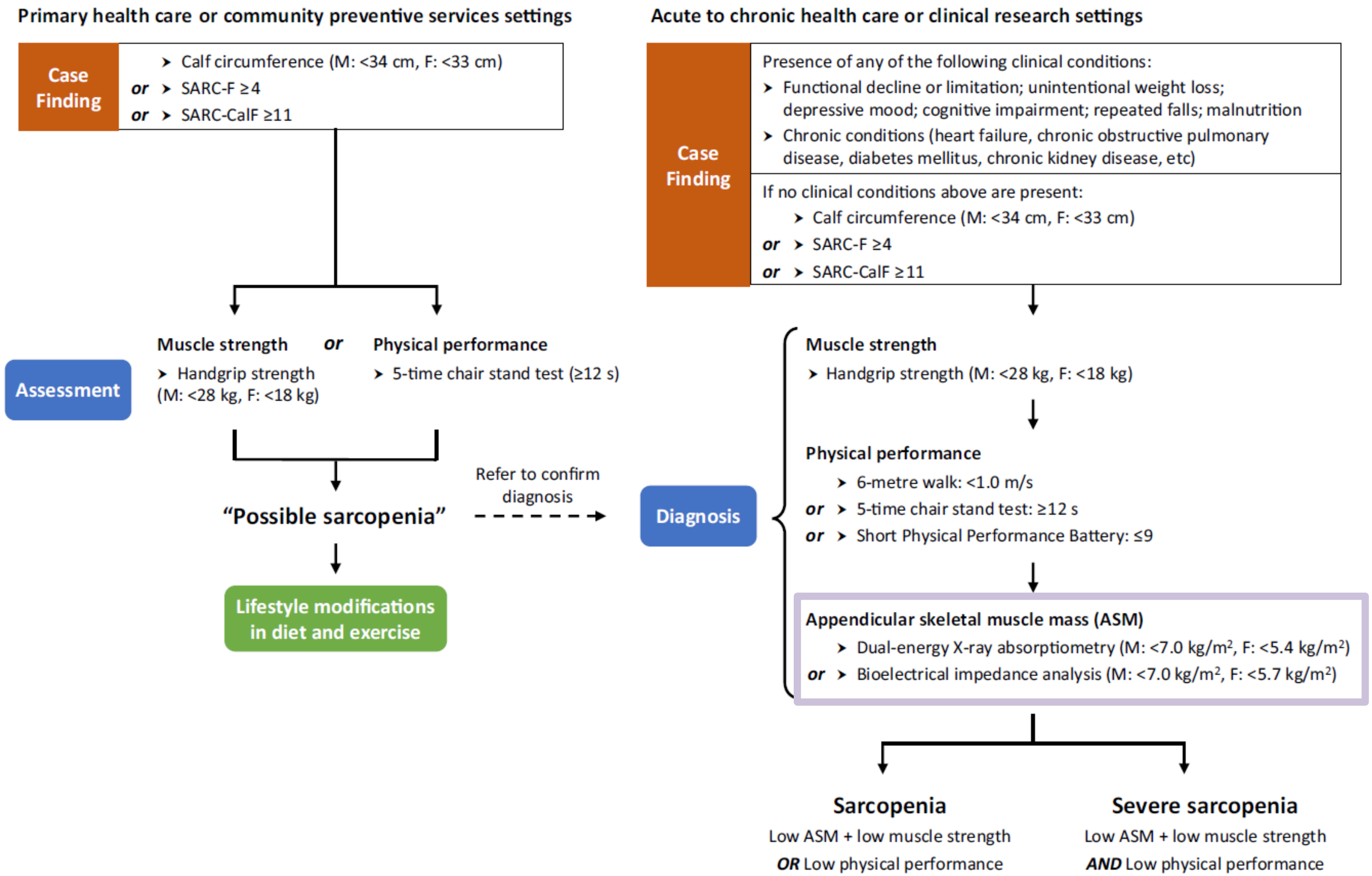


Low performance

Timed up and go test ≥ 20 s



Asian Working Group for Sarcopenia (AWGS) 2019 algorithm for sarcopenia



Liang-Kung Chen et al. 2019 Consensus Update on Sarcopenia Diagnosis and Treatment

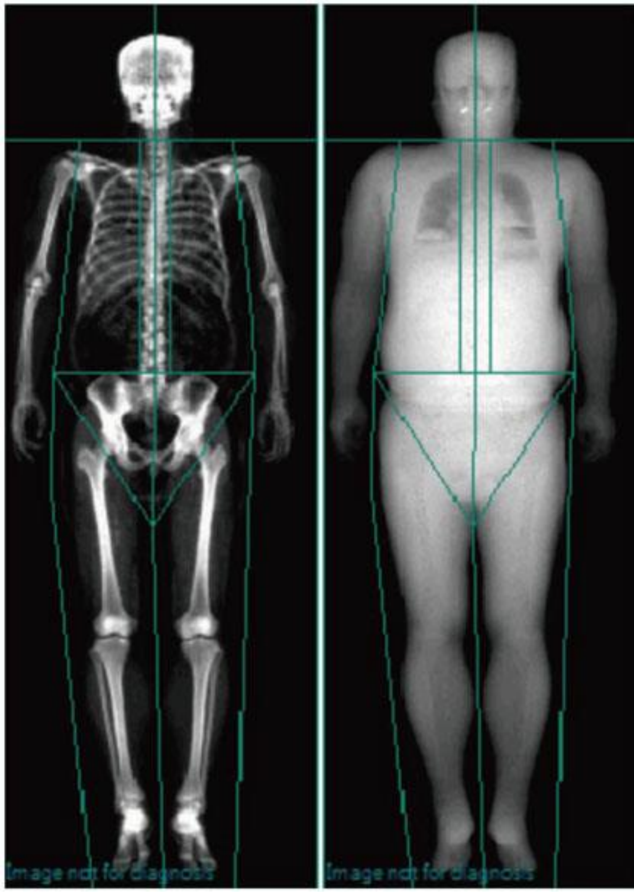
Modalities of measurement for muscle mass

- Dual-energy x-ray absorptiometry (DEXA)
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- Ultrasound (US)
- Bioelectronic impedance analysis (BIA)

Modality	Commonly Used Parameters	Pros	Cons	Error of Lean Mass Estimate
DXA	Whole-body lean mass Appendicular lean mass Apendicular lean mass/height squared	Inexpensive Low radiation exposure Short image acquisition time Simultaneous measurement of whole-body fat mass and bone mass	Lack of portability 2-dimensional data No differentiation between Subcutaneous and visceral fat Does not include trunk muscles	< 5%
CT	Muscle size (CSA, volume) Muscle echo intensity	High accuracy and reproducible results Simultaneous measurement of lean body mass, visceral and subcutaneous fat Differentiate between fat and fat-free mass	Expensive High complexity Radiation exposure	< 8.5%
MRI	Muscle edema, atrophy, fatty infiltration Muscle size (CSA, volume) Muscle adipose tissue content	No radiation exposure Best spatial resolution Body mass composition differentiation Suitable for long-term follow-up, progression monitoring Capable of detecting changes in muscle structure	Expensive High complexity Limited access Longer image acquisition time Some patients with contraindications Lack of standardized assessment protocol	6–8.5%
US	Muscle size (CSA, volume) Muscle thickness Muscle attenuation Echo intensity Fascicle length Pennation angle	Inexpensive No radiation exposure Short image acquisition time Portable Real time visualization of target structure	Operator skills and training required Reliability and accuracy depend on operator Poor reproducibility and accuracy	

Koeun Lee el atl. *Korean J Radiol.* 2019;20(2):205-217

Dual-energy x-ray absorptiometry (DEXA)



Height/Weight : 175.8 cm 95.0 kg
Sex/Ethnic : Male Asian

BODY COMPOSITION

Region	Tissue (%Fat)	Region (%Fat)	Tissue (g)	Fat (g)	Lean (g)	BMC (g)	Total Mass (kg)
Arms	35.0	33.6	8563	3001	5562	365	8.9
Legs	32.1	30.8	27052	8671	18381	1125	28.2
Trunk	50.5	49.3	50363	25415	24948	1206	51.6
Android	57.0	56.5	8686	4950	3736	68	8.8
Gynoid	39.6	38.7	13823	5478	8345	325	14.1
Total	42.0	40.6	91280	38333	52947	3228	94.5

FAT MASS RATIOS

Trunk/Total	Legs/Total	(Arms+Legs)/Trunk
0.66	0.23	0.46

ASM = 23.943 Kg — **M < 20 kg, F < 15 kg** (EWGSOP2 2018)

