Amino Acid supplements, inflammation, and muscle metabolism. Do we know enough to effectively intervene?

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Amino Acids Supplements

- Nutritional status and outcome
- Inflammation and muscle wasting
- Amino acid supplements
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Body composition changes with aging

- Progressive depletion of lean body (fat-free mass =ffm), mainly muscle mass
- Starting in the 4th decade of life
- At the age of 90y, 50% of muscle mass is lost
- BMI often independent of muscle mass (↓~ or ↑BMI with ↓ muscle mass)

Roubenoff. Can J Appl Physiol 2001, Vandervoort. Muscle Nerve 2002, Evans. Nutr 1997, Gallagher. AJP 2000

Aging and BMI

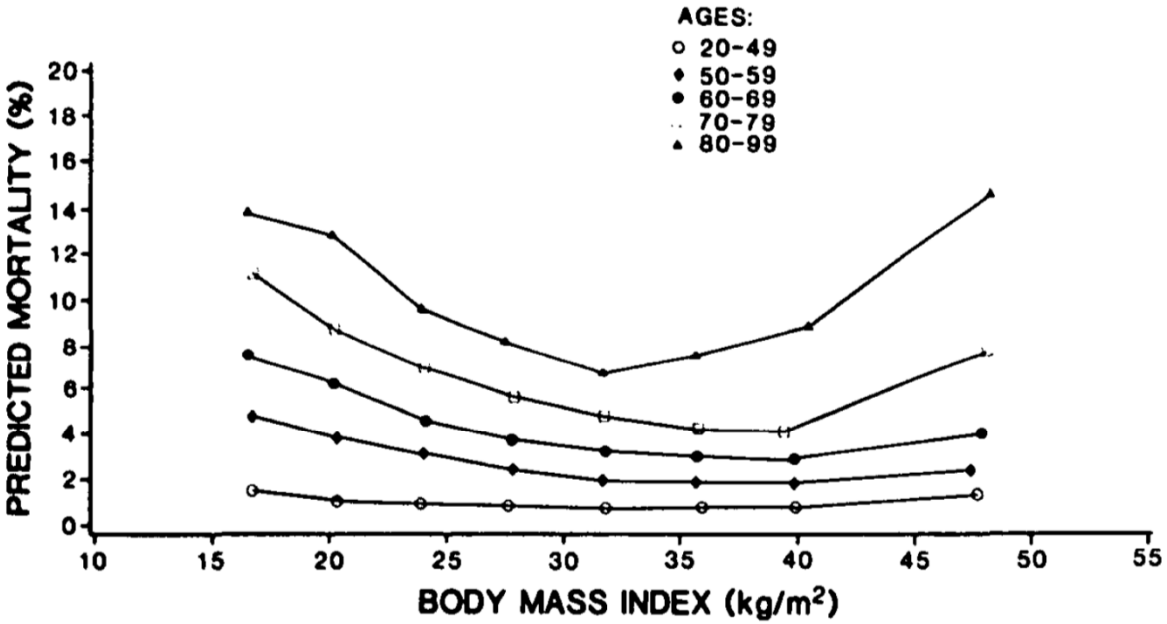
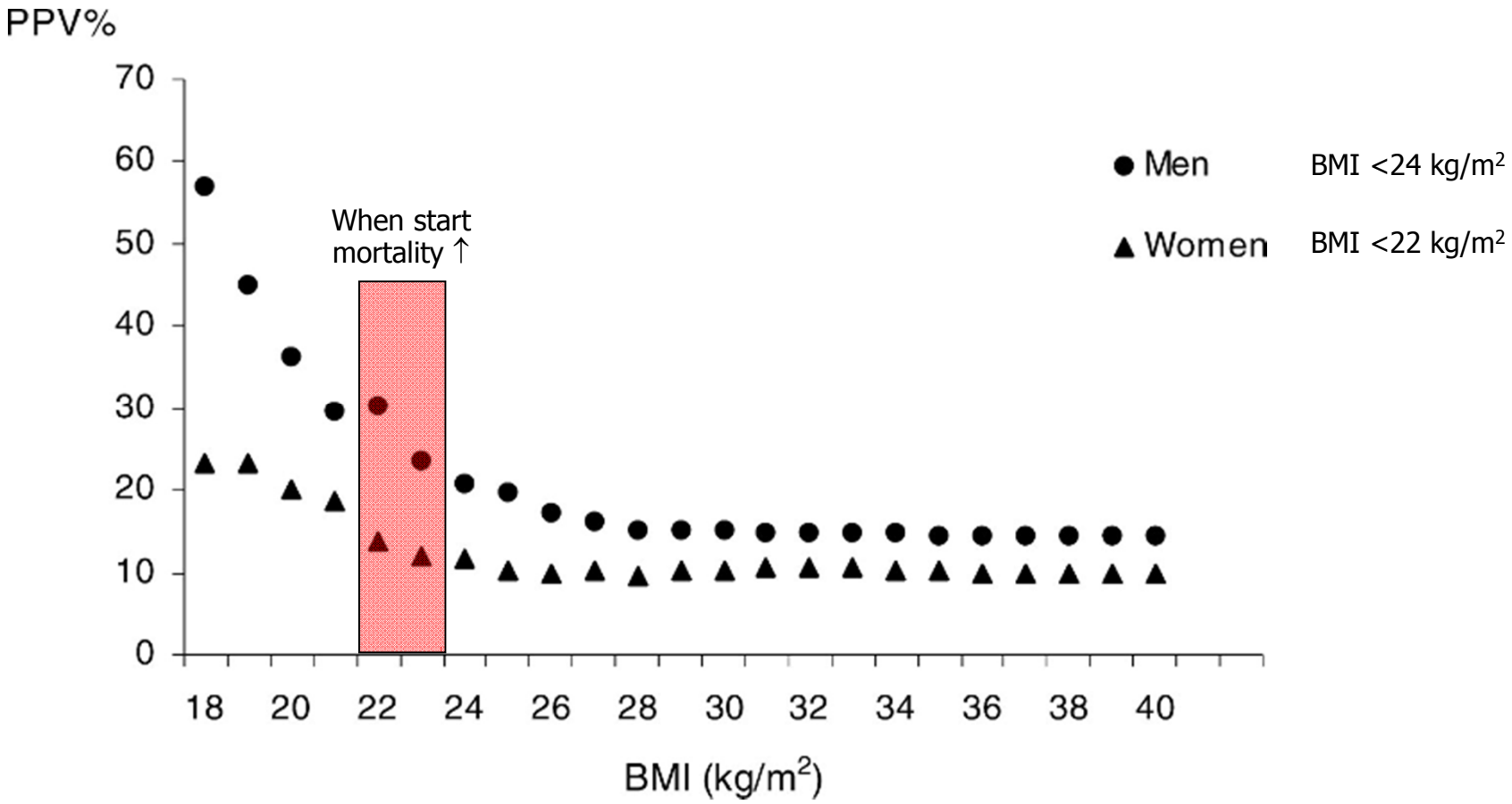


