Casa Sollievo della Sofferenza
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO
OPERA DI PADRE PIO DA PIETRELCINA
SAN GIOVANNI ROTONDO
ITALY

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

POTENZIALI APPROCCI TERAPEUTICI ALLA SARCOPENIA

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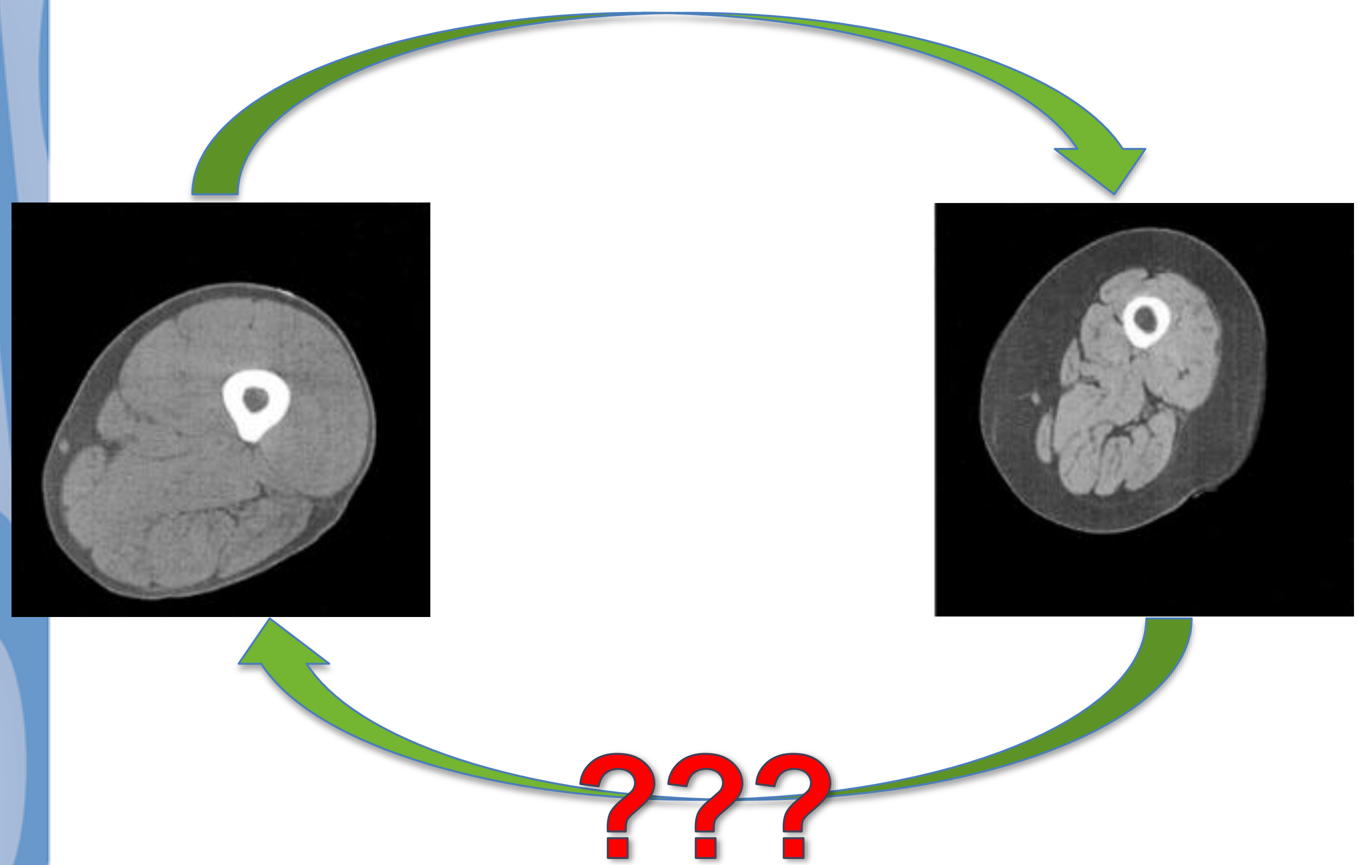
IRCCS "Casa Sollievo della Sofferenza" San Giovanni Rotondo (FG) Italia

57° CONGRESSO NAZIONALE
SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

Can sarcopenia be reversed?



SARCOPENIA

σαρξ – carne
πενια – perdita

riduzione della massa e/o della forza muscolare che si riscontra nel corso di invecchiamento

FATTORI CHE POSSONO CONTRIBUIRE ALLO SVILUPPO DELLA SARCOPENIA

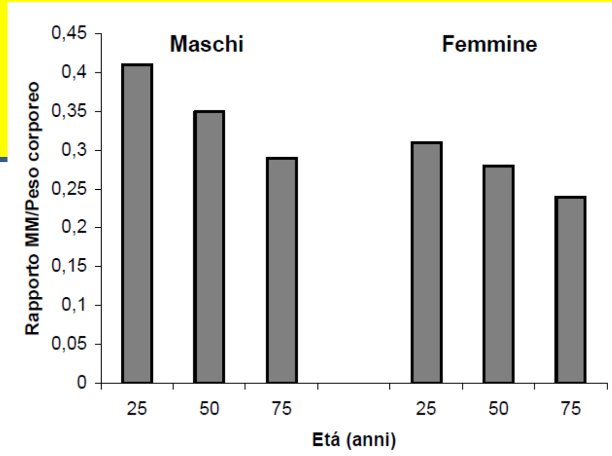
- Diminuzione età correlata delle fibre muscolari

- Riduzione delle attività fisiche

- Declino ormonale: sia riproduttivi che dell'asse hypothalamic-GH-insulinlike growth factor

- Insufficienza nutrizionale

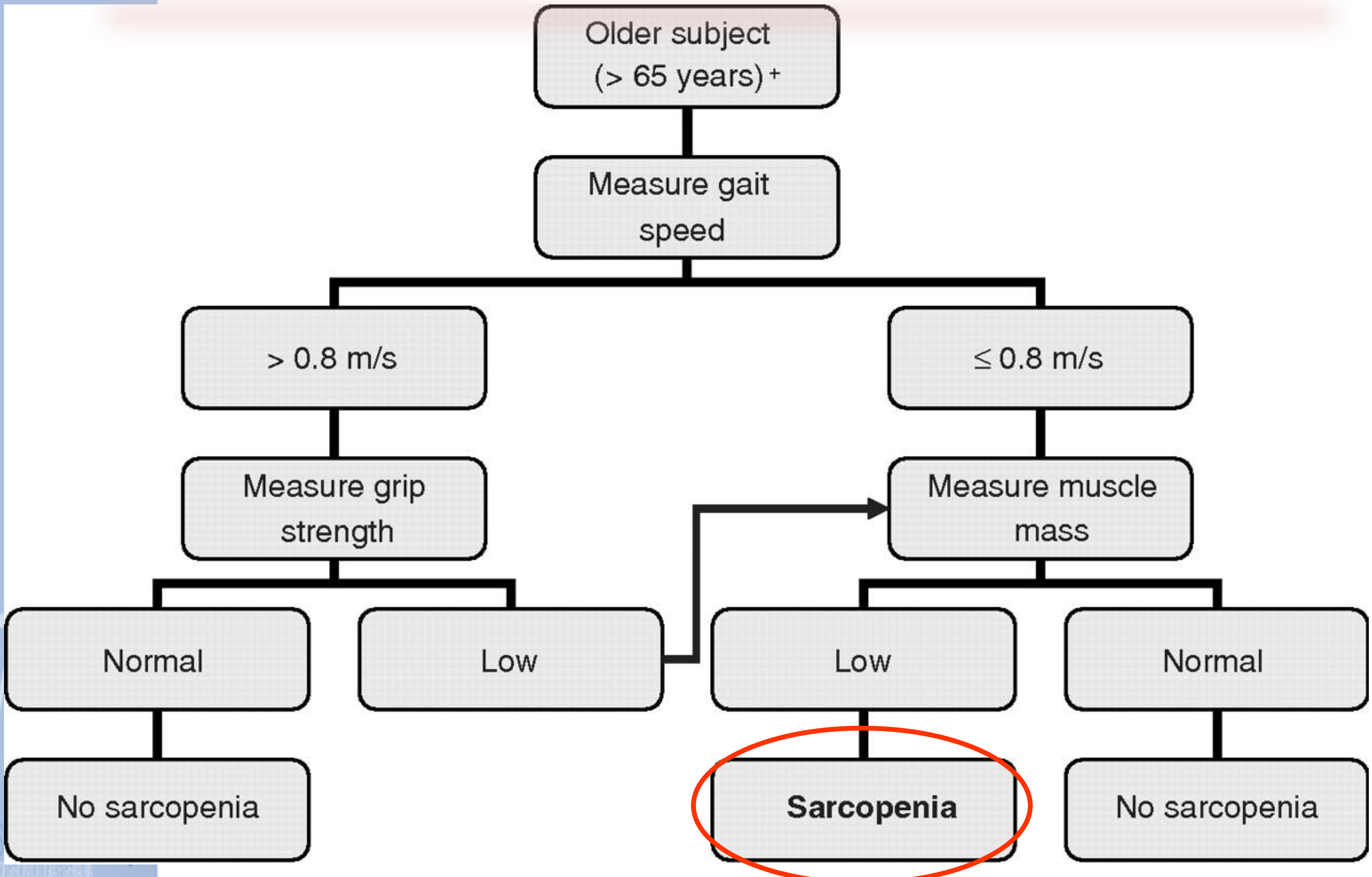
- È stata anche rilevata una componente genetica nella sarcopenia.
[Roth SM, et al: j gerontol biol sci 2004;59a:10–5]



Sarcopenia compares with malnutrition and inactivity

- To fight against sarcopenia, one needs to:
  - Screen
  - Treat

Screening strategy

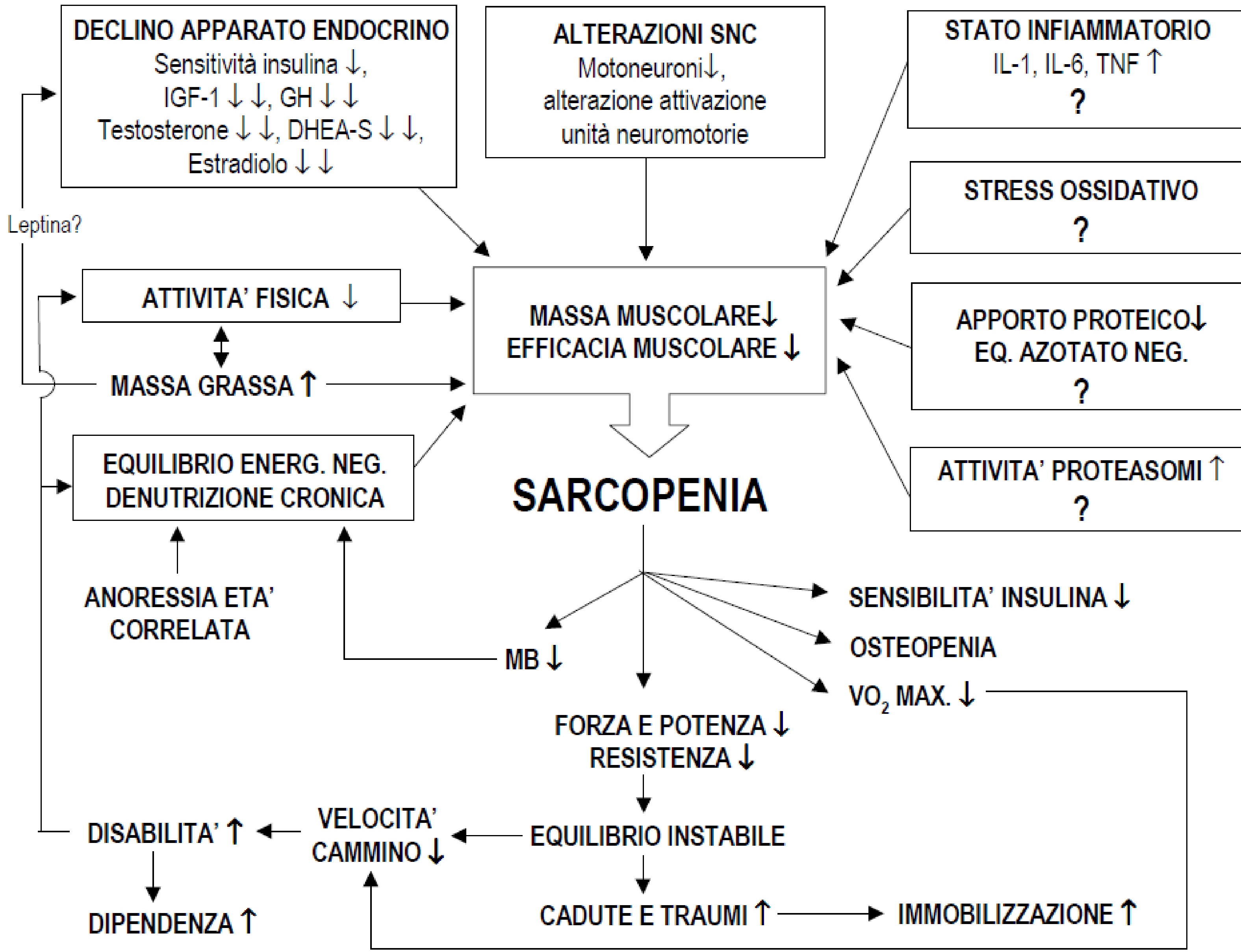


Cruz-Jentoft *et al.* Age Ageing 2010

CONSEGUENZE DELLA SARCOPENIA NELL'ANZIANO

- ↓ forza, potenza e resistenza muscolare
- ↓ massa ossea
- ↓ equilibrio con instabilità posturale
- ↓ isolamento corporeo
- ↓ produzione basale di calore
- ↑ calore specifico
- ↓ contenuto corporeo acqua
- ↓ capacità dispersione cutanea calore
- ↓ metabolismo basale e aumento della massa grassa

CAUSE E CONSEGUENZE DELLA SARCOPENIA



TRATTAMENTO OTTIMALE DELLA SARCOPENIA

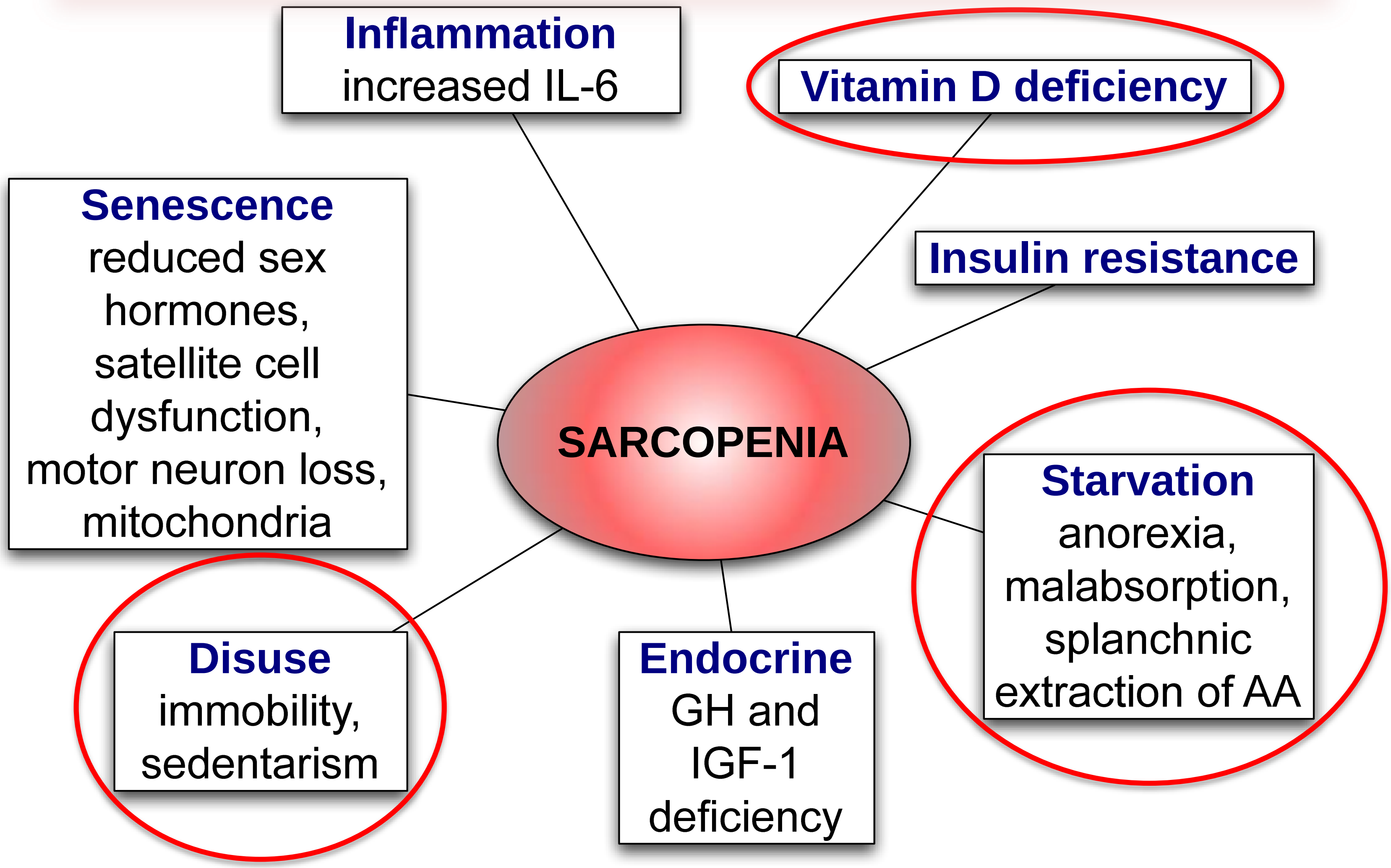
Burton LA, *Clinical Intervention in Aging* 2010