ASM/height^2 = 7.818 Kg/m^2 — **M < 7.0 kg/m^2, F < 6.0 (5.4) kg/m^2**

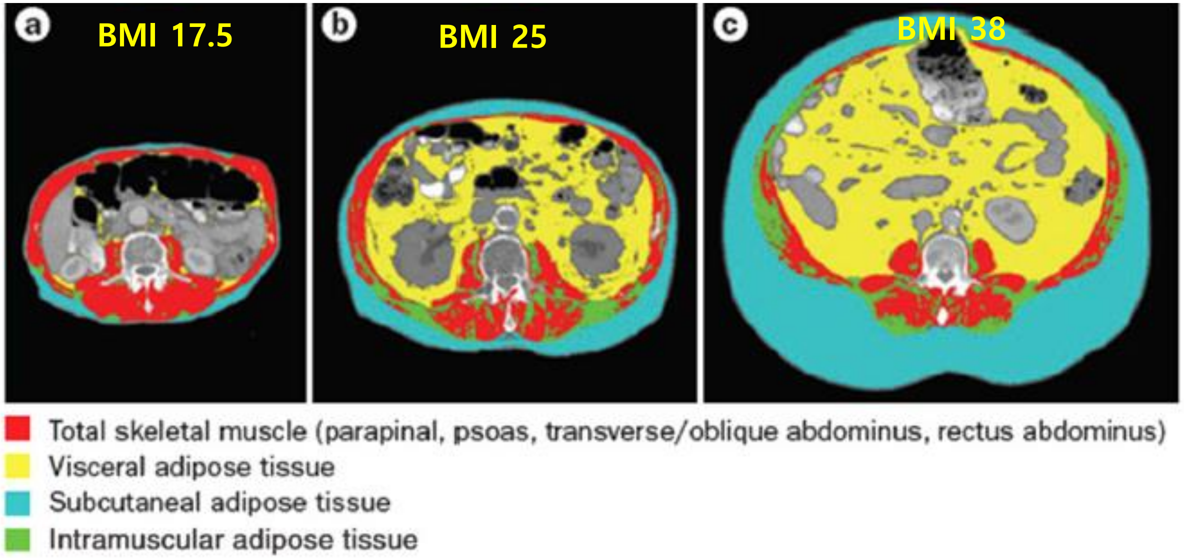
ASM/weight = 0.252

ASM/BMI = 0.771

Koeun Lee el atl. *Korean J Radiol*. 2019;20(2):205-217

Computed tomography (CT); Lumbar 3rd vertebra imaging correlated significantly with whole-body muscle

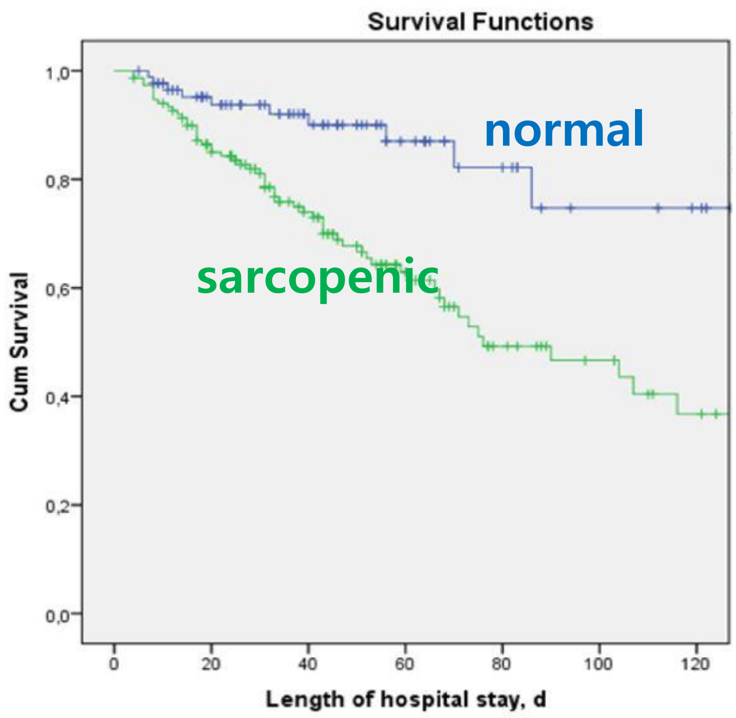
Psoas, erector spinae, quadrates lumborum, transverse abdominus, external and internal obliques, and rectus abdominus



- Skeletal muscle : −29 to 150 HU
- Visceral, subcutaneous, intramuscular adipose tissue : −150 to −50 HU

Fearon K et al. *Nat Rev Clin Oncol.* 2013;10(2):90-99.

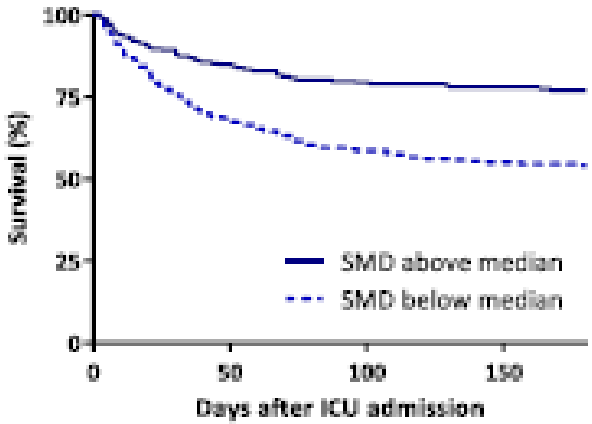
CT-ICU outcomes



- Retrospective analysis
- 240 mechanical ventilated patients
- Abdomen CT on clinical indication between 1 day before and 4 days after admission
- Hospital mortality was significantly higher in those with sarcopenia compared with normal muscle area.
  - females (47.5% vs 20.0%)
  - males (32.3% vs 7.5%)

Weijs PJ et al. *Crit Care*. 2014;18(1):R12.

CT-ICU outcomes



Number at risk	0	50	100	150	
SMD above median	245	187	174	170	167
SMD below median	246	165	144	135	132

Skeletal muscle density (SMD)

- Retrospective study
- 491 mechanically ventilated critically ill adult patients
- Abdomen CT scan, 1 day before to 4 days after ICU admission
- Higher skeletal muscle density was associated with a lower 6-month mortality. HR/10 HU, 0.640 (95% CI, 0.552–0.742), $p < 0.001$

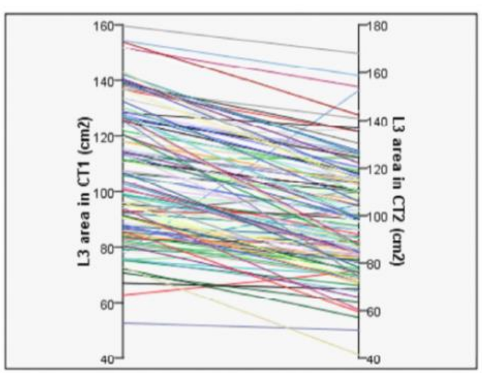
Looijaard WG et al *Crit Care* 2016(20):386

CT-ICU outcomes

❖ Cox proportional hazards regression multivariate analysis of in-hospital mortality of 125 cirrhotic patients admitted to ICU

Variables	aHR	P value
Malignancy (HCC)	2.245	0.004
Alcoholic LC	2.704	0.007
APACHE II	1.064	< 0.001
Accelerated L_3 mass loss (WBMI loss >2%/year)	1.032	0.028

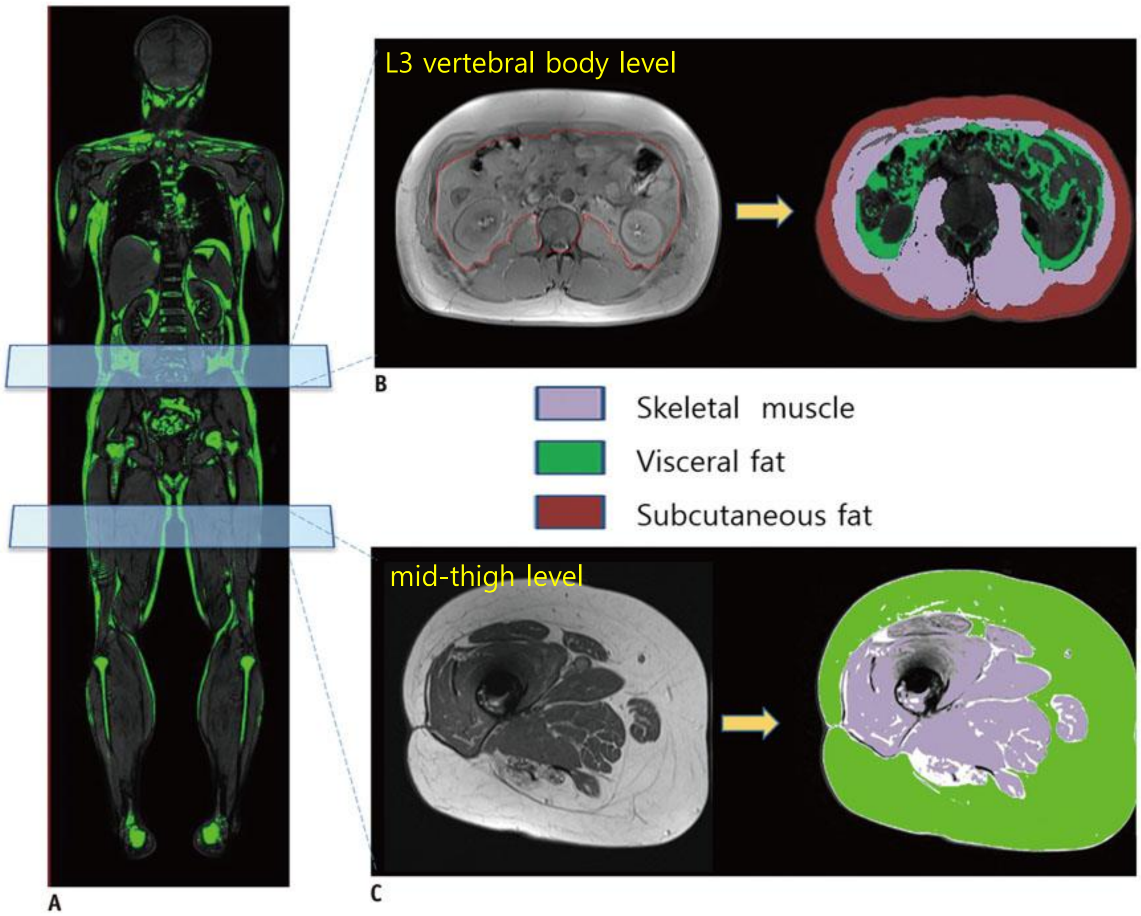
Figure 1. Change in cross-sectional area at the L_3 level between CT1 and CT2 scans



- 125 patients with liver cirrhosis admitted in MICU
- Two separate occasions before admission to the MICU
- 113 patients (90.4%) - sarcopenia
- Rapid muscle decline (WBMI loss >2%/year) is correlated with increased ICU mortality and in-hospital mortality in critically ill patients with cirrhosis.