Figure 1. Predicted probability of death as a function of body mass index (BMI) calculated from the logistic model for each of 5 age groups. The plotted points are mean values for subjects in a given weight group. Highest mortality almost always occurs at lowest BMI and mortality also increases at greatest BMI.

Potter JF et al., J Gerontol 1988;43:M59-63

The Italian Longitudinal Study on Aging (ILSA)



Male (●) and female (▲) proportional positive predictive value (PPV%) of short-period death by body mass index (BMI) values

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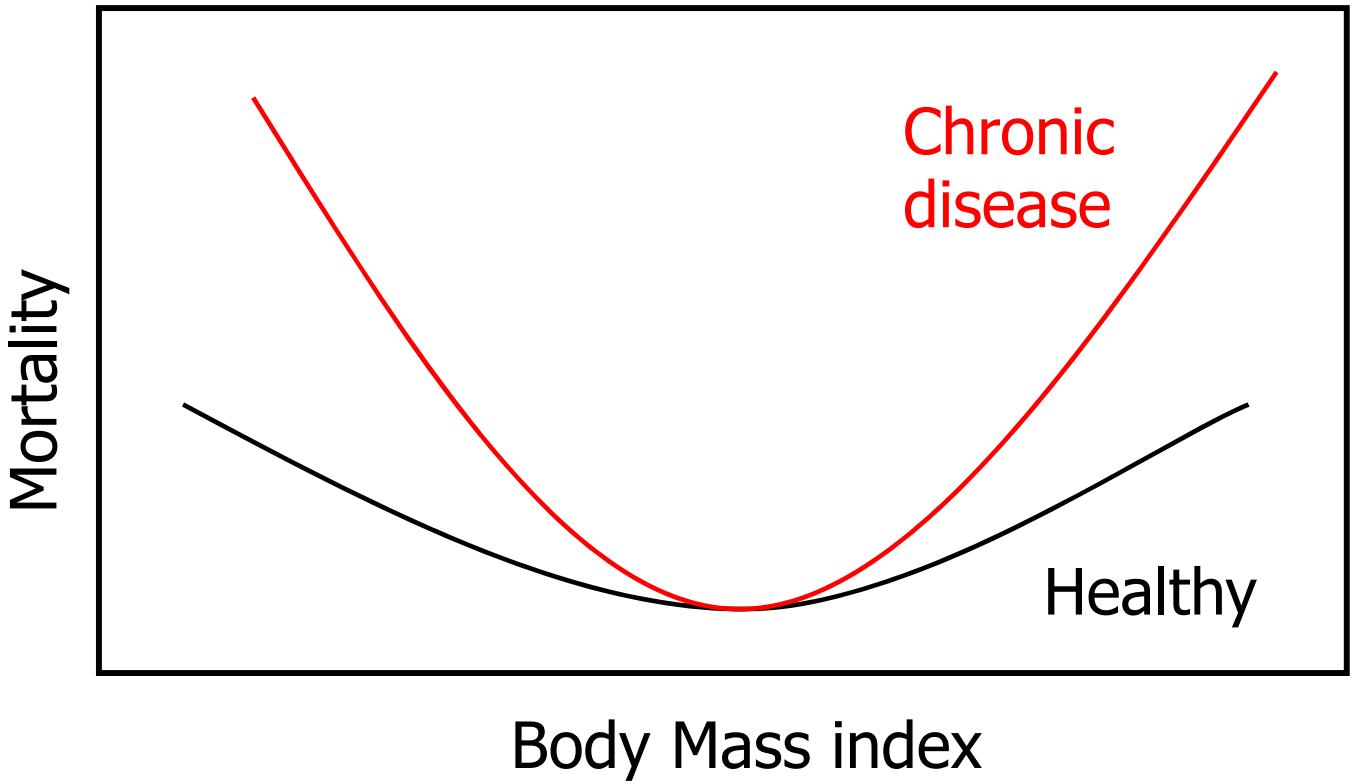
Sergi et al. J Gerontol A Biol Sci Med Sci 2005;60:866-871

Model: Chronic disease and BMI



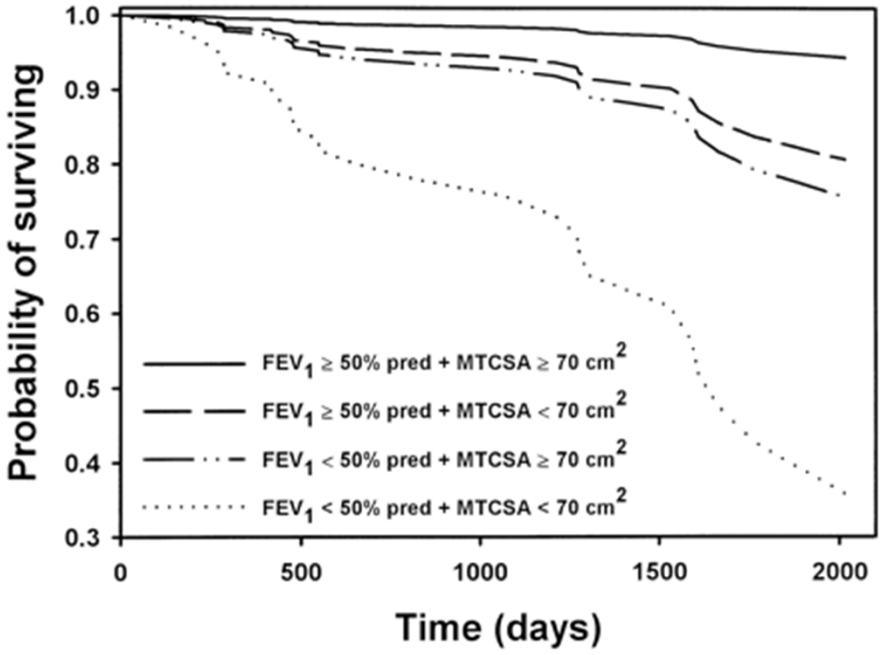
For the elderly:

- Association between BMI and body fat is low
- Higher survival for people with higher BMI
- Threshold Malnutrition BMI: 22-24 kg/m^2

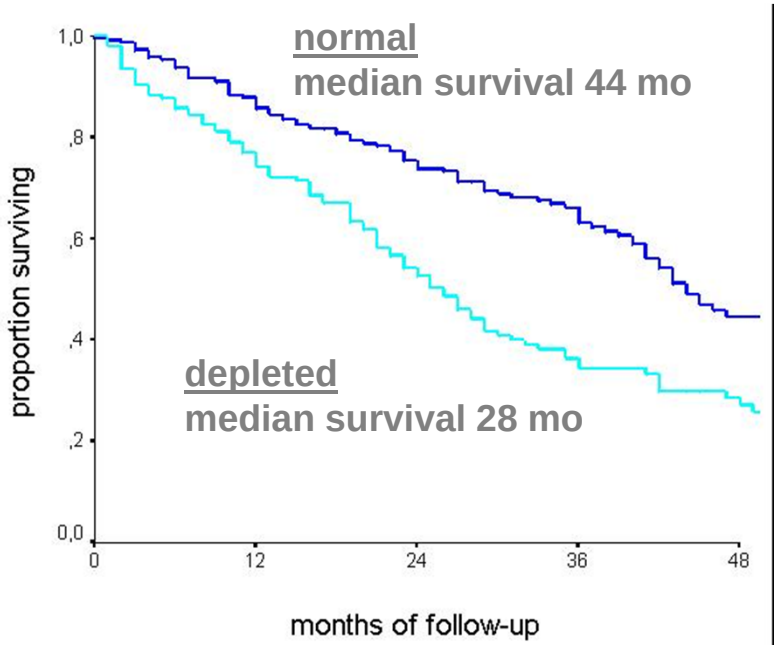
Muscle wasting in elderly with COPD: consequences

↓ survival rate

Muscle cross-sectional area



Fat-free mass



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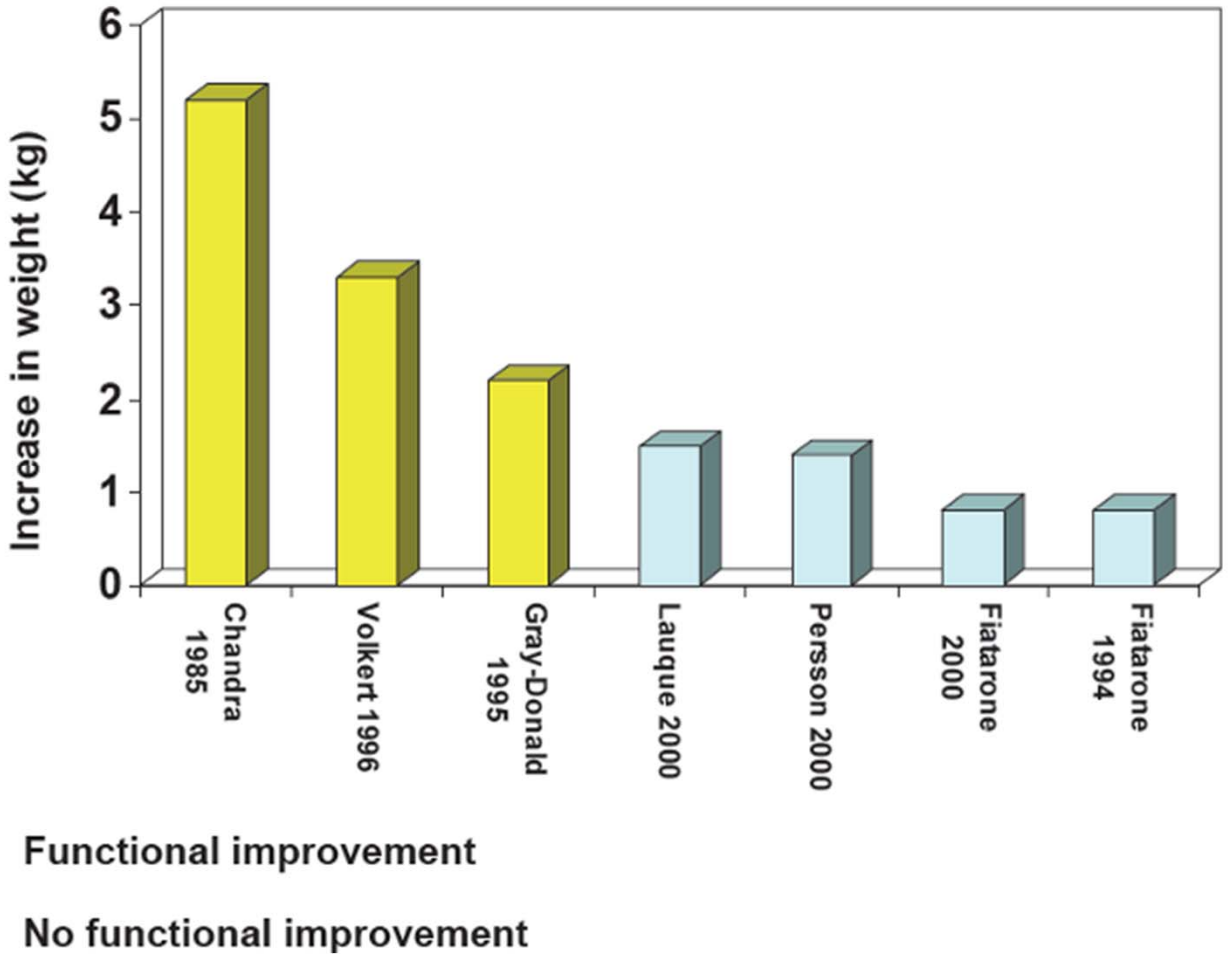
Marquis K et al., Am J Respir Crit Care Med 2002;166:809-13.