Table 2 Summary of treatment options

Intervention	Effect	Comments
Exercise	Increased cardiovascular fitness with increased endurance	Pros: overall beneficial effects of exercise to individual
Aerobic	Increases mitochondrial volume and activity	
Resistance	Increased muscle mass and strength Increased skeletal muscle protein synthesis and muscle fiber size Improvement in physical performance	Cons: motivation to exercise remains low
Nutritional supplement	Varying evidence of increased muscle mass and strength	Pros: ensures good protein intake Cons: may reduce natural food intake
Hormone therapy	Varying evidence of increased muscle mass and strength	Cons: masculinization of women; increased risk of prostatic cancer in men
Testosterone		
Estrogen	Poor evidence of increased muscle mass but not function	Cons: risk of breast cancer
Growth hormone	Some evidence for increased muscle mass. Varying evidence for increased muscle strength	Cons: side effects including fluid retention, orthostatic hypotension
Vitamin D	Variable evidence for increased muscle strength Reduced falls in nursing home residents	Pros: fracture reduction; possible cardiovascular benefits
ACE inhibitors	Some evidence for increased exercise capacity	Pros: other cardiovascular benefits Cons: renal function needs monitoring
Creatine	Variable evidence of increased muscle strength and endurance especially when combined with exercise	Cons: reports of nephritis
Potential new treatments		
Myostatin antagonists	No trials in older people	
PPAR [δ] agonist	No human trials	
AICAR	No human trials	

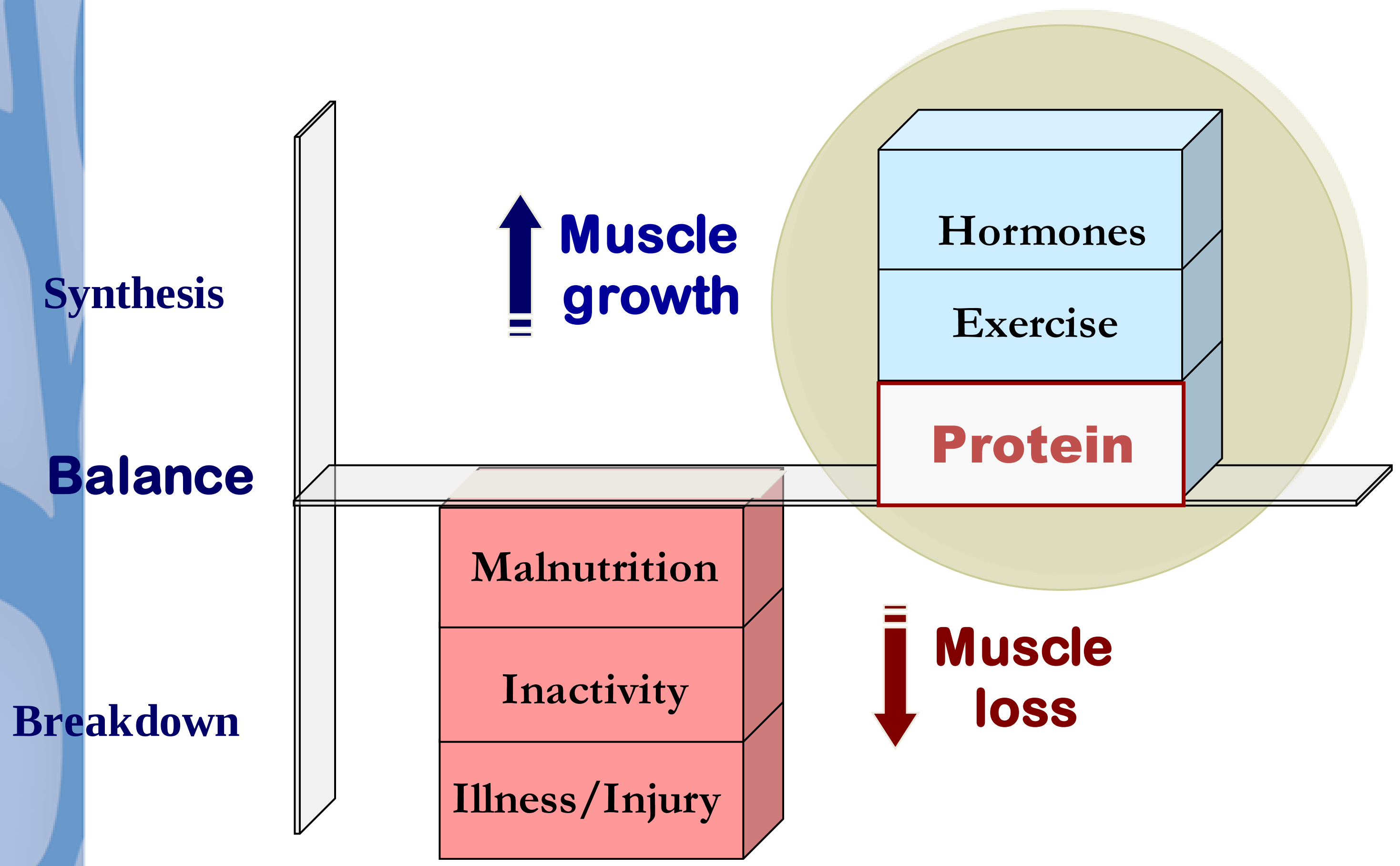
Abbreviations: PPAR-δ, peroxisome-proliferator-activated receptor-δ; AICAR, 5-aminoimidazole-4-carboxamide-1-beta-4-ribofuranoside; ACE, angiotensin-converting enzyme.

Causes of sarcopenia: therapeutic approaches?



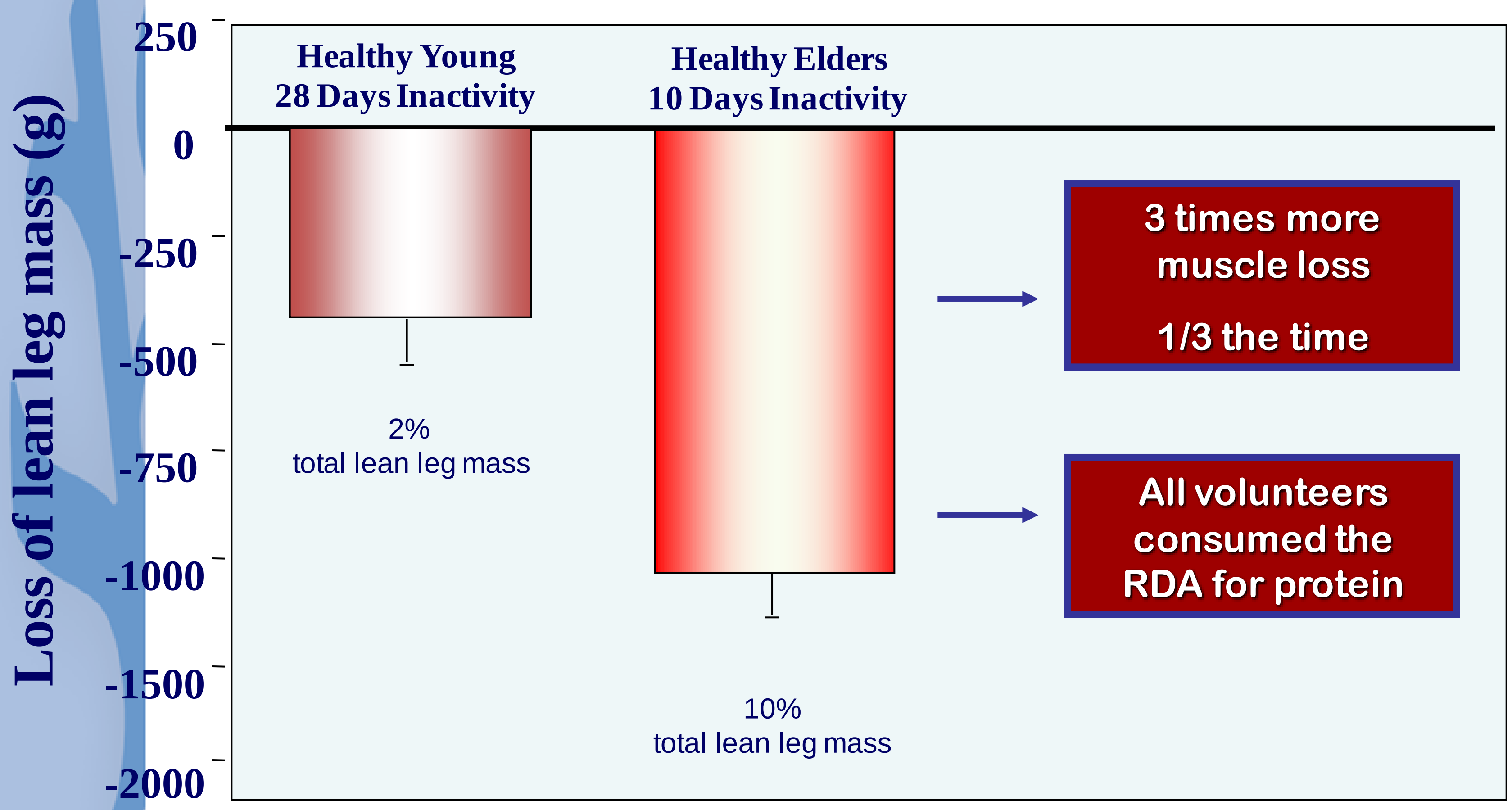
Cederholm *et al.* Clin Geriatr Med 2011

Maintaining Muscle Mass and Function



Exercise – physical activity

Inactivity and Aging Muscle



Paddon-Jones et. al. 2004
Kortebein et al. 2007

Effects of 10 Days of Bed Rest in Older Adults

Table. Effects of 10 Days of Bed Rest in Older Adults

	No. of Participants (N = 12)*	Mean (95% Confidence Interval) Bed Rest Before	After	Change	*P* Value
Muscle fractional synthetic rate, % per h†	10	0.077 (0.059 to 0.095)	0.051 (0.035 to 0.067)	−0.027 (−0.007 to −0.047)	.02
% Change				−30.0 (−7.0 to −54.0)	
DEXA lean mass, kg‡	10				
Whole body		48.05 (40.61 to 55.49)	46.51 (39.57 to 53.45)	−1.50 (−0.62 to −2.48)	.004
% Change				−3.2 (−1.4 to −5.0)	
Lower Extremity		15.01 (12.41 to 17.61)	14.06 (11.85 to 16.27)	−0.95 (−0.42 to −1.48)	.003
% Change				−6.3 (−3.1 to −9.5)	
Isokinetic muscle strength, Nm per s§	11	120 (96 to 145)	101 (81 to 121)	−19 (−11 to −30)	.001
% Change				−15.6 (−8.0 to −23.1)	

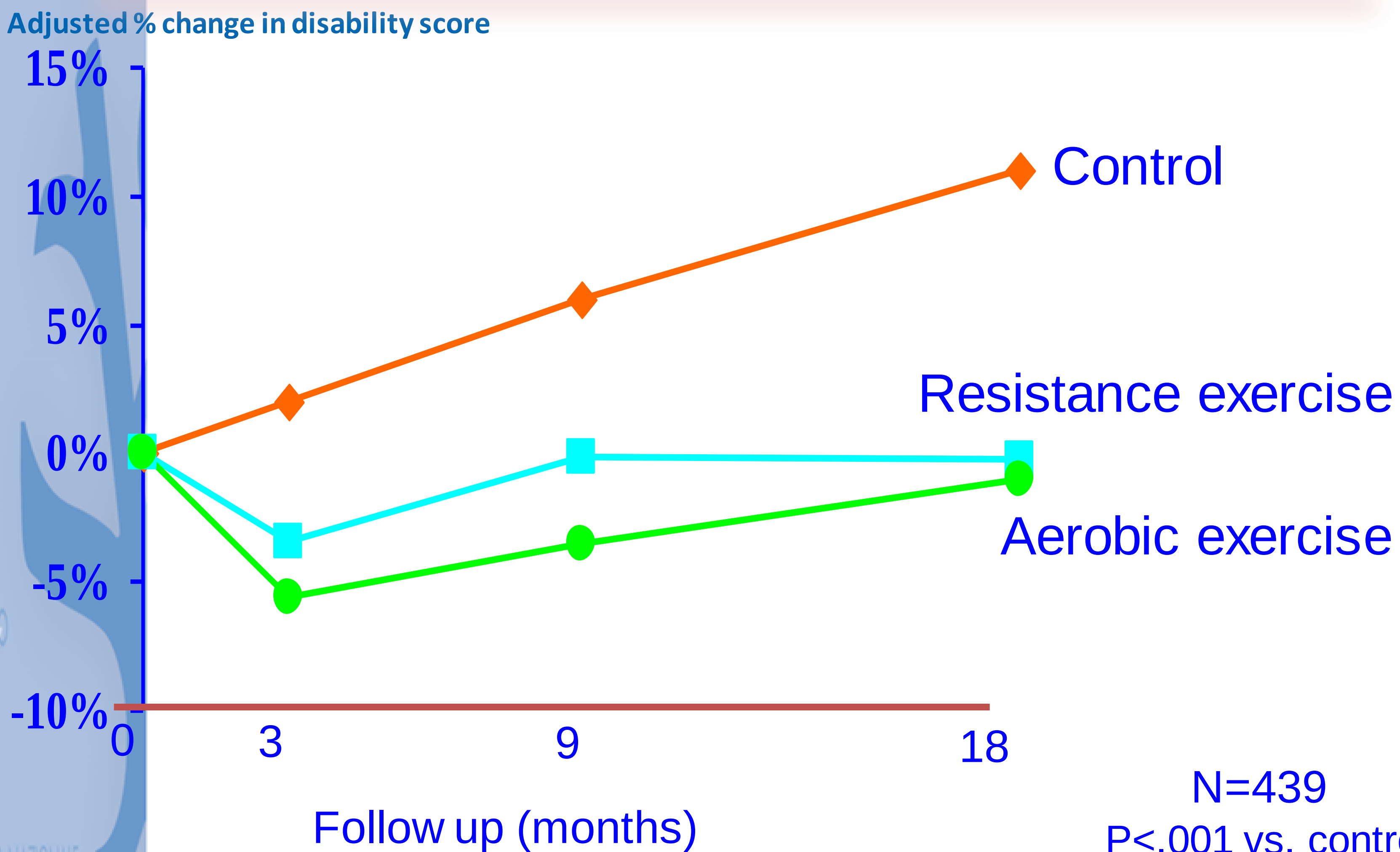
JAMA

Kortebein, P. et al. JAMA 2007

Randomized-controlled trials of exercise benefits on functional impairment (10 RCTs, 1150 persons)