Ju S et al. *J Intensive Care Med* 2018 Jan 1

Magnetic resonance imaging (MRI)



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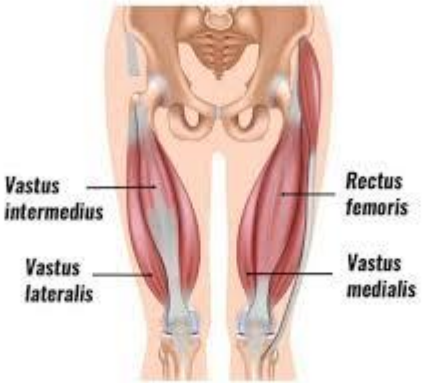
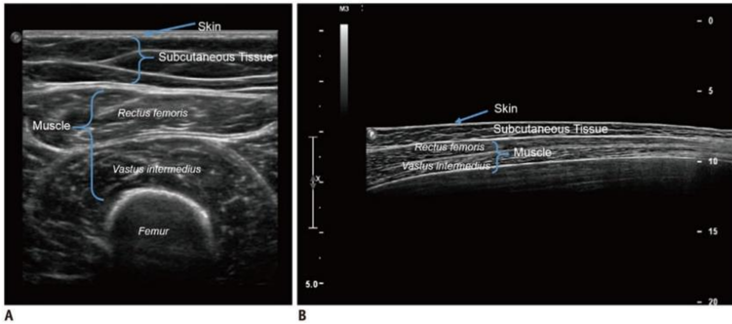
Ultrasound

- Lack of standardization of specific muscles
  - **Rectus femoris** (**CSA** or **thickness**)
  - **Vastus lateralis** (**thickness**)
  - **Limb thickness** (**rectus femoris + vastus intermedius**)
  - Individual muscle groups



- Unknown image acquisition site
  - Mid-thigh, 2/3, and 3/5 of femur length (for the quadriceps)



Mourtzakis M et al. *Ann Am Thorac Soc.* 2017 Oct;14(10):1495-1503.
Koeun Lee el atl. *Korean J Radiol.* 2019;20(2):205-217

Rapid muscle wasting in the ICU

Detection changes in the quality and quantity of muscle
→ Relation with muscle strength and function

Percentage change in ultrasound muscle parameters over the first 10 days of the ICU admission

US muscle parameter measured	Day 3	Day 5	Day 7	Day 10
RF thickness	−8.7%	−16.6%	−24.9%	−30.4%
VI thickness	−1.3%	−18.1%	−20.0%	−29.7%
VL thickness	−0.2%	−5.7%	−6.0%	−14.1%
RF CSA	−1.0%	−11.8%	−16.8%	−29.9%
RF echogenicity	+2.8%	+8.8%	+9.6%	+12.7%
VI echogenicity	+4.0%	+7.1%	+13.6%	+25.2%
VL pennation angle	+4.9%	+18.9%	+1.4%	−7.3%
Subcutaneous tissue thickness	+7.3%	+15.7%	+30.4%	+39.4%

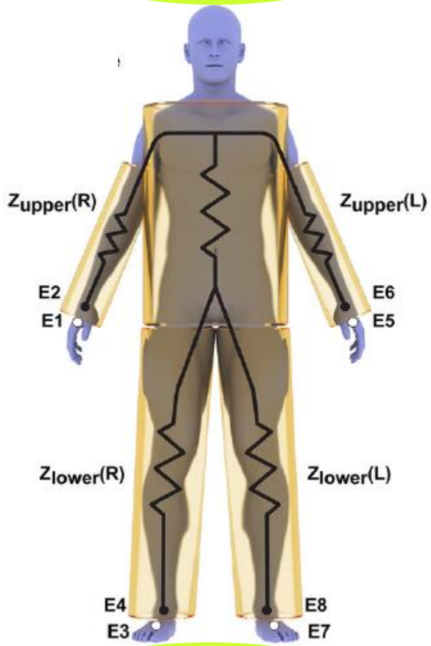
Day 3 measure is a percentage change from baseline.

vastus intermedius (VI)
rectus femoris (RF)
cross-sectional area (CSA)

Parry SM et al. *J Crit Care* 30 (2015)1151.e9–1151.e14

Bioelectronic impedance analysis (BIA)

Muscle, blood



Fat, bone,
air-filled spaces

- Inexpensive
- **No radiation exposure**
- Accessible and can be performed **at the bedside**

- Need of age, gender, and ethnic-specific equation
- **Sensitive to subjects' conditions such as hydration**, recent activity, and time being horizontal

Mundi MS et al. *Nutr Clin Pract* 14(1) 48-58
Buckins F et al. *J Cachexia Sarcopenia Muscle* 2018;9(2):269-278.

BIA-ICU outcomes

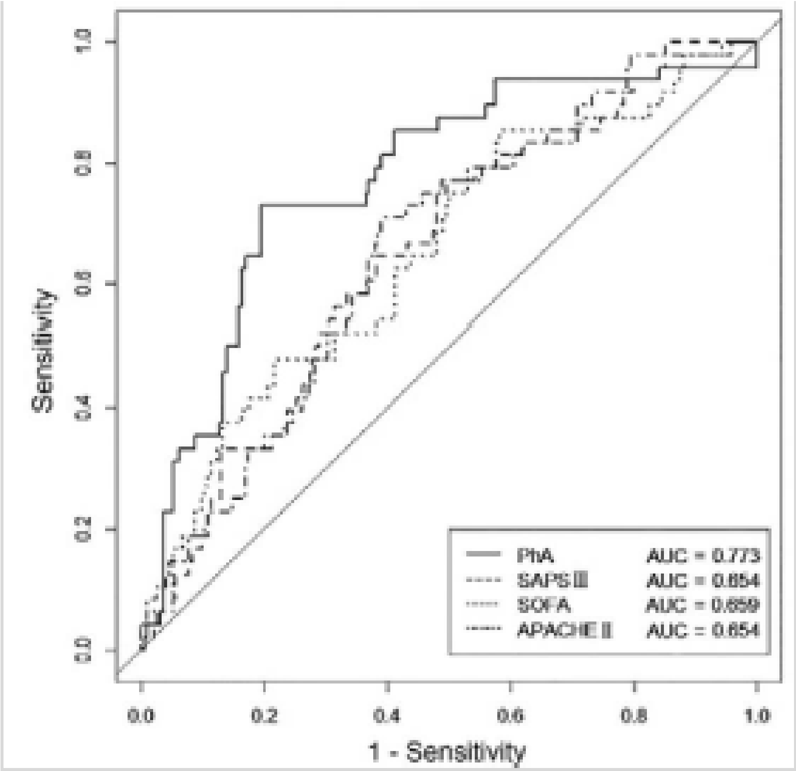


Fig. 1. Covariate-adjusted ROC curves for BIA values (Wholebody phase angle) and severity scorings (APACHE II, SOFA, and SAPS III) as mortality predictive tools. (Adjusted values; age, gender, BMI)

241 critically ill surgical patients

- **Phase angle**

✓ Indicator of **membrane integrity** and **water distribution**

✓ **Prognostic indicator**, **positive association with survival** in patients with HIV, malignancy, hemodialysis, and **critical illness**

Lee YH et al. *J Crit Care* 40(2017) 103-107
Buckins F et al. *J Cachexia Sarcopenia Muscle* 2018;9(2):269-278.

Sarcopenia index

(serum creatinine/serum cystatin C) x 100

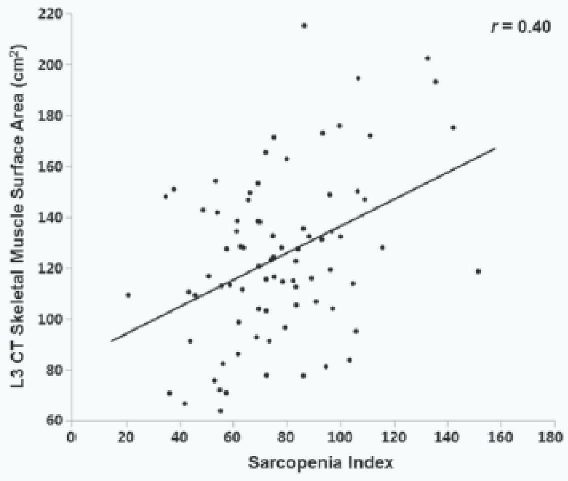


Fig. 1. Correlation between sarcopenia index and skeletal muscle surface area at the L3 level in the 81 patients with an available abdominal CT scan ($r = 0.40$).