Weight *gain* and function among nursing home patients



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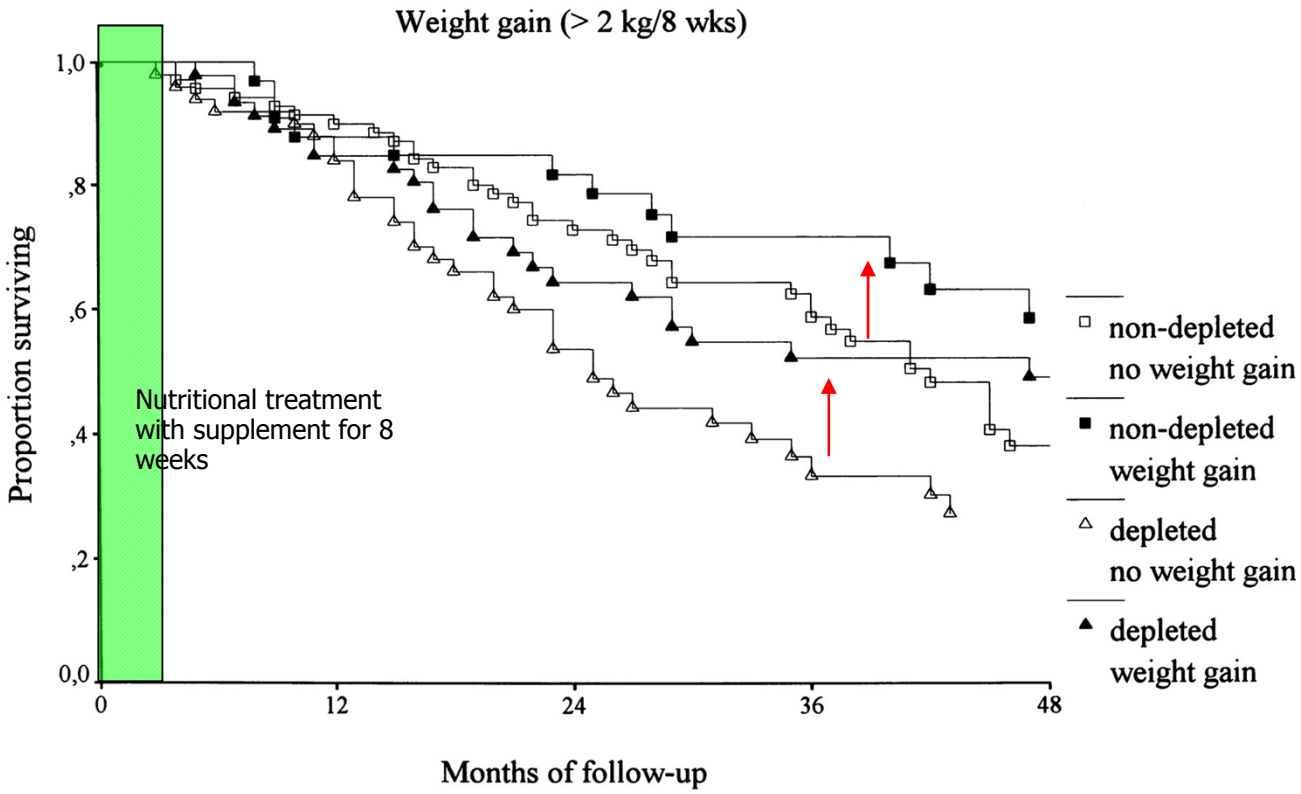
Stratton RJ. Proc Nutr Soc 2005;64:325-33