Brown et al. 00	84 frail m+w, 83 y	↑ muscle strength, ↑ reaction time, ↑ balance
Buchner et al. 97	105 impaired m+w, 75 y	↑ muscle strength
Cress et al. 99	49 healthy m+w, 76	↑ muscle strength
Fiatarone et al 94	100 frail nursing home p, 87y	↑ muscle strength
Jette et al. 97	102 nondisabled m+w, 72 y	↑ muscle strength
Jette et al. 99	215 disabled m+w, 75 y	↑ muscle strength
Lord et al. 95	197 healthy w, 72 y	↑ muscle strength, ↑ balance
Pollock et al. 91	57 healthy m+w, 72 y	↑ muscle strength
Rooks et al. 91	131 healthy m+w, 74 y	↑ muscle strength, ↑ reaction time, ↑ balance
Wolfson et al. 96	110 healty m+w, 80 y	↑ muscle strength, ↑ balance

Exercise and Disability (FAST)



N=439
P<.001 vs. control

Ettinger et al. JAMA 1997;277:25

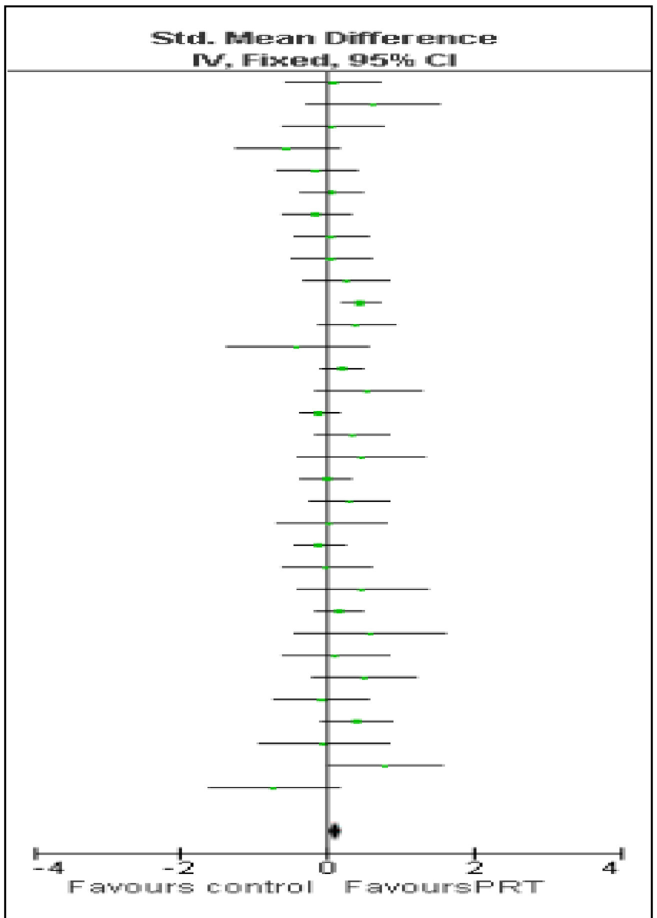
ESERCIZIO FISICO

[Intervention Review]

Progressive resistance strength training for improving physical function in older adults

Chiung-ju Liu[1], Nancy K Latham[2]

Figure 1. Forest plot of comparison: 1 PRT versus control, outcome: 1.1 Main function measure (higher score = better function).



CONCLUSIONI DEGLI AUTORI

La revisione ha interessato 1021 studi per un totale di 6700 pazienti anziani. Dimostra che PRT è un intervento efficace per migliorare le funzionalità fisiche nelle persone anziane, tra cui l' aumento della forza e il miglioramento delle prestazioni nelle attività semplici e complesse

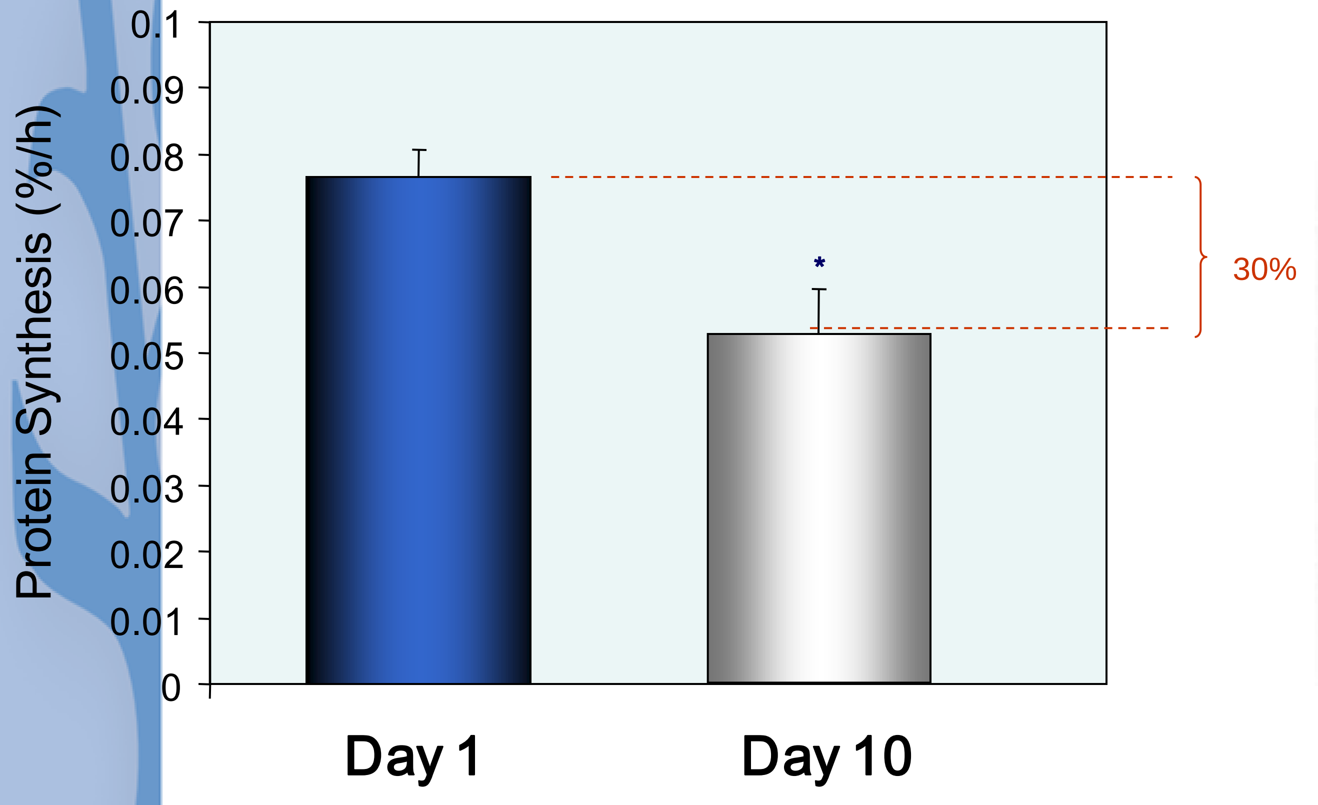
Exercise – physical activity

Is exercise a validated treatment for sarcopenia? Yes, in particular resistance training

Available evidence: Very good

Protein - Nutritional supplements

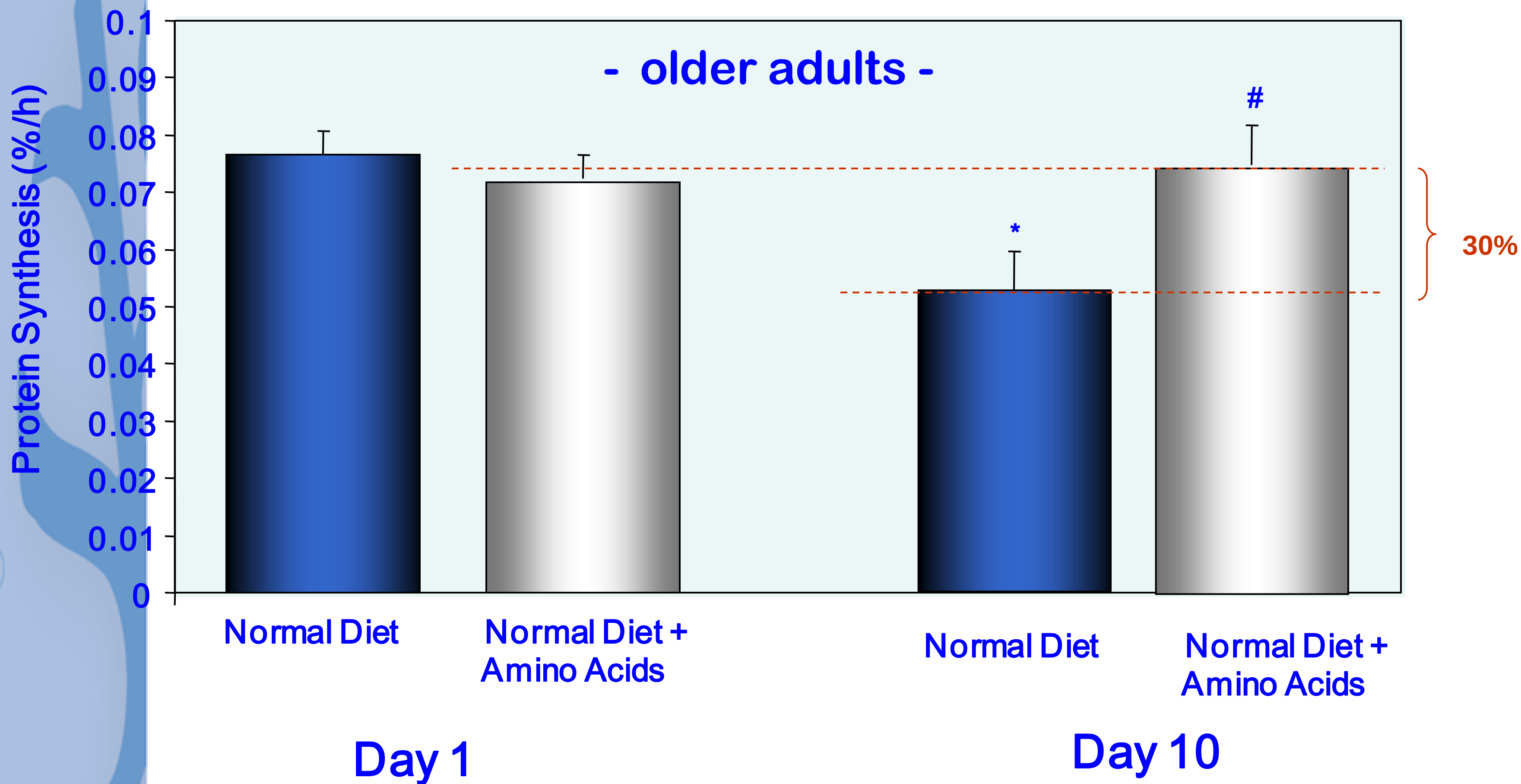
Inactivity reduces muscle protein synthesis



24 h muscle protein synthesis during 10 day of inactivity in elders
(stable isotope methodology)