- Significant correlation with measured muscle mass via CT scan
- Independent predictor of the hospital and 90-day mortality rates (area under ROC, 0.8)
- Correlation with mechanical ventilation

Kashani et al. *Crit care med* 2017;45(1):e23-e29.
Barreto et al. *Clinical nutrition* 2018

Interventions

- **Nutritional supports**
  - Early nutritional support (ICU)
  - High-protein support
  - Leucine
  - β-Hydroxy-β-Methylbutyrate
  - Vitamin D supplement
- **Physiotherapy**
  - Exercise (rehabilitation)
- **Pharmacotherapy..**

Early nutritional support

- Early enteral nutrition reduced in-hospital mortality from sepsis in patients with sarcopenia.

Koga Y et al. *J Crit Care* 47(2018)153-158

- Early nutritional deficits were correlated with muscle quality deterioration.
  - Inpatient gain in psoas density is associated with shorter hospital stay.

Yeh DD et al. *J Crit Care* 45(2018)7-13

Table 2
Background characteristics and outcomes of patients with or without early enteral nutrition.

	Non-sarcopenia (n = 100)		P value	Sarcopenia (n = 91)		P value
	EEN (n = 43)	DEN (n = 57)		EEN (n = 35)	DEN (n = 56)	
Age (years)	72 (66–79)	70 (62–77)	0.273	75 (67–82)	74 (66–79)	0.540
Sex (female)	18 (42)	19 (33)	0.382	10 (29)	18 (32)	0.720
APACHE II score	19 (13–26)	20 (16–24)	0.544	23 (17–30)	23 (18–29)	0.867
SOFA score						
Day 1	9 (4–12)	10 (8–12)	0.064	7 (6–11)	9 (6–11)	0.505
Day 3	6 (3–10)	9 (6–12)	0.013	7 (4–11)	8 (5–10)	0.412
JAAM-DIC score	3 (2–6)	5 (3–7)	0.024	4 (2–5)	3 (2–5)	0.370
Septic shock	19 (44)	33 (58)	0.174	15 (43)	35 (63)	0.067
Multiple vasopressor use	11 (26)	17 (30)	0.640	6 (17)	16 (29)	0.215
Lactate on admission (mmol/l)	2.4 (1.5–4.6)	2.8 (1.8–4.3)	0.480	2.1 (1.5–5.1)	2.8 (1.3–5.4)	0.543
Infection source			<0.001			0.001
Respiratory	18 (42)	10 (18)		19 (54)	20 (36)	
Abdominal	1 (2)	22 (39)		0 (0)	20 (36)	
Urinary tract	8 (19)	1 (2)		10 (29)	6 (11)	
Soft tissue	11 (26)	8 (14)		4 (11)	6 (11)	
Others	5 (12)	16 (28)		2 (6)	4 (7)	
Time to antibiotics (hr)	2.5 (1.5–3.5)	2.2 (1.0–3.0)	0.685	2.0 (1.5–3.5)	2.6 (2.0–4.5)	0.118
Mortality						
ICU	6 (14)	9 (16)	0.799	3 (9)	14 (25)	0.043
In-hospital	7 (16)	9 (16)	0.947	3 (9)	19 (34)	0.005

Values are numbers (percentages) of patients or medians (interquartile ranges).
BMI, body mass index; NUTRIC, Nutrition Risk in the Critically Ill; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation.

Single-center retrospective analysis - septic patients

Yamaguchi University Hospital ICU

January 2010-August 2017

Skeletal muscle area (SMA) at the level of the third lumbar vertebra was measured with CT on admission

Sarcopenia : SMA < 80% of the predicted value

Table 3
Factors associated with in-hospital mortality.

a. Non-sarcopenic patients	OR	95% CI	P value
SOFA score on day 3 (per point)	1.34	(1.12–1.60)	0.002
Sex (female)	7.24	(1.72–30.53)	0.007
Time to antibiotics (per hr)	1.39	(1.10–1.76)	0.006

b. Sarcopenic patients	OR	95% CI	P value
SOFA score on day 3 (per point)	1.24	(1.06–1.46)	0.008
EEN	0.18	(0.05–0.71)	0.014

SOFA, Sequential Organ Failure Assessment; EEN, early enteral nutrition; OR, odds ratio; CI, confidence interval.

Koga Y et al. *J Crit Care* 47(2018)153-158

Protein intake


Older adults need more dietary protein than do younger adults.

Fourth Korea National Health and Nutrition Examination Survey (KNHANES IV)

Table 2 Socioeconomic status and health behavior of the Korean elderly subjects with or without sarcopenia **(≥ 65 years)**

Variables (unit)	Male			Female		
	Non-sarcopenia (*N*=500)	Sarcopenia (*N*=440)	*P* value	Non-sarcopenia (*N*=1,224)	Sarcopenia (*N*=100)	*P* value
Limitation of daily activity	159 (32.0)	182 (42.0)	0.002	576 (47.4)	61 (61.6)	0.007
Regular exercise	335 (76.8)	259 (60.0)	0.013	617 (51.5)	39 (39.0)	0.017
Nutritional status						
Energy intake (kcal)	1,920.6±681.9	1,687.2±577.4	<0.001	1,390.2±541.9	1,212.1±419.8	0.002
Protein (g)	64.4±30.3	54.6±25.2	<0.001	43.6±23.5	40.3±21.0	0.201
Fat (g)	27.1±23.1	21.8±16.3	<0.001	16.5±15.5	14.5±10.9	0.209
Carbohydrate (g)	338.1±109.7	300.5±103.2	<0.001	269.0±103.1	232.3±85.4	0.001
Calcium (mg)	497.1±391.0	414.0±315.2	0.001	354.3±470.7	296.1±206.2	0.242
Vitamin and mineral supplement use	73 (16.0)	59 (14.4)	0.508	216 (19.1)	27 (30.3)	0.010
Food consumption (per week)						
Meat and eggs	3.5±2.9	3.1±2.9	0.022	2.4±2.9	2.2±2.0	0.647
Fishes	5.2±4.5	4.2±4.2	0.001	3.7±3.9	3.1±2.8	0.067

The energy intake was significantly lower in sarcopenic participants.

Kim JE et al. *Osteoporos Int* 25:2189–2198.

Protein intake

How much ?

Recommendation of protein intake

- **0.8 g/kg BW/day**

  – World Health Organization (WHO)

- **1.0–1.5 g/kg BW/day** (with adequate exercise)

  - Society for Sarcopenia, Cachexia and Wasting Disease

- **1.0–1.2 g/kg BW/day** (healthy elderly 65+ years)
- **1.2–1.5 g/kg BW/day** (chronically ill or malnourished elderly with severe illness or injury)
- **1.3 g/kg BW/day, progressively** (critical illness)

  – ESPEN

Franzke B et al. *Nutrients* 2018, 10, 935

Recommendation of protein intake

- **1.0-1.2 g /kg BW/day** (average daily intake)
- **> 1.2 g/kg BW/day** (exercising and otherwise active elderly)
- **1.2-1.5 g/kg BW/day** (elderly with acute or chronic diseases)
- **2.0 g/kg BW/day** (severe illness or injury or marked malnutrition)

Exception) severe kidney disease (GFR <30 mL/min/1.73m^2) with no dialysis

– PROT-AGE Study Group

Bauer J et al. *JAMDA* 14(2013)542-559

Protein intake

Specific amino acids

Types of amino acids

Essential

- Histidine
- Isoleucine
- Leucine
- Methionine
- Phenylalanine
- Threonine
- Tryptophan
- Valine
- Lysine

Conditionally essential

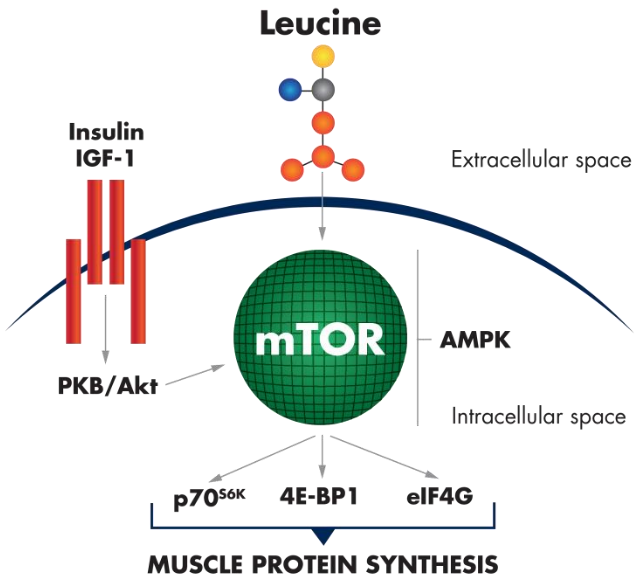
- Arginine
- Asparagine
- Glutamine
- Glycine
- Proline
- Serine
- Tyrosine