Weight Loss Is a *Reversible* Factor in the Prognosis of Chronic Obstructive Pulmonary Disease



Treating weight loss in underweight patients (low BMI or muscle mass) and obtaining more than 2kg/8w weight gain, improves SURVIVAL!

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Schols AM. Am J Respir Crit Care Med 1998;157:1791-7

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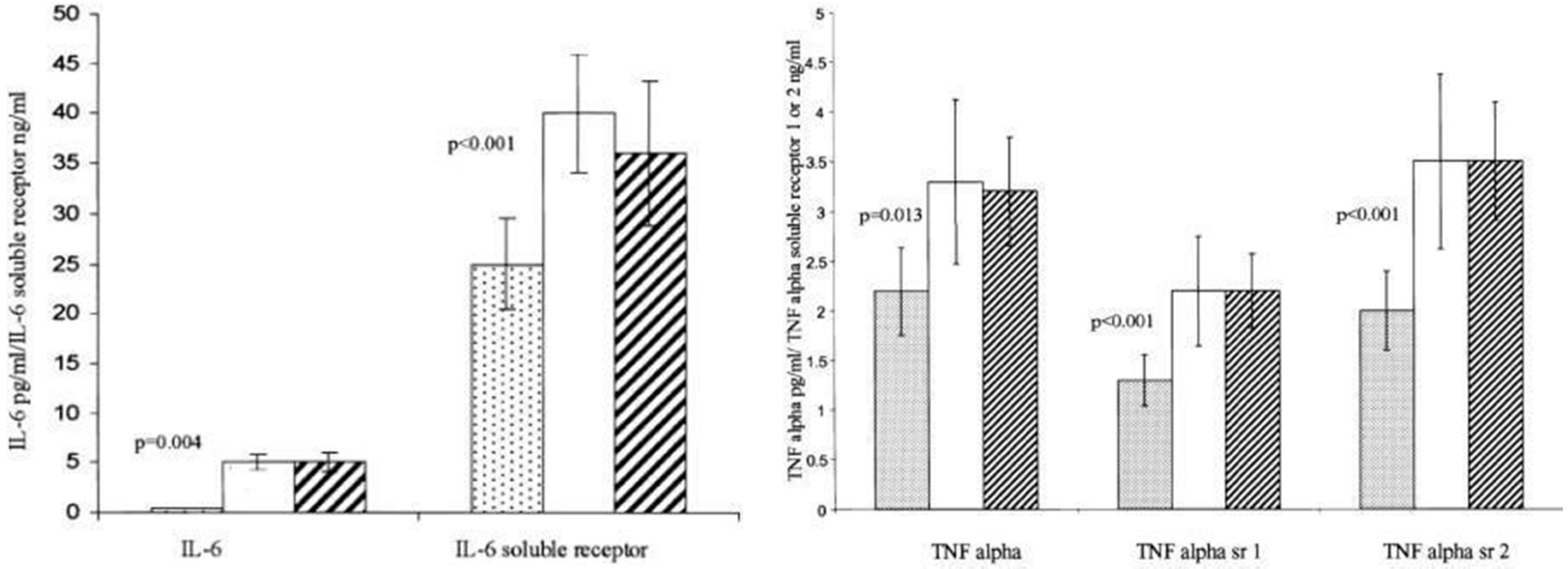
Systemic inflammation and muscle wasting in elderly with COPD

- ↑ levels of pro-inflammatory cytokines (Tumor Necrosis Factor (TNF)-α, Interleukin (IL) 6 and 8
- ↑ levels of soluble TNF-α receptors (55 and 75)
- Pro-inflammatory cytokines have been shown to induce the formation of acute phase reactants.