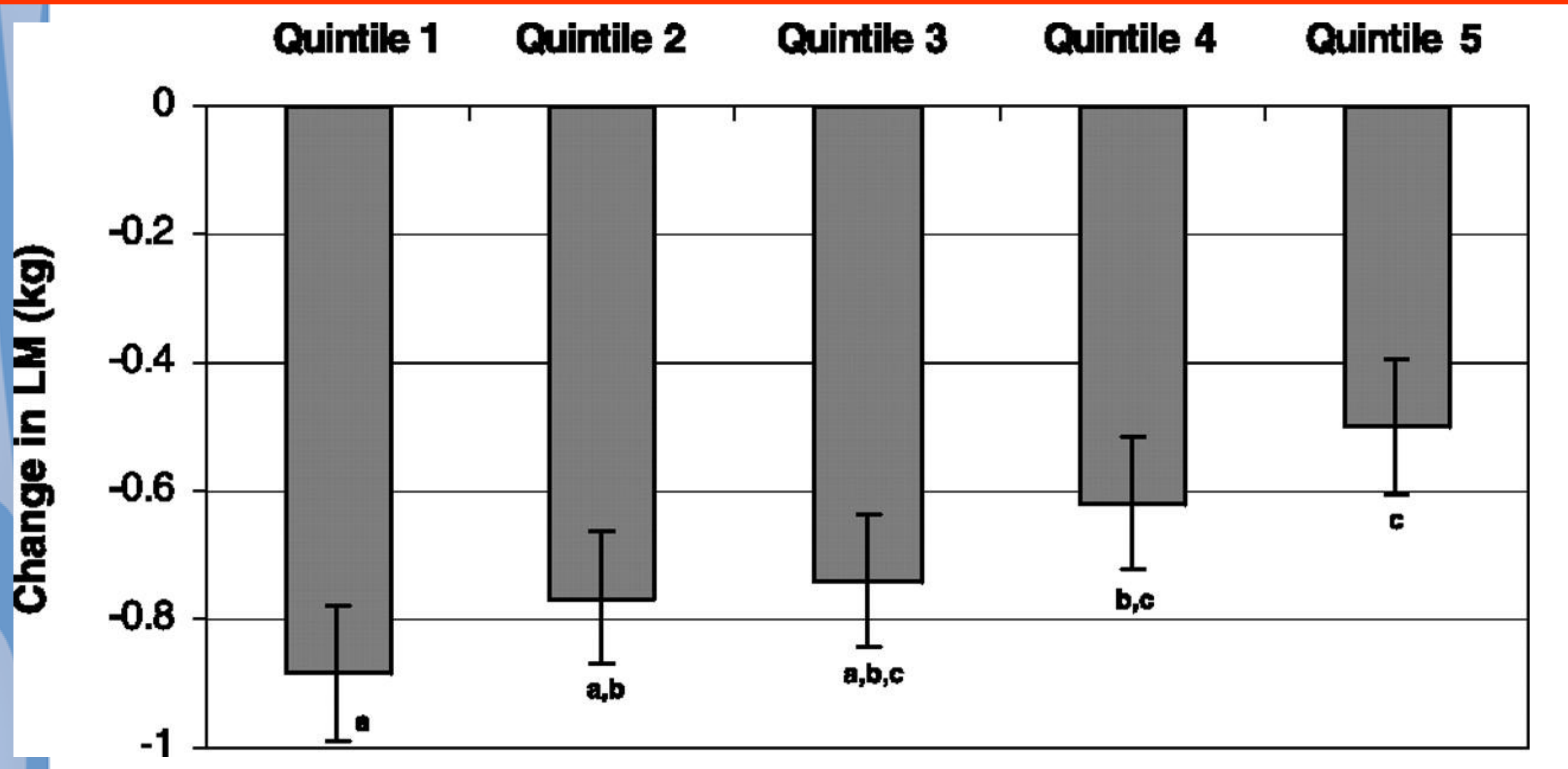
Kortebein et al. 2007

Protein combats inactivity-induced muscle loss



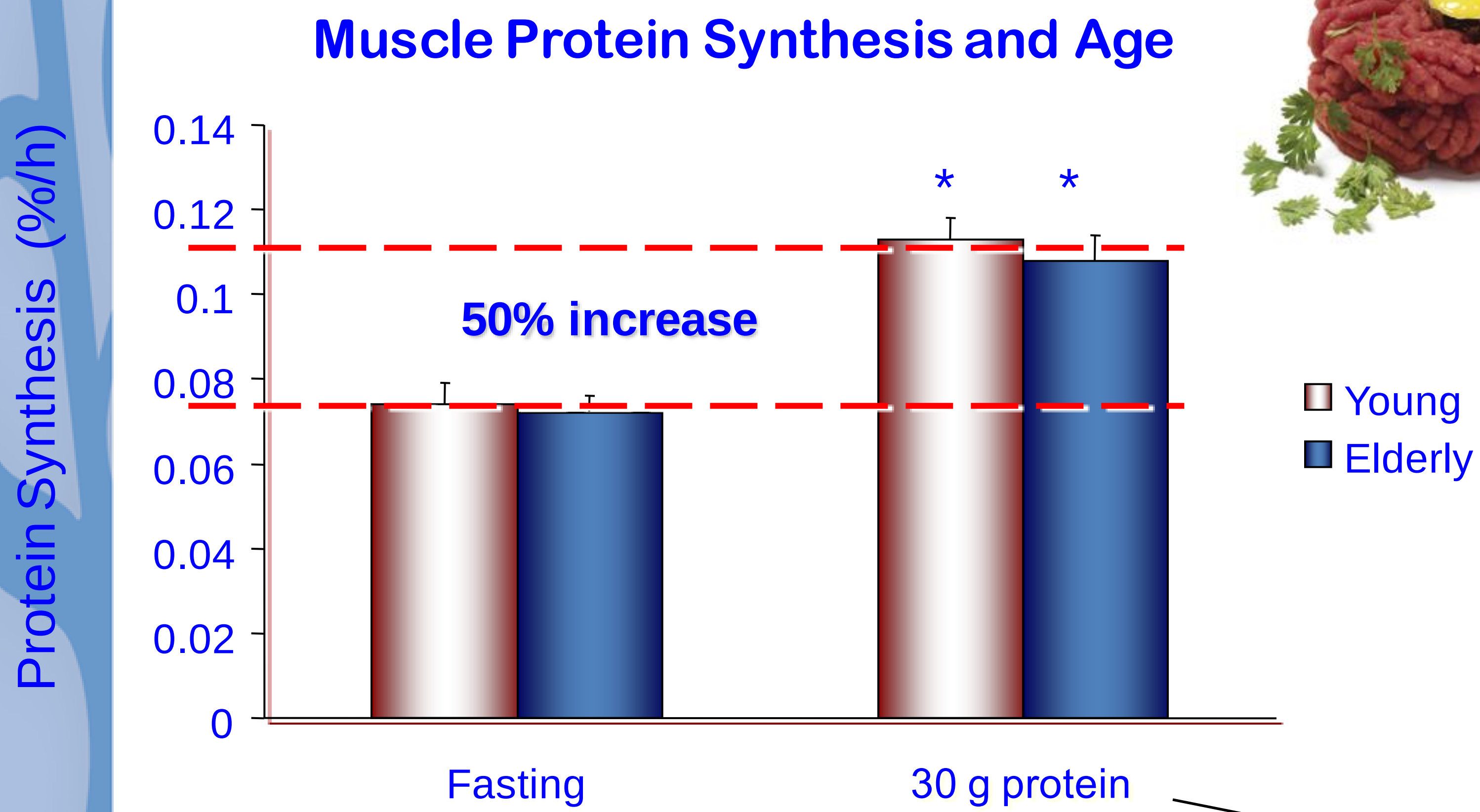
Ferrando & Paddon-Jones et. al. 2009

Lean mass loss by quintile of energy-adjusted total protein intake



Houston, D. K et al. Am J Clin Nutr 2008

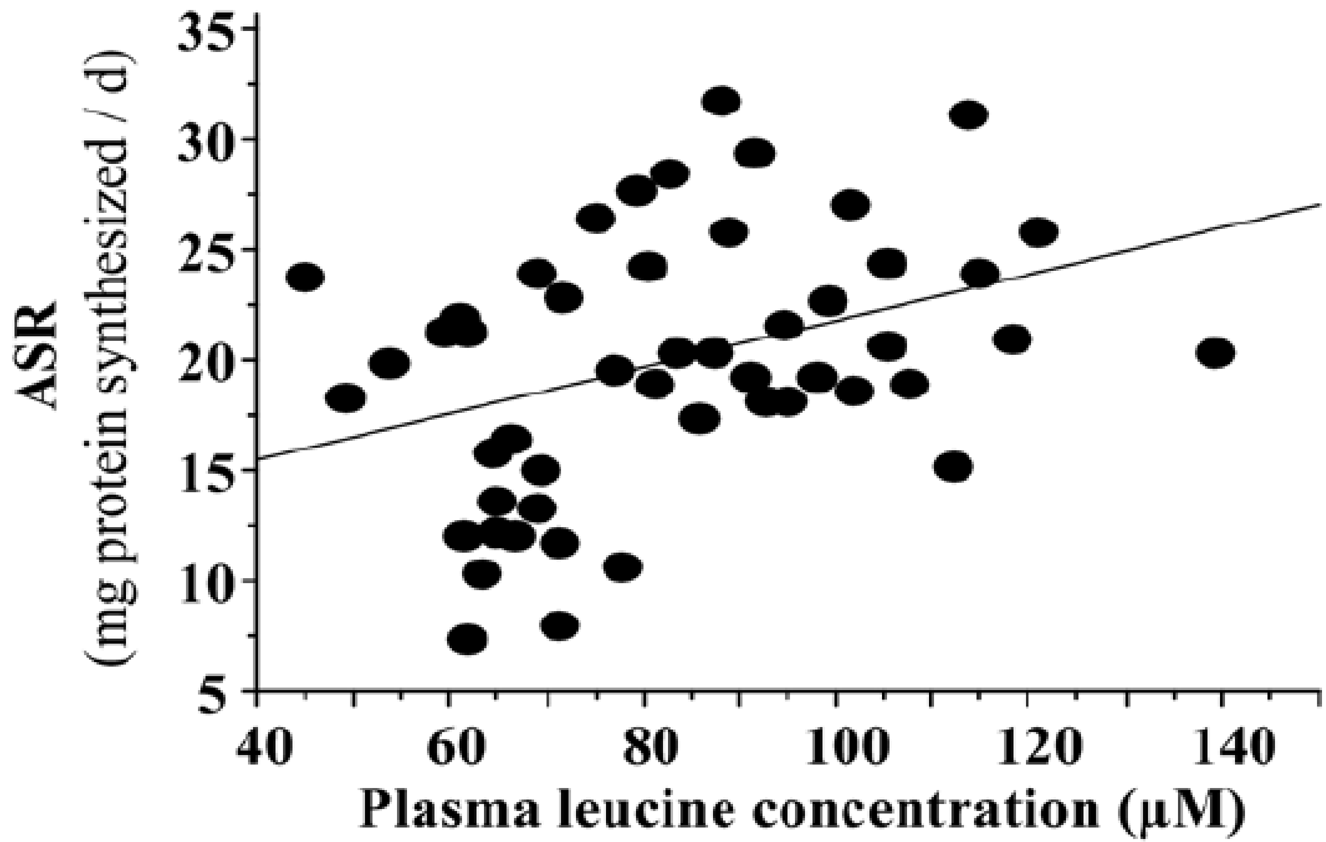
Building muscle in response to protein



* 10 g essential amino acids

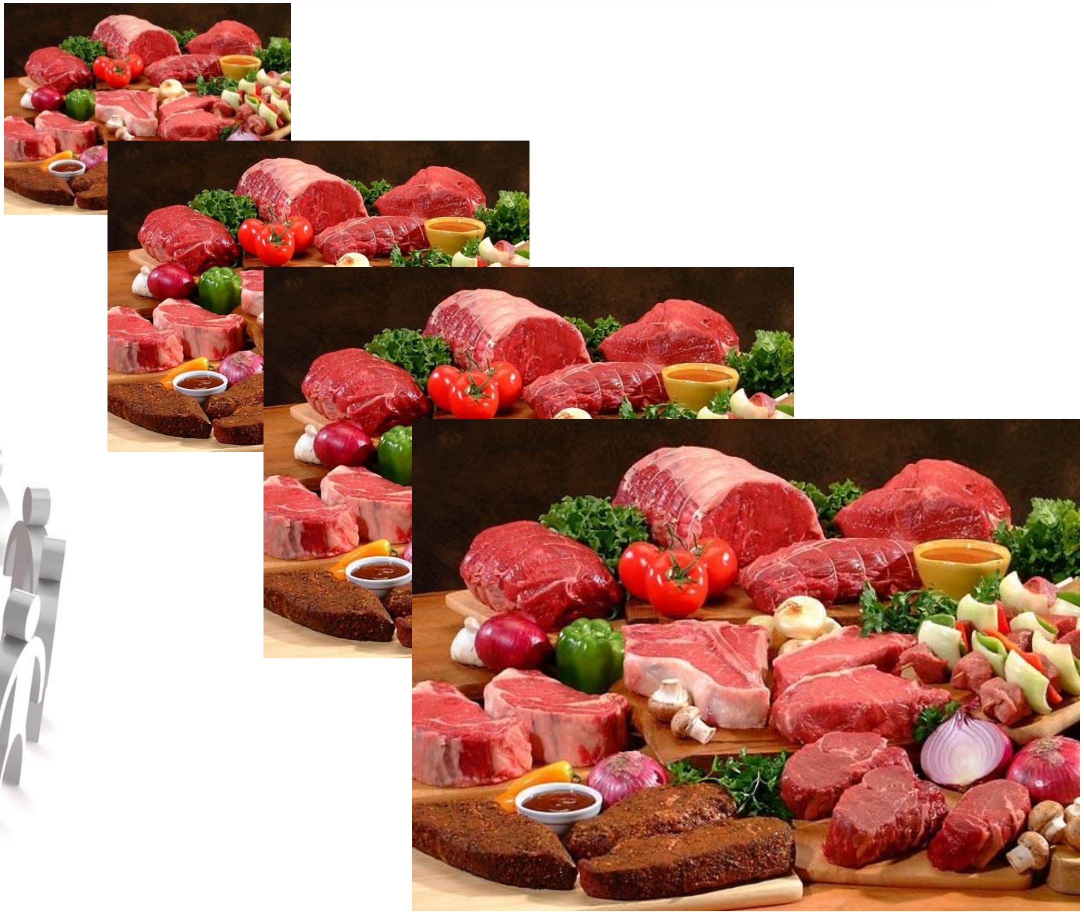
Symons et. al. AJCN, 2007

Plasma leucine concentration and protein synthesis rate



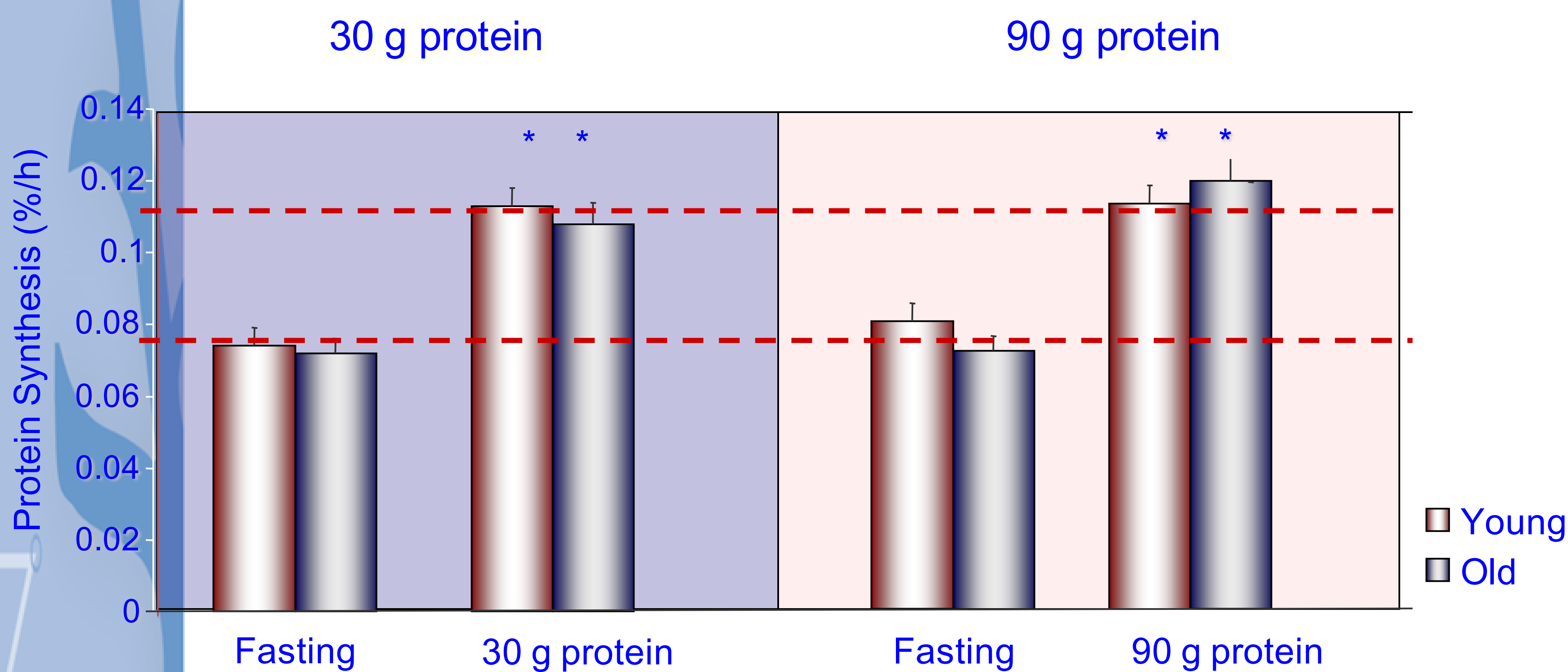
Rieu I et al. Nutrition 2007

How much protein do we need – and when ?