Non-essential

- Alanine
- Asparatate
- Cysteine
- Glutamate

Leucine

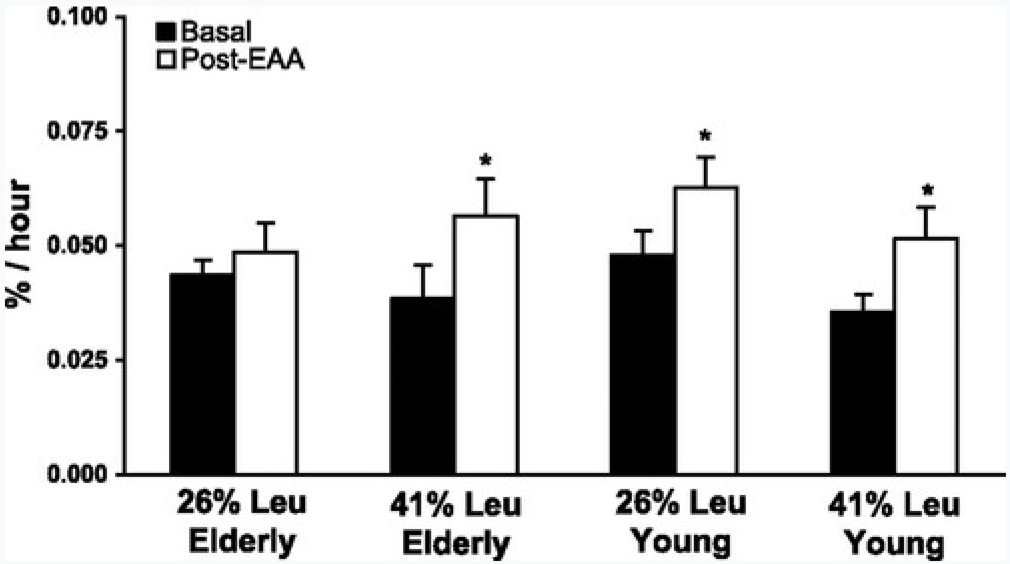
- Essential amino acid
- Promote muscle protein synthesis by stimulating the mammalian target of rapamycin (mTOR) signaling pathway



Moore FA et al. *Nutr Clin Pract*. 2017; 32: 121S-127S

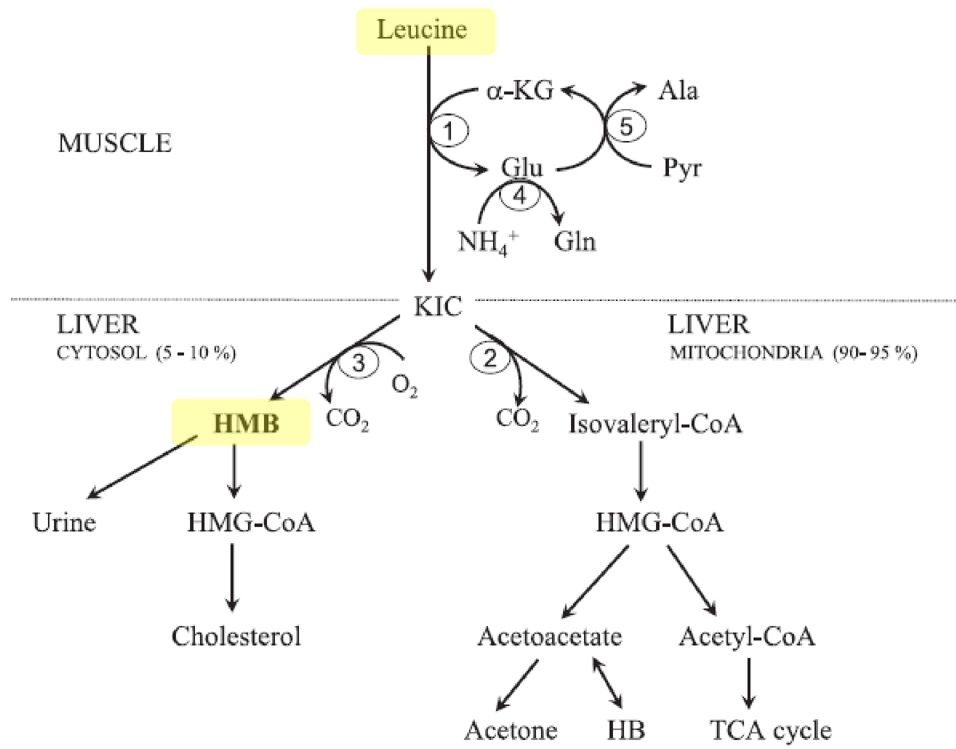
A high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids in the elderly.

Fractional synthetic rate (%/h) of mixed muscle protein



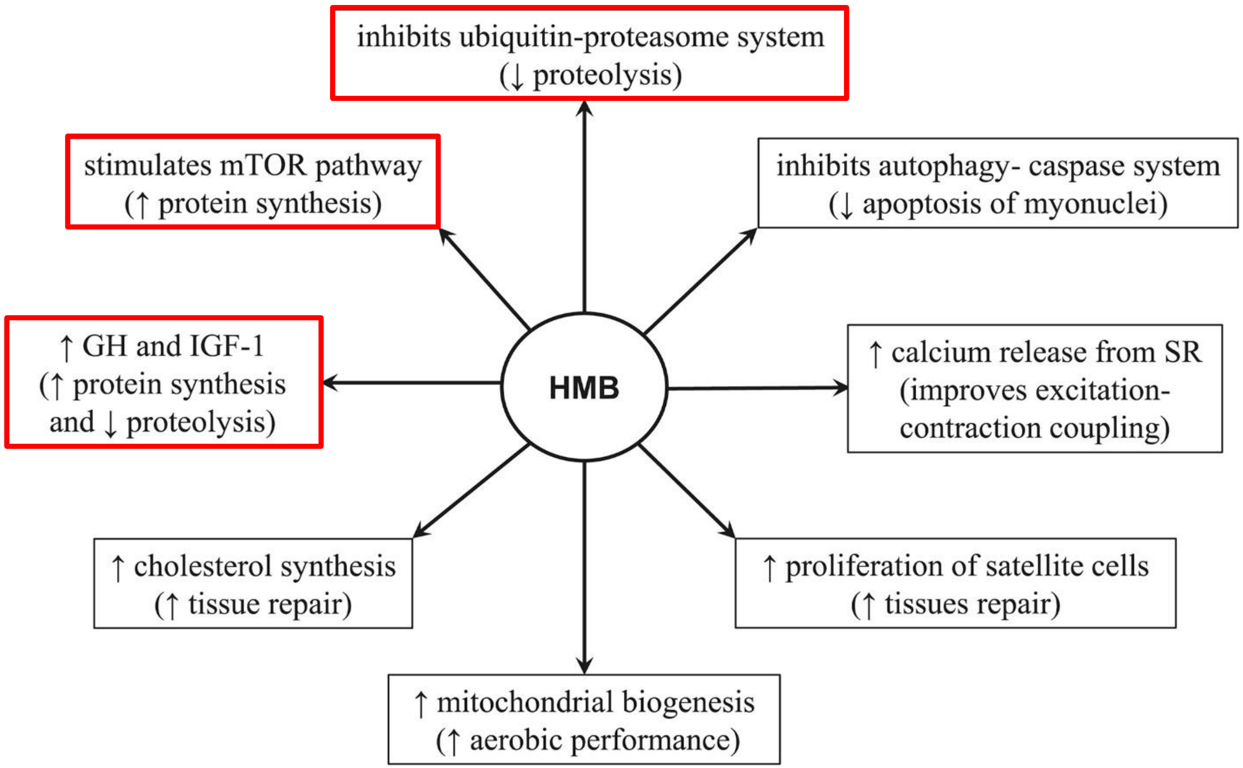
Katsanos CS et al. *Am J Physiol*. 2006; 291:E381-E387

β-hydroxy-β-methylbutyrate (β-HMB)



Milan Horecek, *Journal of Cachexia, Sarcopenia and Muscle* 2017;8:529–541

Suggested mechanisms for the favorable effects of HMB supplementation on skeletal muscle



Milan Horecek, *Journal of Cachexia, Sarcopenia and Muscle* 2017;8:529–541

Effects of β-HMB in humans with muscle-wasting disorder

Origin of muscle loss	Study design	Effects	Reference
AIDS	HMB/Arg/Gln mixture (3/14/14 g per day) for 8 weeks	↑ lean body mass and improved immune status	Clark *et al.*[97]
Cancer	HMB/Arg/Gln mixture (3/14/14 g per day) for 24 weeks	↑ body weight and FFM	May *et al.*[98]
Cancer	HMB/Arg/Gln mixture (3/14/14 g per day) for 8 weeks	Trend towards an increased body mass	Berk *et al.*[99]
AIDS or cancer	HMB/Arg/Gln mixture (3/14/14 g per day) for 8 weeks	Decreased feeling of weakness, increased RBC, haematocrit, lymphocytes, eosinophils, and urea	Rathmacher *et al.*[100]
Chronic obstructive pulmonary disease	HMB (3 g/day) for 7 days	Improved pulmonary function, ↓CRP	Hsieh *et al.*[101]
Chronic cardiac or pulmonary disease	Oral supplementation with proteins and HMB (1.5 g HMB/day) for 90 days	Decreased mortality, improved indices of nutritional status	Deutz *et al.*[102]
Chronic pulmonary disease	Oral supplementation with proteins and HMB (1.5 g HMB/day) for 12 weeks	Improved body composition, health-related quality of life, and muscle strength	Olveira *et al.*[103]
Critically ill trauma patients, bed rest, enteral nutrition	HMB (3 g/day), HMB/Arg/Gln mixture or placebo via feeding tube for 28 days	Improvement in nitrogen balance	Kuhls *et al.*[104]
Total knee arthroplasty	HMB/Gln/Arg mixture (2.4/14/14 g per day) for 4 weeks	Prevention of reduction of maximal strength of quadriceps muscle	Nishizaki *et al.*[105]
Hip fracture	HMB (3 g)/vitamin D/protein combination for 30 days	Accelerated healing, shortening immobilization period, ↑ muscle strength	Ekinci *et al.*[106]
Gastric bypass	HMB/Gln/Arg mixture (1.5/7/7 g per day) for 8 weeks	No benefits when compared with controls	Clements *et al.*[107]
Renal failure	HMB (3 g/day) for 6 months	No benefits	Fitschen *et al.*[108]
Rheumatoid arthritis	HMB/Gln/Arg mixture (3/14/14 g per day) for 12 weeks	No benefits when compared with placebo	Marcora *et al.*[109]