Dentener MA et al. Thorax 2001;56:721-6.

Inflammation and muscle wasting in stable COPD



1. *Normal muscle mass*
2. *Underweight and low muscle mass*
3. *Normal weight and low muscle mass*

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Eid AA at al. Am J Respir Crit Care Med 2001;164:1414-8

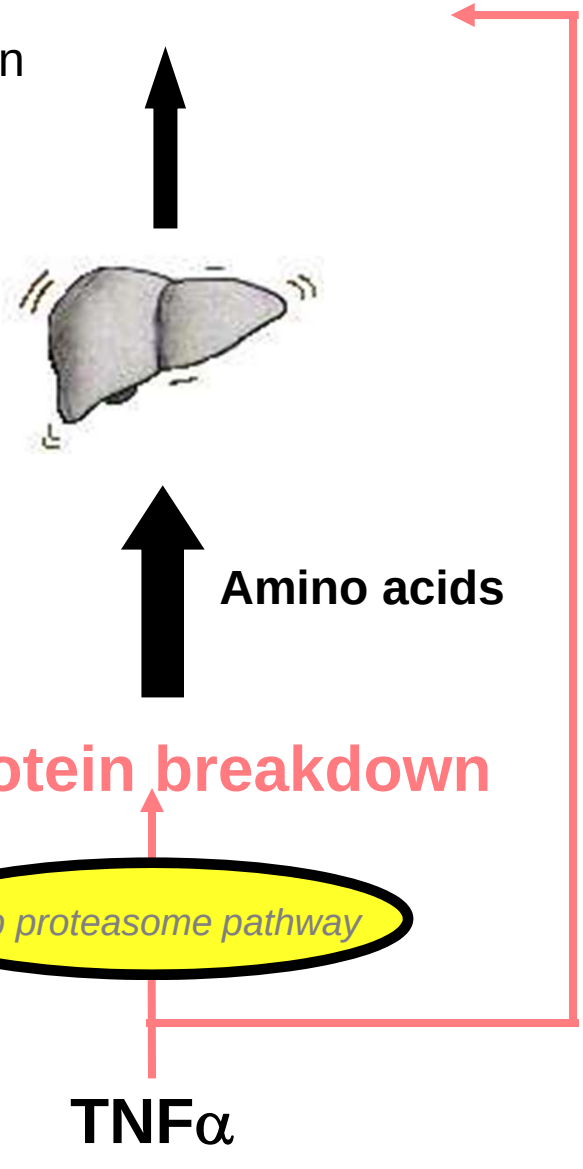
Inflammation and muscle wasting in stable COPD

- Association ↑ CRP levels in COPD with
  - ↓ quadriceps strength
  - ↓ maximal and submaximal exercise capacity
  - ↑ morbidity

Broekhuizen, Thorax 2006, Yende, Thorax 2006

Amino acids released from muscle protein breakdown provide the precursors to synthesize the hepatic proteins involved in the inflammatory response, leading to loss of lean tissue.

➔Accelerated hepatic protein synthesis creates drain on body protein stores !!!



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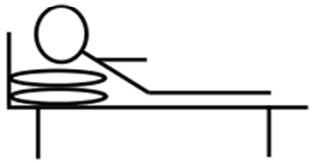
Hofford, AJRCCM 1997; Pouw, AJRCCM 1998; Engelen, AJCN 2001

Model for the development of muscle wasting in elderly with COPD

	CHANGES IN PROTEIN METABOLISM	PRESUMED PRINCIPLE CATABOLIC FACTORS	DISEASE STAGE
	Increased whole body protein synthesis and degradation	Progressive reduction in muscle activity secondary to breathlessness Low grade inflammatory response	EARLY DISEASE
		Disuse/Inactivity Hypoxaemia Acidosis Acute inflammatory response Negative energy balance Steroid treatment	ACUTE EXACERBATIONS
	Reduced whole body protein synthesis ? Increased muscle proteolysis	Severely reduced muscle activity Negative energy balance Chronic inflammatory response Hypoxaemia Reduced anabolic hormones ? Insulin resistance Apoptosis	LATE DISEASE