Protein Synthesis and Portion Control

- a message of moderation -

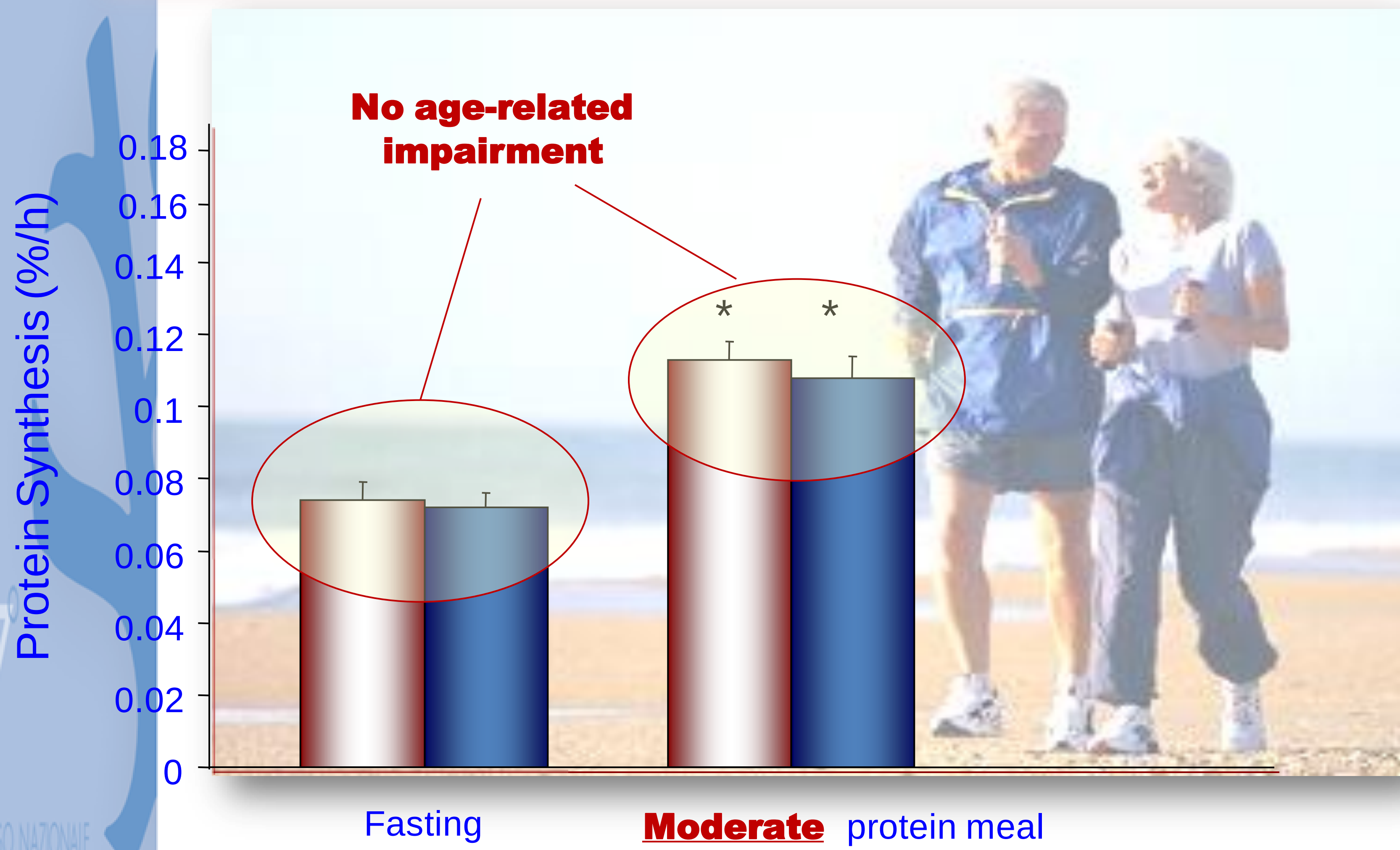


~1.2 g/kg/day for 180 lb individual

Symons et. al. AJCN, 2007

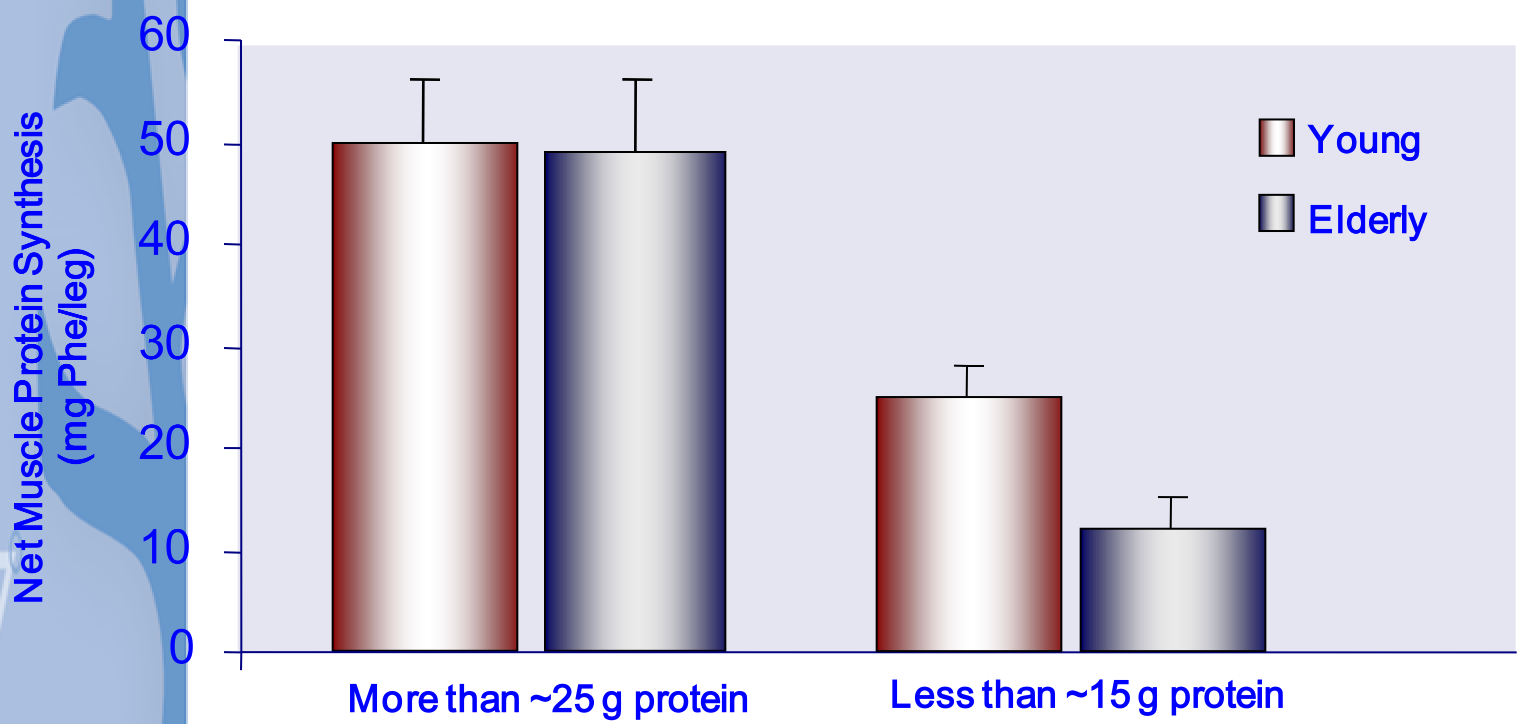
Symons et. al. JADA. 2009

Key points



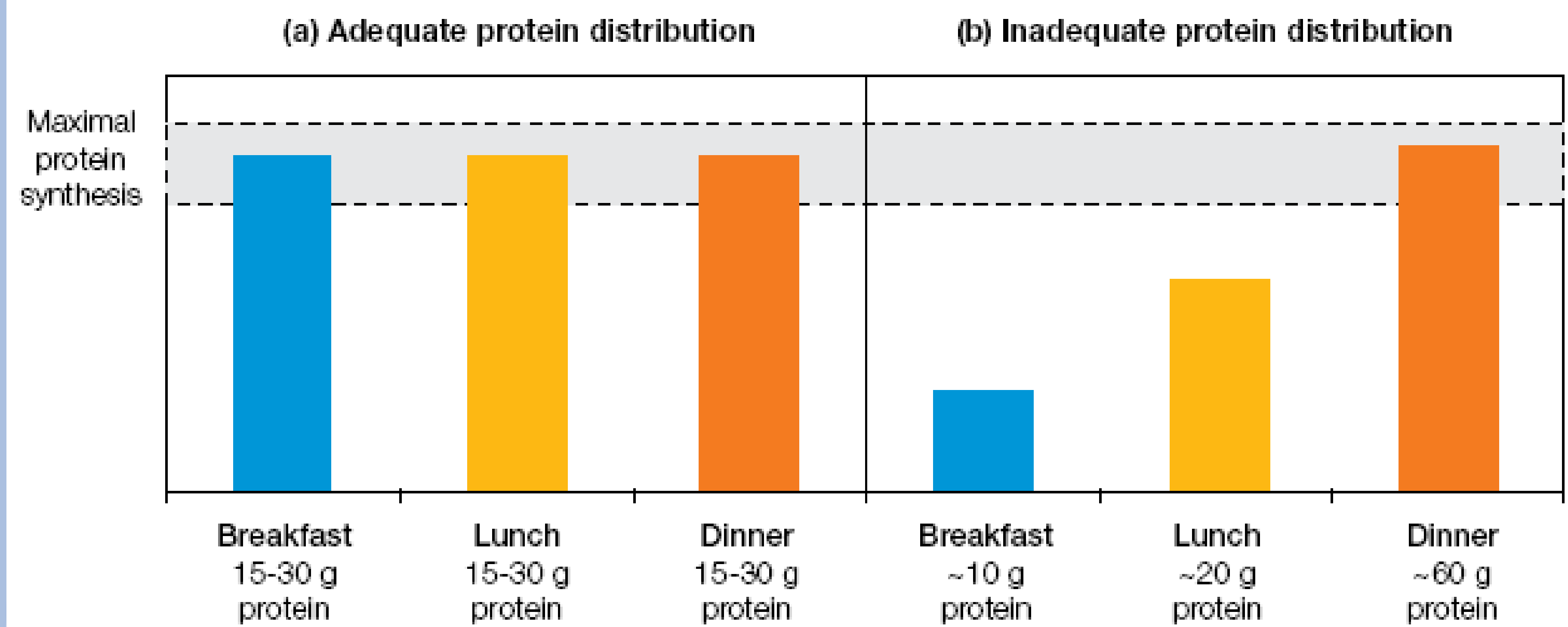
Symons et. al. AJCN, 2007

Age-related dose-response



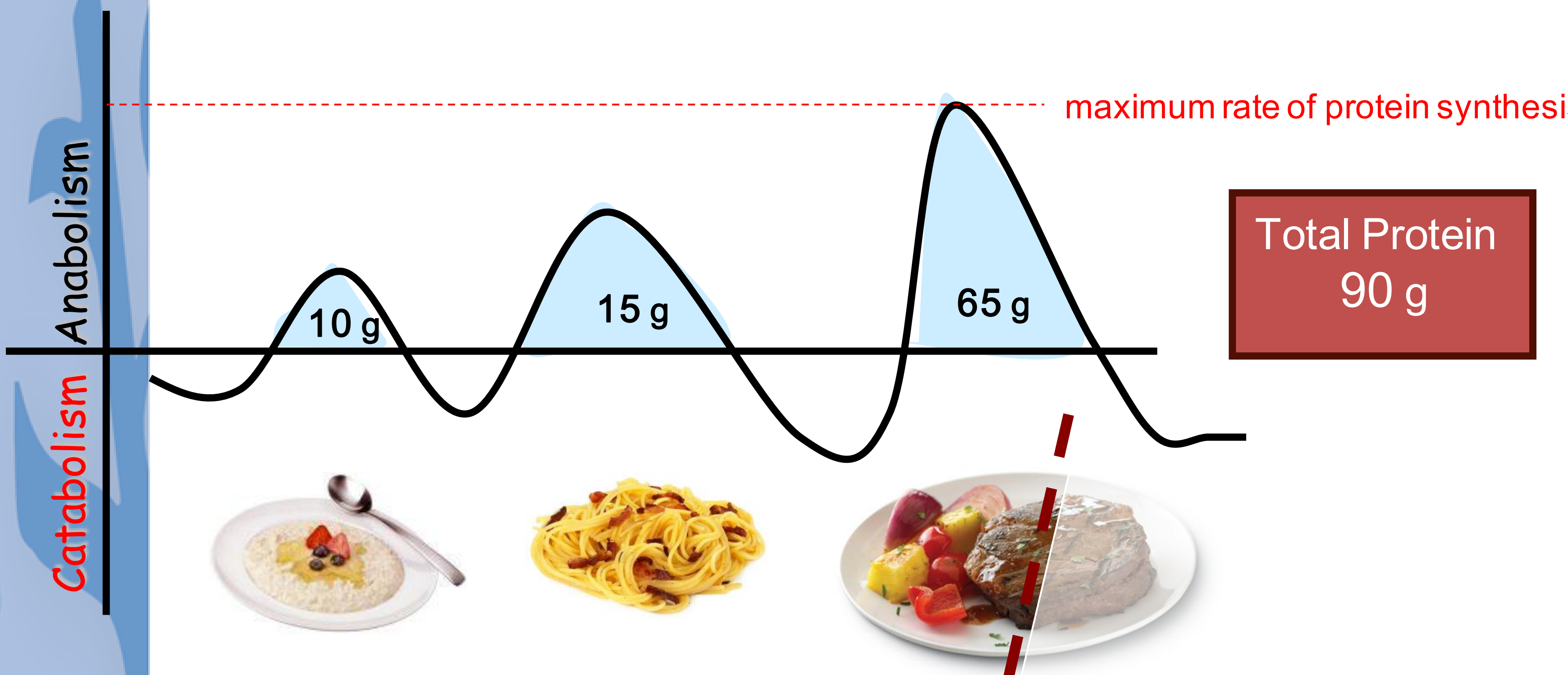
Katsanos et. al. AJCN, 2005

Relationship between the amount of protein per meal and the resultant anabolic response



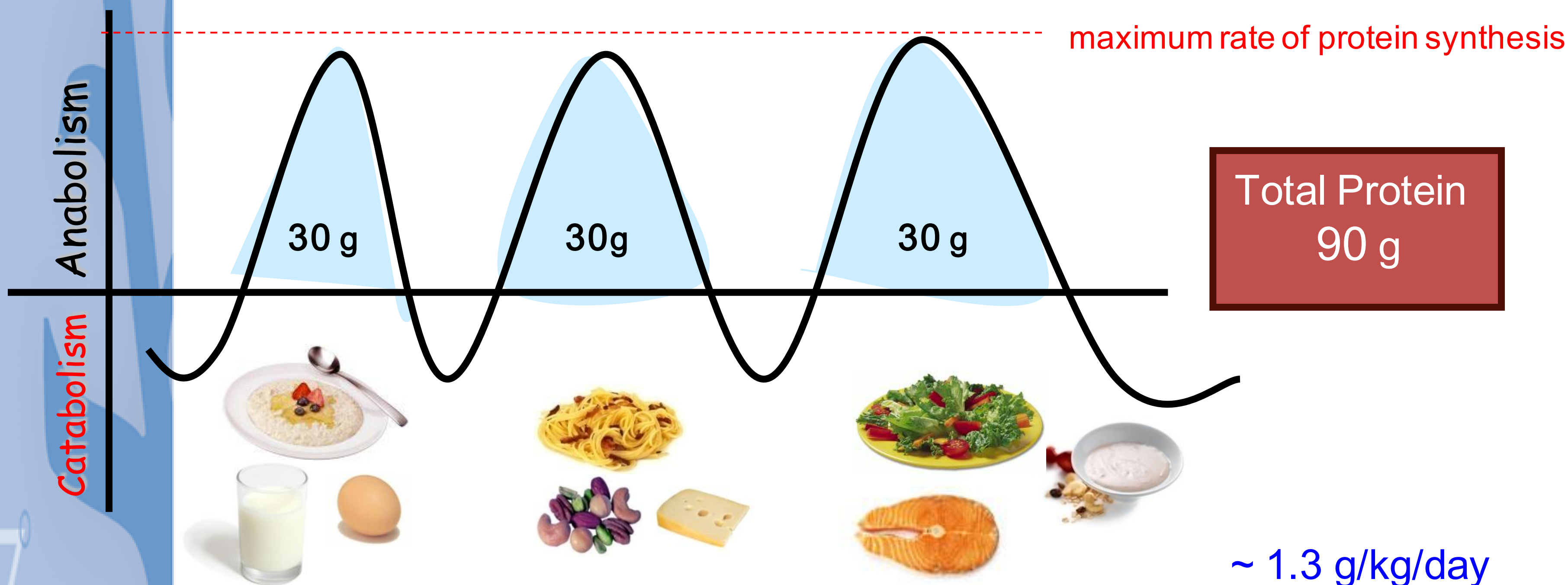
Adapted from Paddon-Jones, 2009

Daily protein distribution
- typical ? -



A skewed daily protein distribution fails to maximize potential for muscle growth