Milan Horecek, *Journal of Cachexia, Sarcopenia and Muscle* 2017;8:529–541

Oral supplement enriched in **HMB** combined with **pulmonary rehabilitation** **improves body composition and health related quality of life** in patients with bronchiectasis

- Single center randomized controlled trial, parallel treatment design
- Patients with non cystic fibrosis bronchiectasis, 18-80 years
- Normally nourished (BMI > 18.5 kg/m^2 < 65 years old,
  BMI > 20 kg/m^2 in > 65 years old)

PR (pulmonary rehabilitation)

- **Twice-weekly 60 min exercise program** at the Hospital and one unsupervised session per week for 12 weeks

PRONS (PR + oral nutritional supplement)

- ONS: hyperproteic oral nutritional supplement enriched with **beta hydroxy-beta-methylbutyrate (HMB)**

Olveira G et al. *Clin Nutr.* 2016 Oct;35(5):1015-22

Evolution of the parameters of body composition by DXA, anthropometric, phase angle, dynamometer and quality of life.

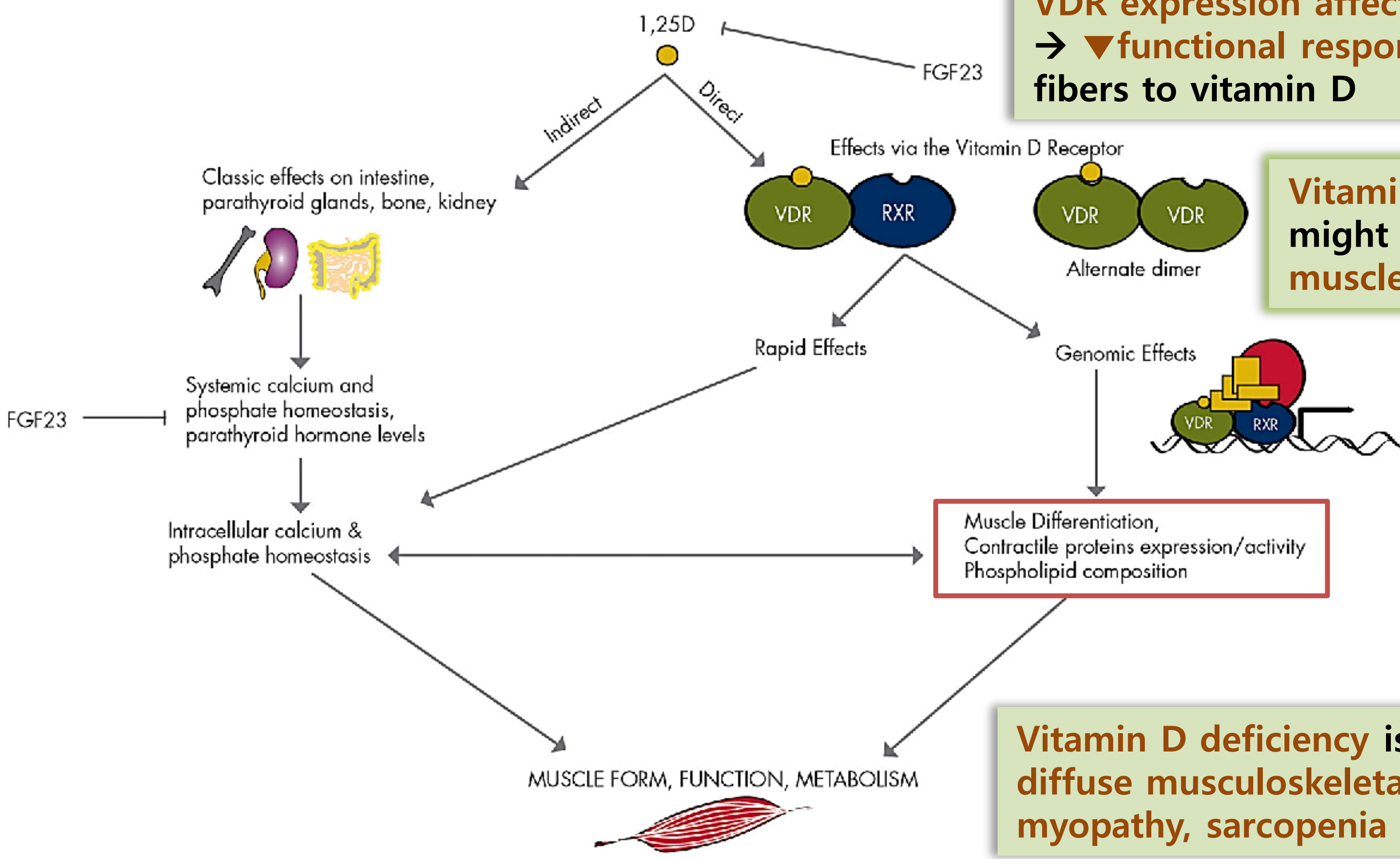
		Basal	3 Months	6 Months
Weight (kg)				
PR	(m ± DE)	69.8 ± 19.3	70.1 ± 18.2	70.5 ± 18.4
PRONS	(m ± DE)	69.5 ± 12.2	70.5 ± 11.8*	69.9 ± 11.3
Fat mass (kg)				
PR	(m ± DE)	27.4 ± 13.3	27.2 ± 12.5	28 ± 12.9*
PRONS	(m ± DE)	24.5 ± 6.9	24.4 ± 6.4	24.3 ± 6.1
Fat free mass (kg)				
PR	(m ± DE)	42.1 ± 10	42.7 ± 9.8	42.5 ± 9.6
PRONS	(m ± DE)	44.9 ± 9.2	46 ± 9.3**	45.4 ± 9.6
FFMI (kg/m^2)				
PR	(m ± DE)	17.1 ± 2.3	17.3 ± 2.3	17.3 ± 2.2
PRONS	(m ± DE)	17.4 ± 2.4	17.8 ± 2.4**	17.6 ± 2.5
BMD (g/cm^2)				
PR	(m ± DE)	1.142 ± 0.106	1.139 ± 0.106	1.142 ± 0.104
PRONS	(m ± DE)	1.141 ± 0.138	1.154 ± 0.136**	1.150 ± 0.137**
FFM legs (kg)				
PR	(m ± DE)	13.1 ± 3.4	13.4 ± 3.2	13.6 ± 3.3
PRONS	(m ± DE)	14.1 ± 3.1	14.3 ± 3.3	14.1 ± 3.5
FFM Arms (kg)				
PR	(m ± DE)	4.4 ± 1.5	4.4 ± 1.4	5.4 ± 3.6
PRONS	(m ± DE)	5 ± 1.4	5.2 ± 1.5*	5.2 ± 1.5*
FFM trunk (kg)				
PR	(m ± DE)	21 ± 5.3	21.1 ± 5	20.7 ± 5
PRONS	(m ± DE)	21.7 ± 4.4	22.3 ± 4.3*	21.9 ± 4.6
Phase angle				
PR	(m ± DE)	5.3 ± 0.8	5.3 ± 0.7	5.1 ± 0.7
PRONS	(m ± DE)	5.4 ± 0.9	5.6 ± 0.8	5.6 ± 0.9
Mid-arm muscle circumference (centil)				
PR	(m ± DE)	56.2 ± 25.6	62.2 ± 26.7	64 ± 29.6
PRONS	(m ± DE)	68.8 ± 22.5	74.2 ± 17.3*	70 ± 17.9
Maximal handgrip dynamometry (kg)				
PR	(m ± DE)	29.1 ± 14.3	30.4 ± 15.2	30.4 ± 15.3
PRONS	(m ± DE)	30 ± 11.9	32.2 ± 11.9**	32.6 ± 11.4**
Mean handgrip dynamometry				
PR	(m ± DE)	27.1 ± 13.5	28.6 ± 14.9**	29.1 ± 14.6*
PRONS	(m ± DE)	28.2 ± 11.2	30.3 ± 11.4**	30.8 ± 11.2**
QOL-B-V3.0				
Physical Functioning scale				
PR	(m ± DE)	46.6 ± 31.5	52.1 ± 27.8	53.1 ± 24.2
PRONS	(m ± DE)	59.3 ± 30.1	67.4 ± 25.5*	68.8 ± 25.7*

M ± SD: mean ± standard deviation. PR pulmonary rehabilitation. PRONS pulmonary rehabilitation plus oral nutritional supplement. FFMI: Fat free Mass index. There were no differences between groups at baseline in any measures. *$p < 0.05$; **$p < 0.01$.

Olveira G et al. *Clin Nutr*. 2016 Oct;35(5):1015-22

Vitamin D

Vitamin D



VDR expression affected by aging → ▼functional response of the muscle fibers to vitamin D

Vitamin D receptor (VDR) might be localized in muscle fibers.

Vitamin D deficiency is related with diffuse musculoskeletal pain, myopathy, sarcopenia and falls.

Girgis CM et al. *Endocrinology*, 2014. 155(2): 347–357
Wagatsuma et al. *Biomed Res int*. 2014:2014:121254

Vitamin D

- Vitamin D supplementation of 800 to 1000 IU/day is associated with increased muscle strength in the elderly.