Daily protein distribution
- Optimal -



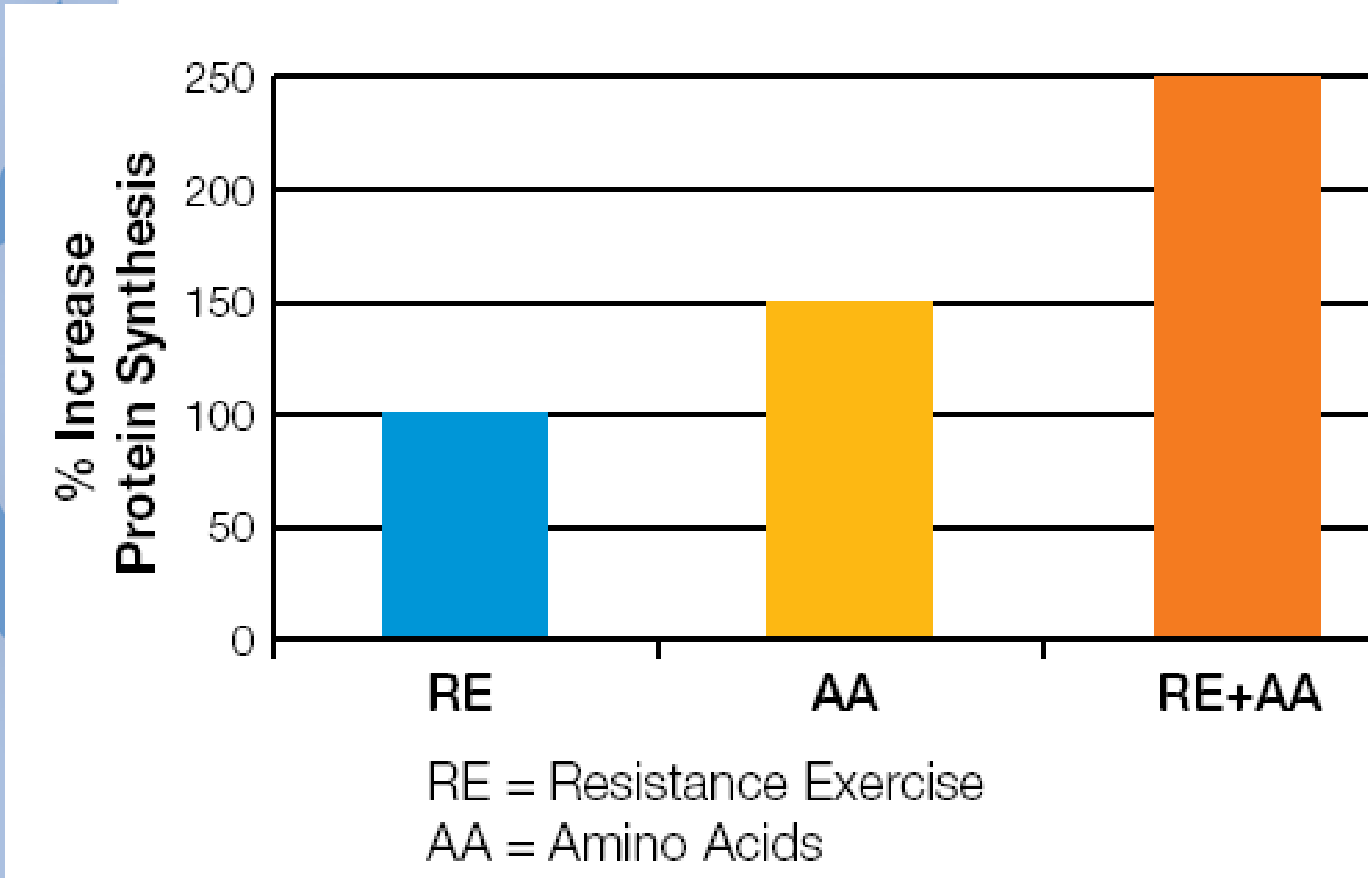
Total Protein
90 g

~ 1.3 g/kg/day

Repeated maximal stimulation of protein synthesis
→ increase / maintenance of muscle mass

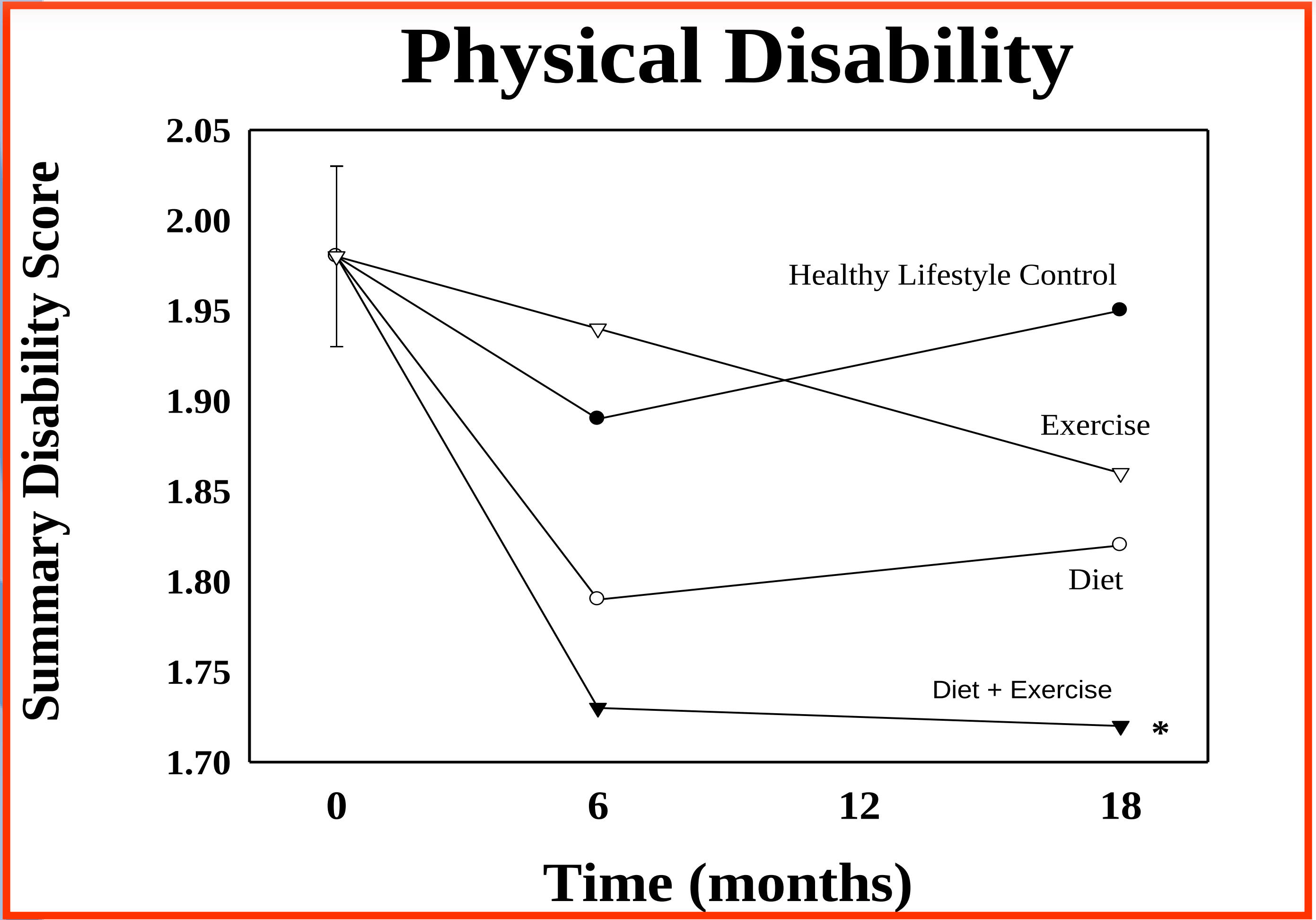
Protein-exercise interaction

Resistance exercise + nutrition (protein)



Adapted from Biolo, 1997

ADAPT – Diet, exercise and disability

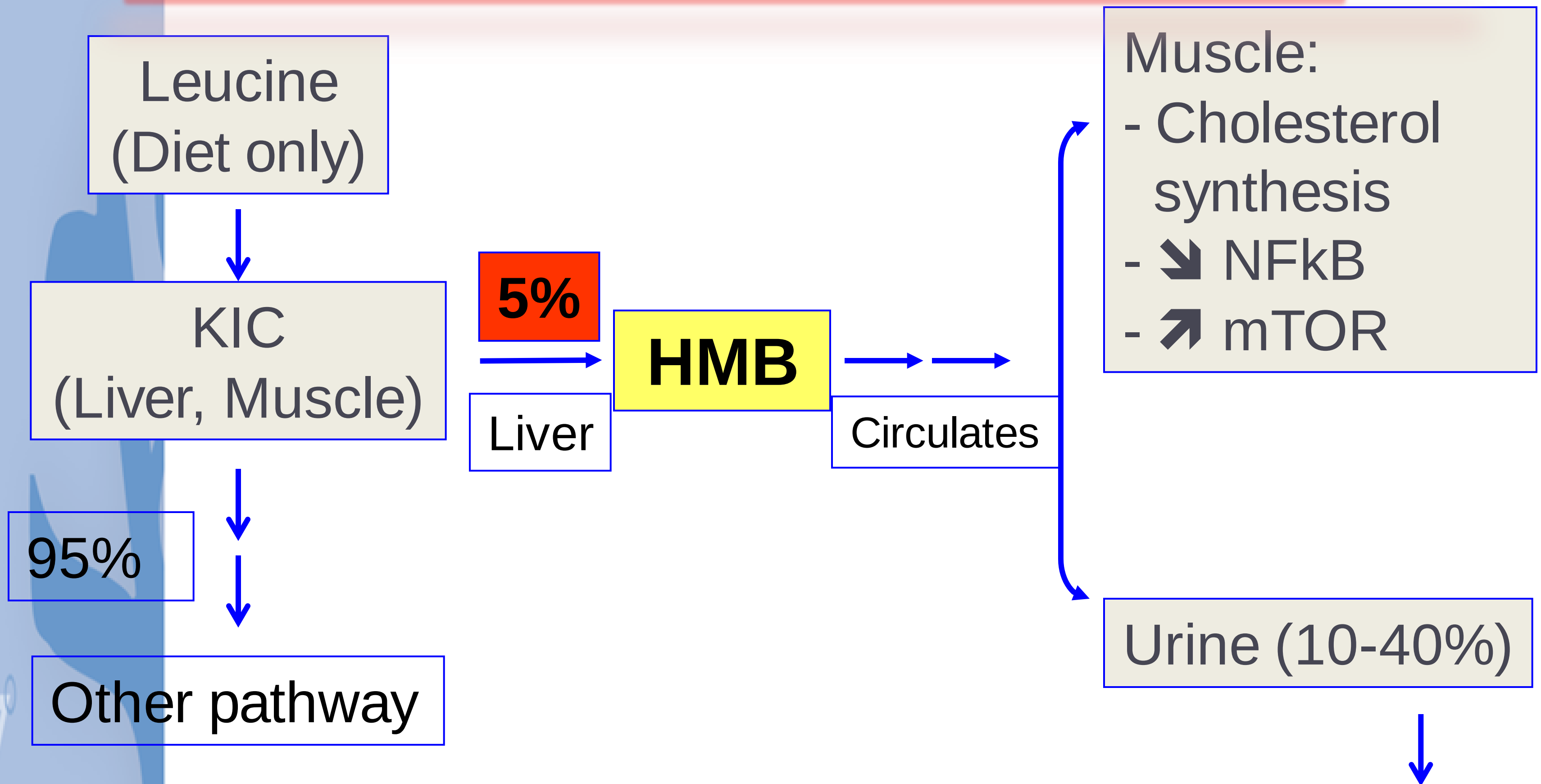


Messier et al Arthritis & Rheumatism 2004;50:1501

Options to optimize post-prandial anabolic action of dietary proteins

- Increase protein intake
  - Age-specific RDAs
- Increase amino acid bioavailability
  - Distribution of protein intake
  - Digestion rate
- Use specific substrates
  - Leucine
  - **ß-hydroxy-ß-methylbutyrate (HMB)**
  - **Vitamin D**

Leucine-HMB Metabolic Pathway



The is an amino acid metabolite that occurs naturally in human muscle cells. Traditionally, HMB has been used by athletes to enhance performance and build muscle mass. Recent studies have focused on the use of HMB to preserve or rebuild muscle mass.

Role of HMB on muscle function

Protective effects

- Substrate for cholesterol synthesis
- Stabilize muscle cell membrane
- Protect muscle cells

Protein synthesis

- Inhibition activation caspase - 8
- Attenuate protein degradation
- Activation mTOR signal pathway
- Stimulation protein synthesis

Studies in Elderly with HMB

Citation	Population	Intervention	Results
Vukovich *et al.* J Nutr 2001	31 elderly individuals 70 ± 1 years old	8-week study CaHMB: 3 g/d or Placebo Trained with walking and stretching	Greater reduction in % body fat* Lean mass increased Greater upper and lower body strength*
Panton *et al.* Med Sci Sports Ex 1998	35 M/F elderly adults	8-week study CaHMB group or Placebo group Resistance training	Greater functional mobility*
Coelho *et al.* Med Sci Sports Ex 2001	12 Males 50–72 years old with high cholesterol	3 grams CaHMB or Placebo Endurance and resistance training	Reduced LDL-cholesterol Increased LBM Greater weight lifting and strength*

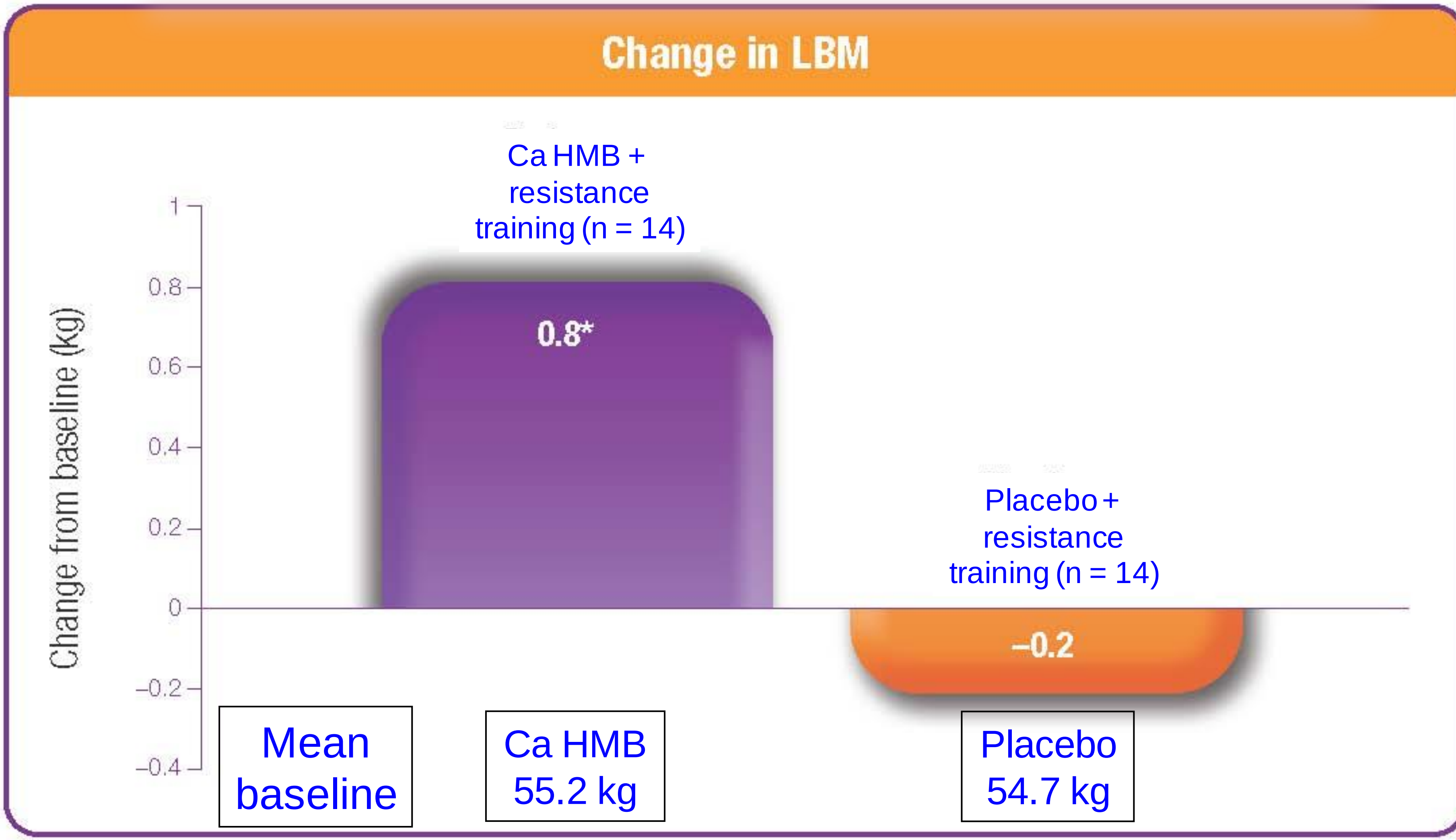
*P<0.05

Study in elderly subjects receiving HMB

- **Objective:**
  - *Can HMB increase LBM and strength in older adults engaged in resistance training?*
- Prospective, randomized, blinded, placebo-controlled trial
- 31 subjects (age > 70 yrs); male and female
- 8-week supplementation + exercise (5 d / wk)
- 3 g HMB/day versus placebo

Vukovich *et al.* J Nutr 2001

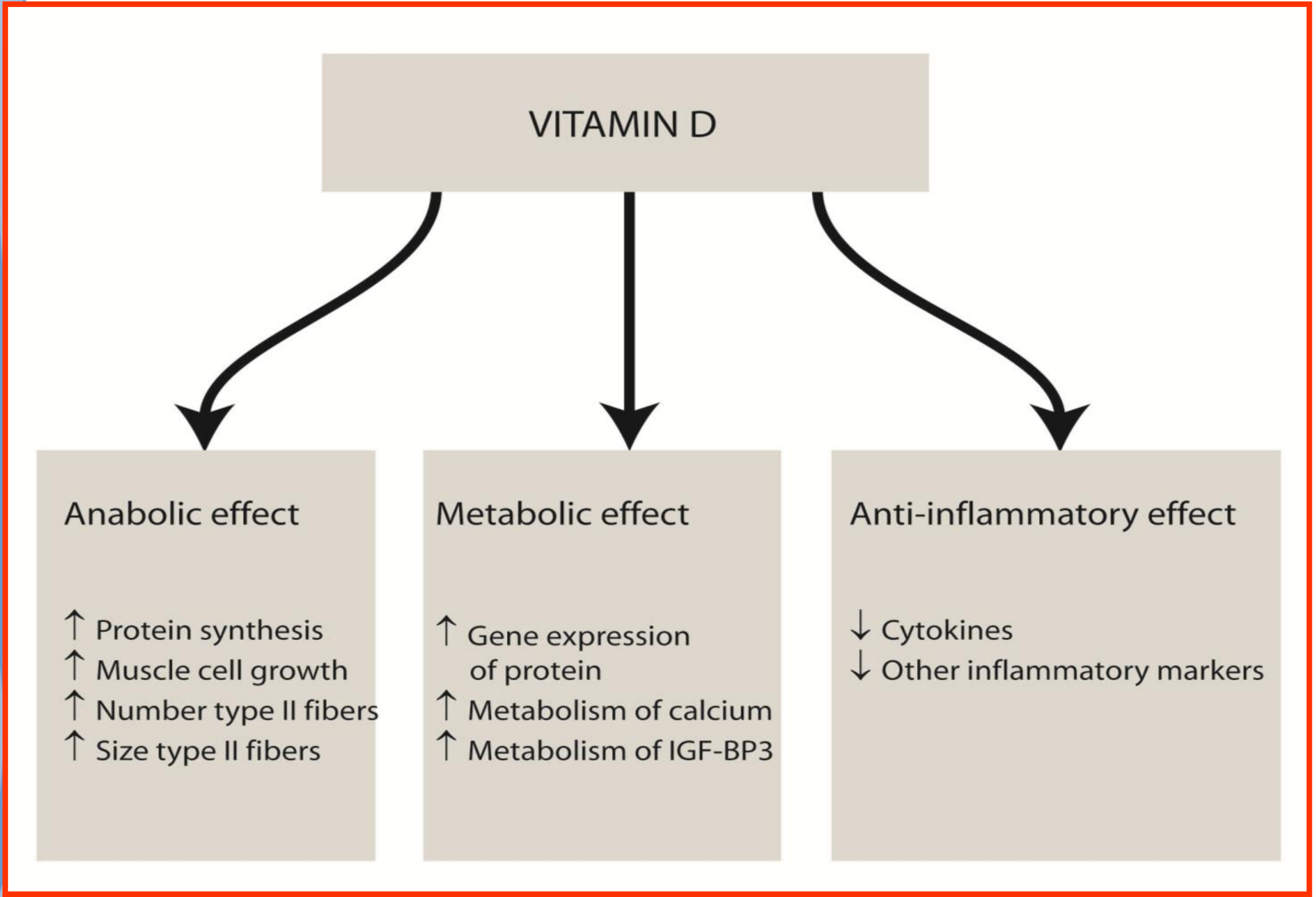
Improved LBM in elderly subjects receiving HMB (p=0.08)



Vukovich *et al.* J Nutr 2001

Mechanism of action Vitamin D

- **Role of Vitamin D on muscle function :**



Vitamin D and muscle function

- Institutionalized elderly
- Vitamin D : 150,000 IU per month for 2 months, then 90,000 IU per month for 4 months

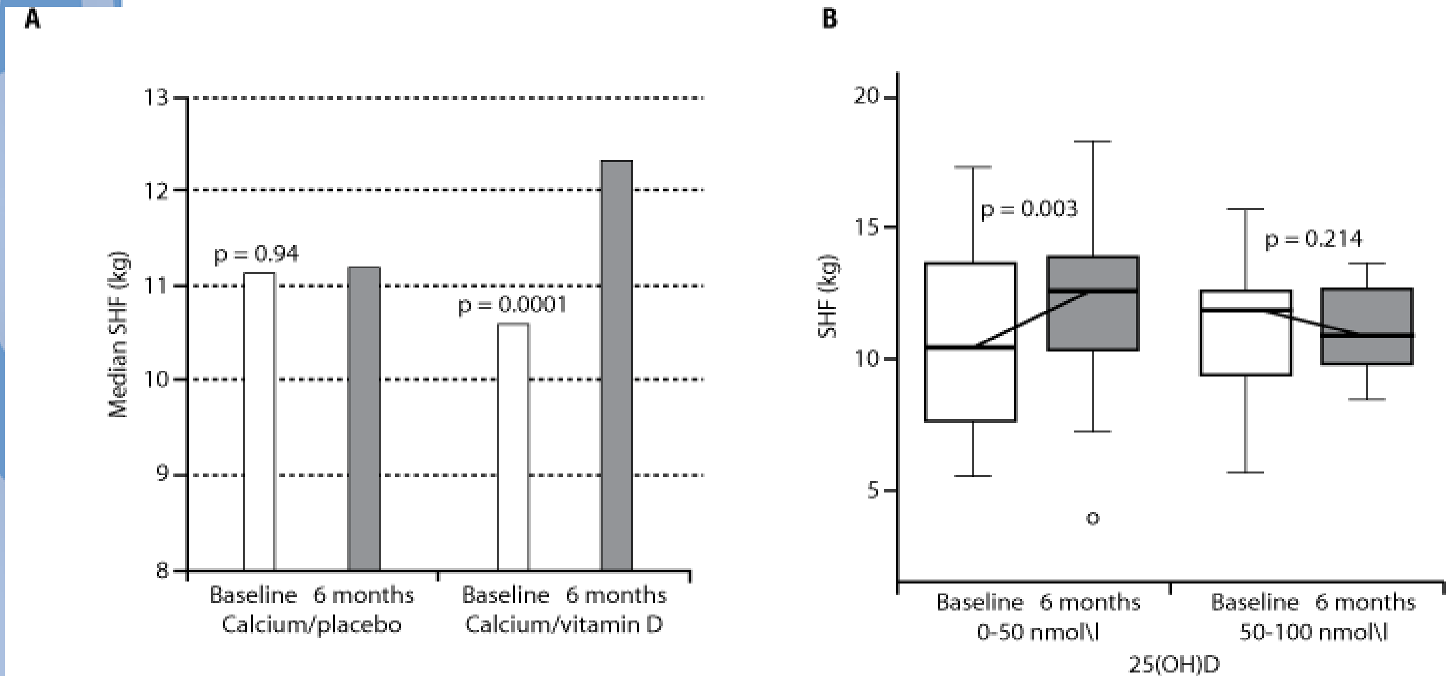


Figure 3. Evaluation of the Strength of Hip Flexors (SFH) after six-month vitamin D replacement in institutionalized elderly. (A) Shows the significant increment in SFH observed in the group that received vitamin D_3 treatment (average of 3600 UI/day), which was not seen in the placebo group. (B) Demonstrates that the SFH increment was seen only in those who had lower levels of 25OHD levels at baseline (< 50 nmol/L) (43).

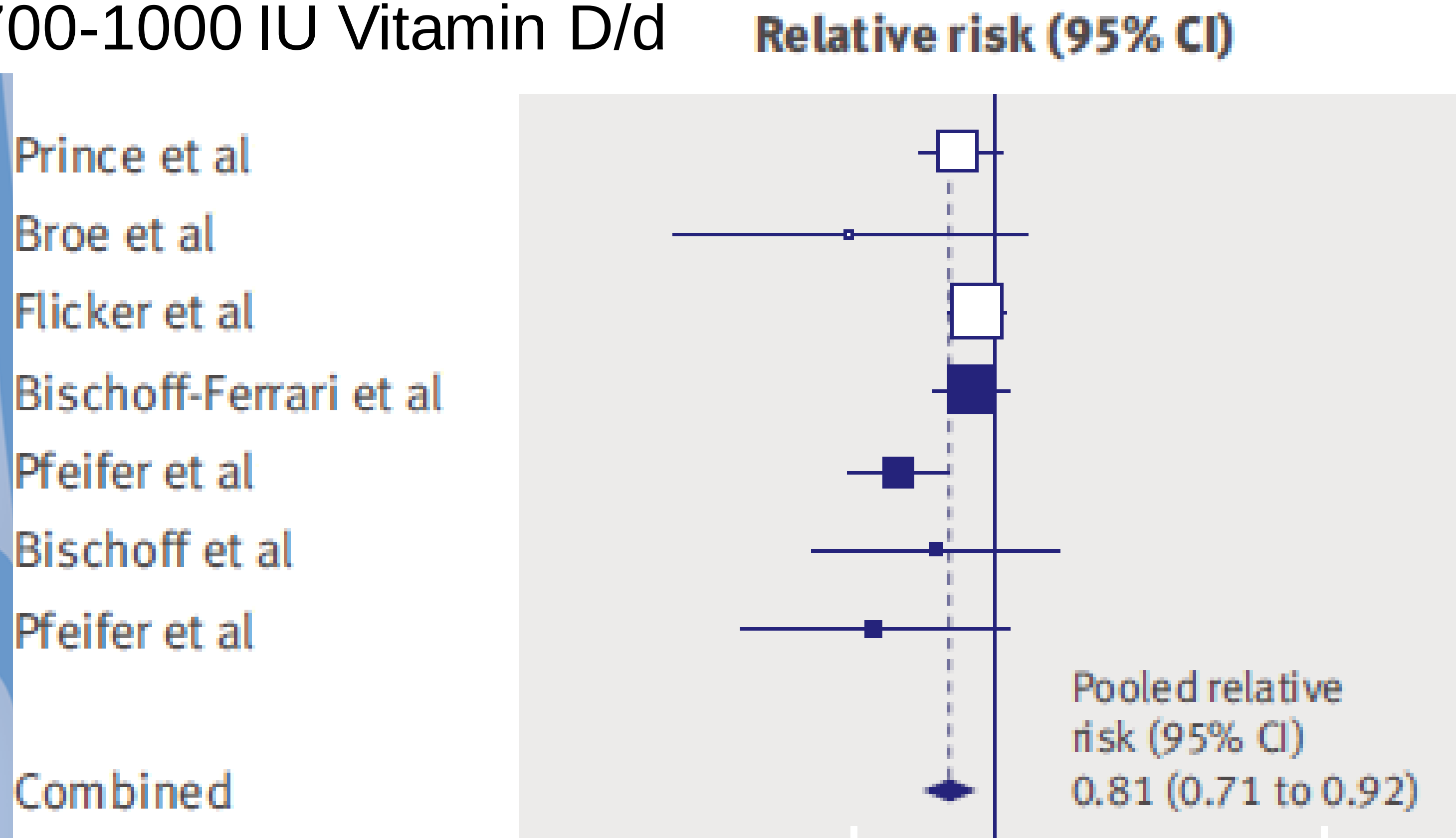
Moreira-Pfrimer *et al.* Ann Nutr Metab 2009

RCTs: Vitamin D and Physical Performance

Bischoff et al. 2003	122 ♀ 85,3 y NH	800 IU D3/d +Ca vs. Ca, p.o. 3 months	+ Strength M. quadriceps, Handgrip, TUG
Latham et al. 2003	243 ♀ ♂ 79,1 y Rehab	300000 IU D3 vs. Placebo, p.o. 3/6 months	- Strength M. quadriceps, TUG, Balance
Dhesi et al. 2004	139 ♀ ♂ 76,6 y Amb	600000 IU D2 vs. Placebo, i.m. 6 months	+ Physical performance, Reaction time, Body sway - Strength
Pfeifer et al. 2009	242 ♀ ♂ 77 y Amb	800 IU D3/d +Ca vs. Ca, p.o. 12 months	+ Strength M. quadriceps, TUG, Body sway
Zhu et al. 2010	302 ♀ 77 y Amb, VD deficient	1000 IU D3/d +Ca vs. Ca, p.o. 12 months	+ Strength hip extensor and adductor, TUG, Body sway