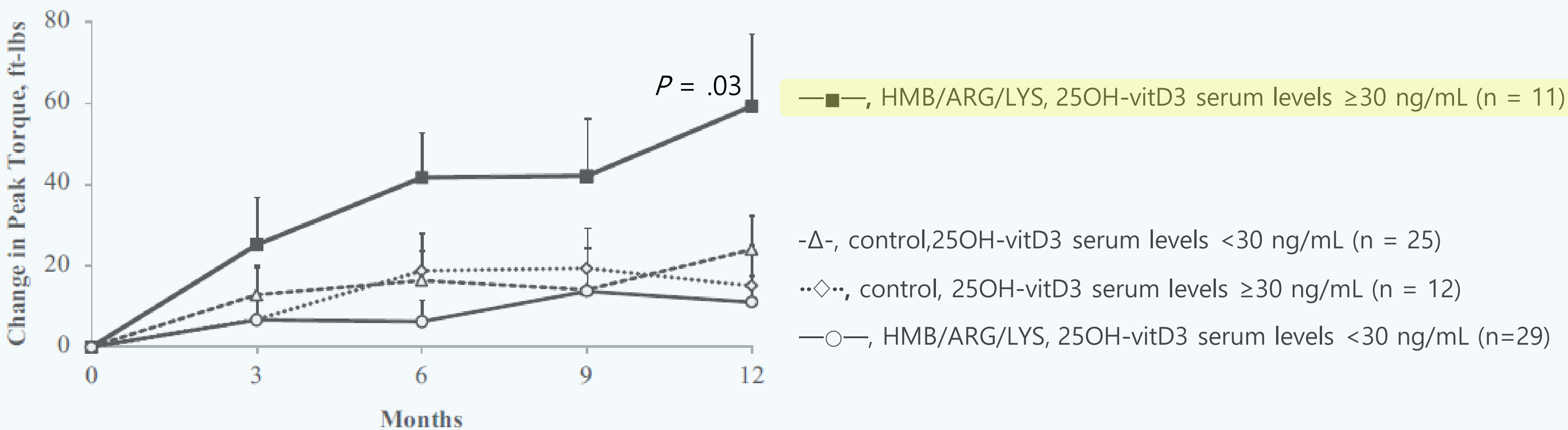
- Vitamin D could potentially contribute to the changes in phenotype of existing muscle fibers and/or the maintenance of type II muscle fibers.
  - Anabolic effect on myotubes by modulating multiple intracellular signaling pathways probably through genomic and nongenomic mechanisms

Wagatsuma et al. *Biomed Res int*. 2014:2014:121254
Hangelbroek RWJ et al, *BMC Geriatr*. 2019: 28;19(1):151.

Vitamin D supplementation can improve muscle strength, in particular in those most deficient.

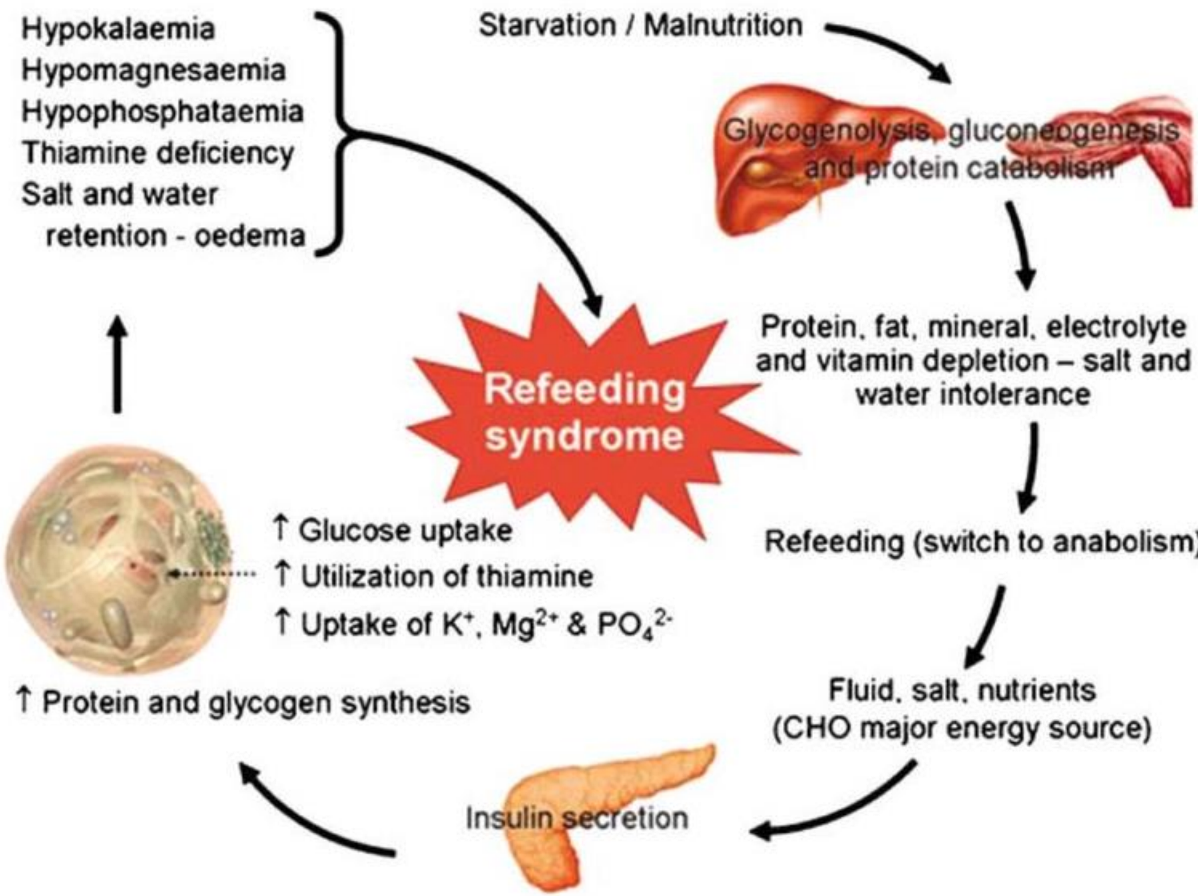
- Double-blinded, controlled study
- Elderly (age 76.0 ± 1.6 years) adults
- Isonitrogenous control (n = 37) or HMB/ARG/LYS (n = 40) for the year long study
- Vitamin D status of either <30 or ≥30 ng 25OH-vitD3/mL serum

Change in total leg strength



Fuller JC et al. *JPEN* 35, 757–762.

Pathogenesis and features of the refeeding syndrome



Patients of high risk of refeeding syndrome

Either the patient has one or more of the following:

- Body mass index (kg/m^2) ‹16
- Unintentional weight loss ›15% in the past three to six months
- Little or no nutritional intake for ›10 days
- Low levels of potassium, phosphate, or magnesium before feeding

Or the patient has two or more of the following:

- Body mass index ‹18.5
- Unintentional weight loss ›10% in the past three to six months
- Little or no nutritional intake for ›5 days
- History of alcohol misuse or drugs, including insulin, chemotherapy, antacids, or diuretics

-Malabsorptive syndrome (such as inflammatory bowel disease, chronic pancreatitis, cystic fibrosis, short bowel syndrome)

- Long term users of antacids (magnesium and aluminium salts bind phosphate)
- Long term users of diuretics (loss of electrolytes)

Mehanna HM et al. *BMJ* 2008;336:1495-8

Prevention of the refeeding syndrome

- Immediately vitamin (thiamine) supplementation
- Close monitoring and correction of phosphate, potassium, calcium, and magnesium
  - Once daily for the first week
  - Refeeding hypophosphatemia : < 2.0 mg/dl, ▼ 0.5 mg/dl
- Slow progression to energy target during the first 72 h

P. Singer et al. *Clin Nutr* 2019 Feb;38(1):48-79.

Exercise

Exercise

- General recommendation
  - Muscle strengthening activities +/- balance training
  - Warm-up and stretching
  - Supervision, monitoring, teaching, and encouragement
  - Protein intake ; best outcome in administration after exercise

Montero-Fernandez N et al. *Eur J Phys Rehabil Med*. 2013;49(1):131-43.

Types of exercise

- Aerobic exercise
- Progressive resistance exercise
- Flexibility exercise
- Balance training

Montero-Fernandez N et al. *Eur J Phys Rehabil Med*. 2013;49(1):131-43.

Aerobic exercise

- Rhythmic and repetitive movement of large muscles, for sustained periods
- Use of oxygen to meet energy demands through aerobic metabolism
- Brisk walking, jogging, swimming, water aerobics, tennis, aerobic exercise classes, dancing and bicycle riding

Montero-Fernandez N et al. *Eur J Phys Rehabil Med*. 2013;49(1):131-43.

★ Progressive resistance exercise

- Require muscles to generate force to move or resist weight, with the intensity increasing
- Anaerobic metabolism
- Lifting weights, working with resistance bands, doing calisthenics using body weight for resistance (push-ups, pull-ups, and sit-ups), climbing stairs, carrying heavy loads, and heavy gardening


Montero-Fernandez N et al. *Eur J Phys Rehabil Med*. 2013;49(1):131-43.

Progressive resistance exercise

- Improving muscle size and function
- Reducing balance and flexibility problems
- Reducing the risk of development of many sarcopenia-related comorbidities
- Training frequency: 3-5 days/week

Montero-Fernandez N et al. *Eur J Phys Rehabil Med*. 2013;49(1):131-43.