Meta-analysis: Fall prevention

700-1000 IU Vitamin D/d



n=1921

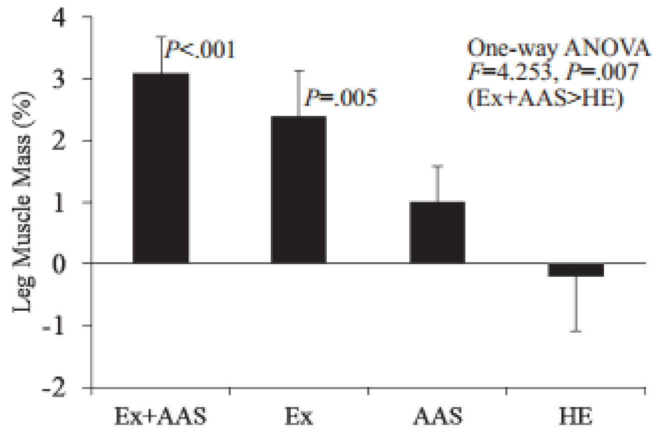
Bischoff-Ferrari *et al.* BMJ 2009

ESERCIZIO FISICO E NUTRIZIONE

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‡*

JAGS 60:16–23, 2012



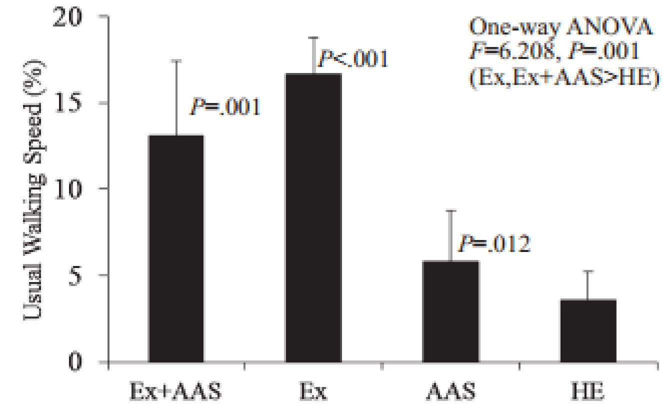


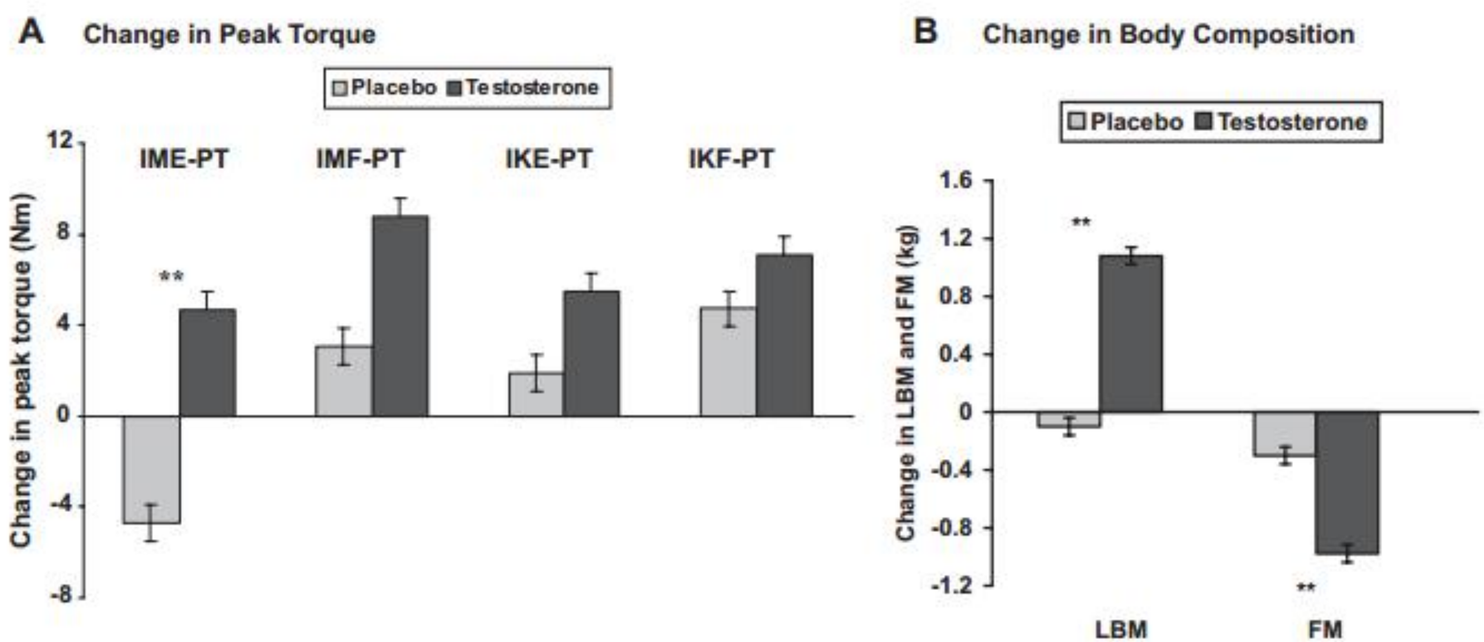
Table 3. Change in Leg Muscle Mass and Functional Fitness After Intervention According to Study Group

	Adjusted Odds Ratio (95% Confidence Interval)		
Dependent Variable*	**AAS**	**Exercise**	**Exercise + AAS**
Change in leg muscle mass and knee extension strength	1.99 (0.72–5.65)	2.61 (0.88–8.05)	4.89 (1.89–11.27)
Change in leg muscle mass and usual walking speed	1.35 (0.45–4.08)	2.41 (0.79–7.58)	4.11 (1.33–13.68)

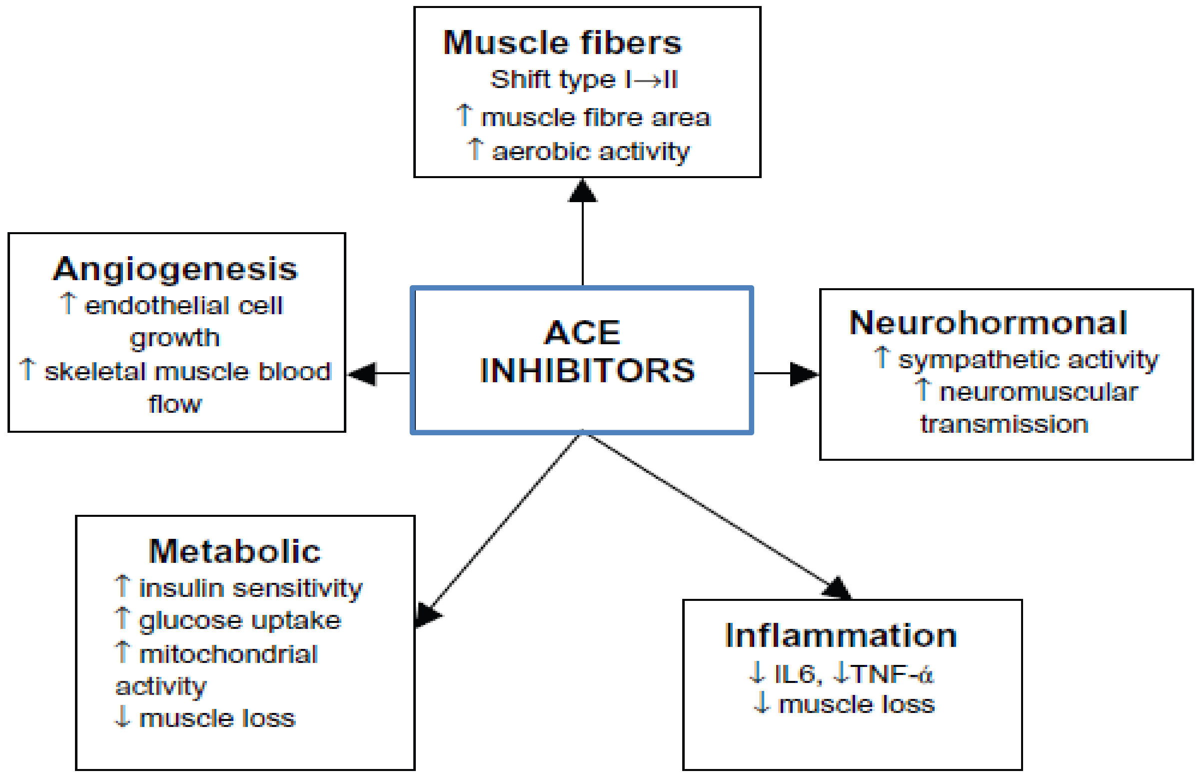
TERAPIA ORMONALE

Effects of Testosterone on Muscle Strength, Physical Function, Body Composition, and Quality of Life in Intermediate-Frail and Frail Elderly Men: A Randomized, Double-Blind, Placebo-Controlled Study

J Clin Endocrinol Metab, February 2010, 95(2):639–650



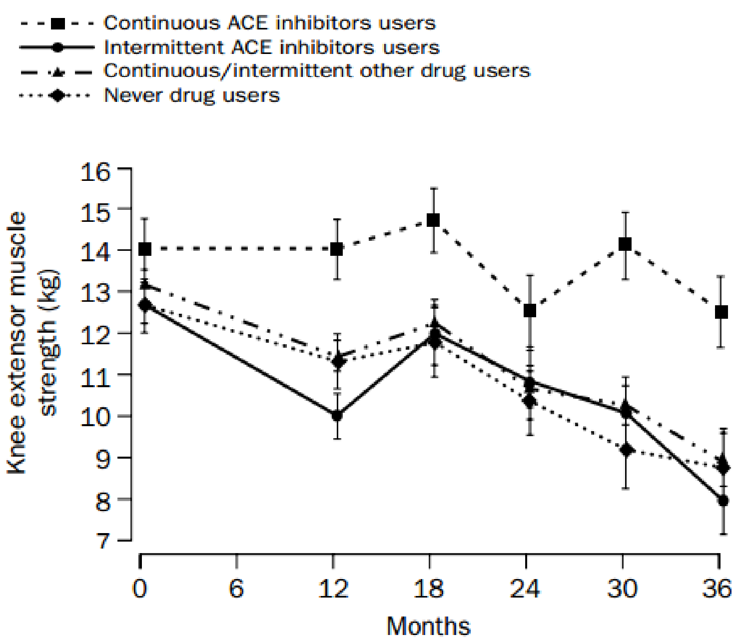
TERAPIA FARMACOLOGICA NON ORMONALE



Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study

Graziano Onder, Brenda W J H Penninx, Rajesh Balkrishnan, Linda P Fried, Paulo H M Chaves, Jeff Williamson, Christy Carter, Mauro Di Bari, Jack M Guralnik, Marco Pahor

THE LANCET • Vol 359 • March 16, 2002 • www.thelancet.com



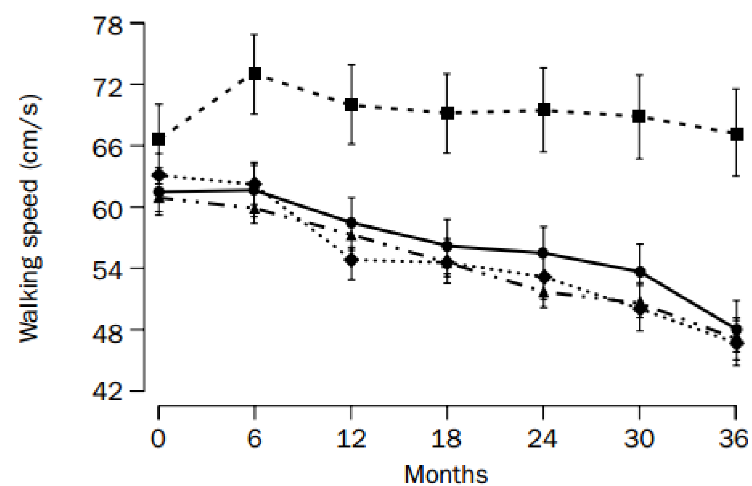


Figure 1: **Mean knee extensor muscle strength and walking speed over 3 years of follow-up among patients with hypertension**

	Continuous users of ACEi (n=61)	Intermittent users of ACEi (n=133)	p*	Continuous/intermittent users of other drugs (n=301)	p*	Never drug users (n=146)	p*
Muscle strength (mean [SE], kg)	–1·0 (1·1)	–3·0 (0·7)	0·096	–3·7 (0·5)	0·016	–3·9 (0·7)	0·026
Walking speed (mean [SE], cm/s)	–1·7 (4·1)	–13·6 (2·7)	0·015	–15·7 (1·8)	0·002	–17·9 (2·7)	0·001

Results of random-effect models, adjusted for age, race, body-mass index, baseline systolic blood pressure, presence of diabetes, ischaemic heart disease, and stroke. ACEi=Angiotensin converting enzyme inhibitors. *p values indicate comparisons with continuous users of ACEi as a reference.

Table 2: **Mean 3-year decline in knee extensor muscle strength and walking speed**

PROSPETTIVE FUTURE

- Anticorpi della MIOSTATINA → inibisce rigenerazione muscolare
- CREATINA → aumenta la massa muscolare e le performance fisiche
- TRICOSTATINA A → antagonista della miostatina
- PGC-1α → regolatore della mitocondrogenesi
- Attivatori della AMP-activator protein
- CELLULE STAMINALI

Polymorphic Variation in the Human Myostatin (GDF-8) Gene and Association with Strength Measures in the Women's Health and Aging Study II Cohort

Michael J. Seibert, MS, Qian-Li Xue, PhD, Linda P. Fried, MD, MPH, and Jeremy D. Walston, MD

JAGS 49:1093–1096, 2001

Table 2. Linear Regression Analyses of Association Between Strength Measures and Genotype, Adjusting for Race and BMI

	Overall Strength		Hip Flexion		Knee Flexion		Grip Strength	
	Mean (SE)[#]	P-value	Mean (SE)[#]	P-value	Mean (SE)[#]	P-value	Mean (SE)[#]	P-value
Genotype*:								
K/R or R/R	−5.04 (2.98)	.09	−4.00 (1.58)	.01	−2.11 (1.29)	.10	0.76 (1.23)	.54
Race†:								
African American	6.30 (2.09)	<.01	4.15 (1.10)	<.01	1.47 (0.90)	.11	1.36 (0.89)	.13
Body mass index (BMI)	0.58 (0.14)	<.01	0.36 (0.07)	<.01	0.18 (0.06)	<.01	0.07 (0.06)	.21

*reference group: K/K.
†reference group: Caucasian.
SE = standard error.
#mean values in kg.

Ann Neurol 2008;63:561–571

A Phase I/II trial of MYO-029 in Adult Subjects with Muscular Dystrophy

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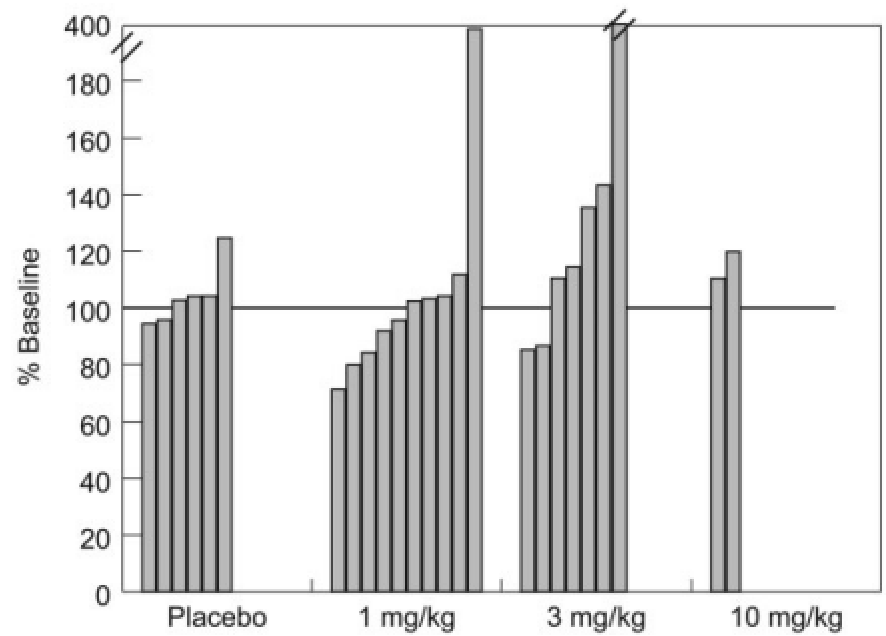

Fig 3. Muscle fiber diameters show the percentage change in muscle fiber diameter before and after treatment. Each vertical bar represents one patient. There was an increase in muscle fiber diameters in the 10 (median = +15.2% change from baseline) and 3mg/kg groups (+14.4%) compared with the 1mg/kg treatment (−0.93%) and placebo groups (+2.7%). A trend toward larger fibers with increasing dose (differences did not reach statistical significance) is shown; only two patients in the 10mg/kg group had muscle biopsies.

EDITORIALS

BMJ

Sarcopenia

A research agenda has been set, but recognition in clinical practice is lagging behind

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Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2010;341:c4097
doi: 10.1136/bmj.c4097

- What should clinicians look for?
- Well recognized risk factors for sarcopenia include increasing age, low levels of physical activity, inadequate nutrition, and comorbidity.
- Identifying high risk groups of older people is straightforward, but making a diagnosis is more difficult.
- In the European guidelines, sarcopenia is diagnosed firstly on the basis of impaired physical performance, characterized by slow gait speed, and then either by low muscle strength assessed by handheld dynamometry or low muscle mass measured, for example, by bioimpedance.

Sayer AA. BMJ 2010; 341:952.

BMJ

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- In terms of managing sarcopenia, meta-analyses show that resistance exercise can improve muscle mass and strength in older adults.
- The evidence for the role of nutrition in the prevention and treatment of sarcopenia is less clear. In particular, more information is needed on protein and specific amino acids, such as leucine.
- Protein intake may become insufficient with the reduction in total food intake seen in later life and dietary reference intake for protein may be set too low to ensure optimal intake in healthy older adults.

Sayer AA. BMJ 2010; 341:952.

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- Attempts to improve muscle mass and function with protein supplementation have had variable results.
- Similarly, findings from observational studies and randomized controlled trials reporting the effects of vitamin D on muscle strength have not been consistent, although some do report benefit.
- Sarcopenia is firmly on the agenda for research into ageing and now needs to be recognized in routine clinical practice.

Sayer AA. BMJ 2010; 341:952.

Il movimento è lo stato dell' uomo e la base della sua essenza.
La vita umana non può essere concepibile in senso statico.
Dal battere delle palpebre alla massima velocità in corsa,
nel sonno o nella piena attività, l'uomo è in movimento.

(Kaplan A)

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