Flexibility exercise

- Ability to move a joint through a complete raging of motion
- Paramount to overall good physical health
- Stretches: static (assume positing, hold stretch, then relax), dynamic (fluid motion), active (yoga), or combination
- Neck, shoulder, elbow, wrist, hip, knee and ankle
- ≥ 2 days/week, 10 min/d


Montero-Fernandez N et al. *Eur J Phys Rehabil Med*. 2013;49(1):131-43.

Balance training

- Maintaining stability during daily activities and other exercises, preventing falls
- Tandem walking, standing on heels or toes, walking on compliant surface (foam mattresses), maintaining balance on moving vehicles (bus or train), walking backward
- ≥ 3 days/week


Montero-Fernandez N et al. *Eur J Phys Rehabil Med*. 2013;49(1):131-43.

Effects of Exercise and Amino Acid Supplementation on Body Composition and Physical Function in Community-Dwelling Elderly Japanese Sarcopenic Women: A Randomized Controlled Trial

Hun Kyung Kim, PhD,[*] Takao Suzuki, MD, PhD,[†] Kyoko Saito, PhD,[*] Hideyo Yoshida, MD, PhD,[*] Hisamine Kobayashi, DVM,[‡] Hiroyuki Kato, MS,[‡] and Miwa Katayama, DVM[‡]

- 5 min of warm up
  → **30 min of strengthening exercises**
  → **20 min of balance and gait training**
  → 5-min cool down
- Chair exercises, standing exercises using the chair to maintain balance, ankle-weight exercises, resistance band exercises, and balance and gait training

Exercise intervention

- **Amino acid supplementation twice a day (6 g per day)**
- Packets of powdered amino acid supplements (**42.0% leucine**, 14.0% lysine, 10.5% valine, 10.5% isoleucine, 10.5% threonine, 7.0% phenyl-alanine and 5.5% other)

Nutritional supplementation

Kim HK et al. *Am Geriatr Soc.* 2012 Jan;60(1):16-23

Effects of Exercise and Amino Acid Supplementation on Body Composition and Physical Function in Community-Dwelling Elderly Japanese Sarcopenic Women: A Randomized Controlled Trial

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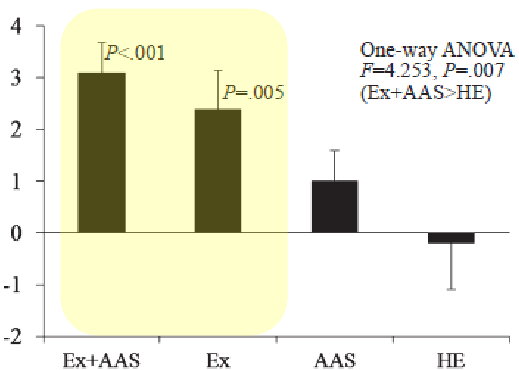
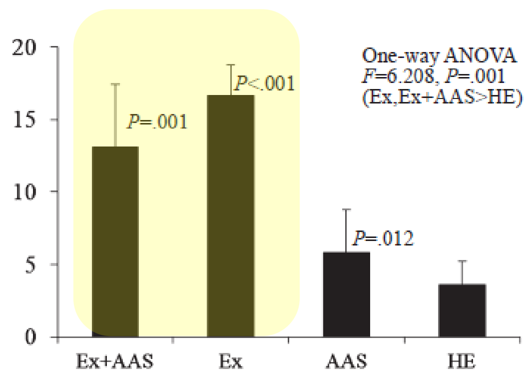
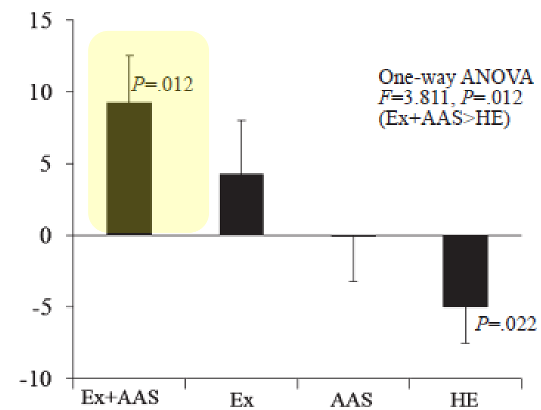
Leg muscle mass (%)



Usual walking speed (%)



Knee extension strength (%)



Kim HK et al. *Am Geriatr Soc.* 2012 Jan;60(1):16-23

Long-term effects of exercise and amino acid supplementation on muscle mass, physical function and falls in community-dwelling elderly Japanese sarcopenic women: A 4-year follow-up study

Hunkyung Kim,[1] Takao Suzuki,[2] Kyoko Saito,[1] Narumi Kojima,[1] Erika Hosoi,[1] Hideyo Yoshida[1]

[1]*Research Team for Promoting Independence of the Elderly, Tokyo Metropolitan Institute of Gerontology, Tokyo, and* [2]*National Institute for Longevity Sciences, Aichi, Japan*

Table 3 Comparison of 4 year percent change in selected variables between intervention participants and non-participants

Variables	Participants Mean ± SE	Non-participants Mean ± SE	Absolute difference (95% CI for difference)	*P*-value
Bodyweight	0.2 ± 0.8	–1.2 ± 1.2	1.3 (–4.2 to 1.6)	0.362
BMI	1.6 ± 0.8	0.2 ± 1.2	1.5 (–4.3 to 1.4)	0.321
Total skeletal muscle mass	–16.0 ± 0.6	–18.1 ± 0.9	2.1 (–4.2 to 0.1)	0.054
Appendicular skeletal muscle mass	–21.5 ± 0.7	–24.5 ± 1.0	2.9 (–5.4 to –0.5)	0.019
Leg muscle mass	–16.7 ± 0.8	–20.4 ± 1.2	3.7 (–6.5 to –0.8)	0.012
Grip strength	–2.1 ± 2.3	–2.2 ± 5.6	0.1 (–10.1 to 10.0)	0.990
Knee extension strength	–2.9 ± 2.2	–13.6 ± 3.7	10.7 (–21.0 to –0.4)	0.011
Usual walking speed	–6.8 ± 2.3	–15.2 ± 2.8	8.4 (–16.0 to –0.9)	0.029

Data reported as mean percent change ± standard error (SE). BMI, body mass index; CI, confidence interval.

Kim H et al. *Geriatr Gerontol Int.* 2016 Feb;16(2):175-81

Modality	Effects	Side effects
Testosterone	**Increase muscle mass, strength, power and function**	Fluid retention; increased hematocrit; short term worsening of sleep apnea; effects on prostate cancer; possible increase in cardiovascular events
Selective androgen receptor modulators (SARMS)	**Increase muscle mass small increase in power**	Increased cardiac failure
Growth hormone	**Increase nitrogen retention increase muscle mass**	Arthralgia; muscle pain; edema; carpal tunnel syndrome; hyperglycemia
Ghrelin agonists	**Increased muscle mass and appetite**	Fatigue; atrial fibrillation; dyspnea
Myostatin antibodies	**Increased lean body mass and handgrip**	Urticaria; aseptic meningitis; diarrhea; confusion; fatigue
Activin 11R antagonists (Bimagramab)	**Increase thigh muscle volume, muscle mass, and 6-min walk distance**	Acne; involuntary muscle contractions
Angiotensin converting enzyme inhibitor (perindopril)	**Increased distance walked decreased hip fracture**	Hypotension; hyperkalemia; muscle cramps; numbness
Espindolol (B1/B2 adrenergic receptor antagonist)	**Maintains muscle mass increased hand grip strength**	?
Fast skeletal muscle troponin activators (Tirasemtiv)	**Improves muscle function**	?

Morley JE. *Calcif Tissue Int*

Summary

- **Definition of sarcopenia**
  - Low muscle strength + low muscle quantity or quality + low performance
- **Pathophysiology of sarcopenia**
  - Primary : aging
  - Secondary: stress catabolism, inactivity, and malnutrition
- **Modalities to measure muscle mass**
  - DEXA : ASM, repeatable, not portable
  - BIA : accessible at the bedside, phase angle – prognostic factor
  - CT : L_3 vertebrae level, measuring quantity and quality of muscle
  - US : Rectus femoris & vastus intermedius mm., no radiation, accessible at the bedside, measuring quantity and quality of muscle

Summary

- **Nutritional support**
  - **Early nutritional supports**
  - **High-protein support**
    - **Average daily intake in elderly ; 1.0-1.2 g/kg BW/d**
    - **Acute or chronic disease; 1.2-1.5 g/kg BW/d**
    - **Severe illness or injury or marked malnutrition; 2.0 g/kg BW/d**
  - **Leucine & β-hydroxy-β-methylbutyrate (β-HMB) may help enhance muscle mass and muscle function.**
  - **Vitamin D (in deficient case); increase muscle strength.**

Summary

- **Refeeding syndrome**
  - **Close monitoring and correction of serum levels of electrolytes, especially phosphate**
  - **Prevention : slow progression of nutrition in patients of high risk**

- **Combination of timely exercises with protein intake**
  - **Synergistically stimulate muscle protein synthesis, leading to improved muscle mass and strength.**
  - **Best outcome in administration of protein after exercise**
  - **Exercise is recommended at individualized levels that are safe and tolerated.**

Thank you for your attention!!

GNUH
경상대학교병원
Gyeongsang National University Hospital