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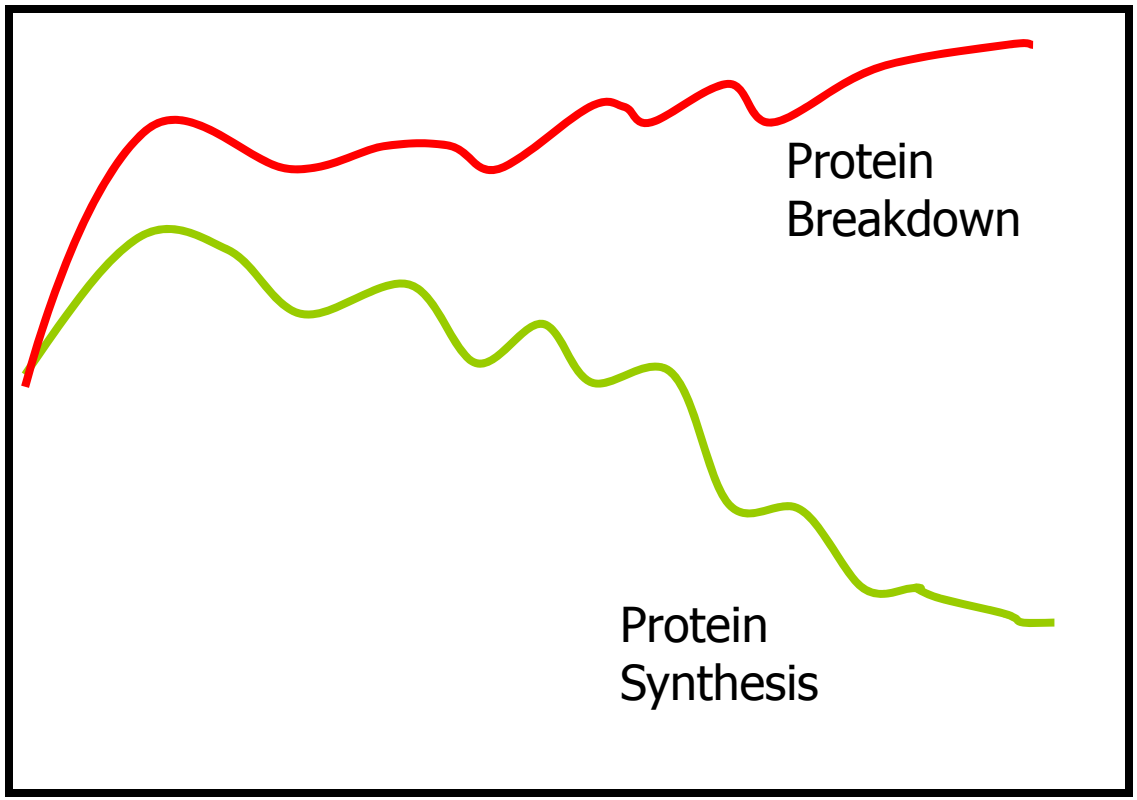
Jagoe RT and Engelen MP. Eur Respir J Suppl 2003;46:52s-63s

Model of muscle wasting in elderly with COPD



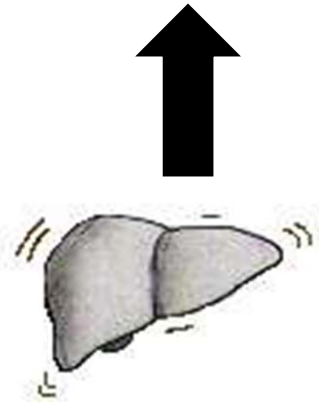
Healthy----Early-----Transitional----Progressive late

Disease Stage

Response to feeding in cachectic COPD patients

- Supplying large amounts of proteins or calories is only partially successful in reversing muscle loss in COPD *(Efthimiou ARRD 1988, Lewis ARRD 1987, Rogers ARRD 1992)*
- A substantial number of patients failed to respond to the nutritional support *(Creutzberg, AJRCCM 2000)*
- This is of clinical relevance as weight gain is a significant, independent predictor of mortality rate in patients with COPD *(Schols, AJRRM 1998)*

Non-response to nutritional intervention might be related to the effects of the ↑ systemic inflammatory profile on metabolism, resulting into protein need because of an ↑ acute phase protein synthesis rate in the liver.



protein synthesis ⟷ **protein breakdown**

Ub proteasome pathway

Pro-inflammation

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Hofford, AJRCCM 1997; Pouw, AJRCCM 1998; Engelen, AJCN 2001

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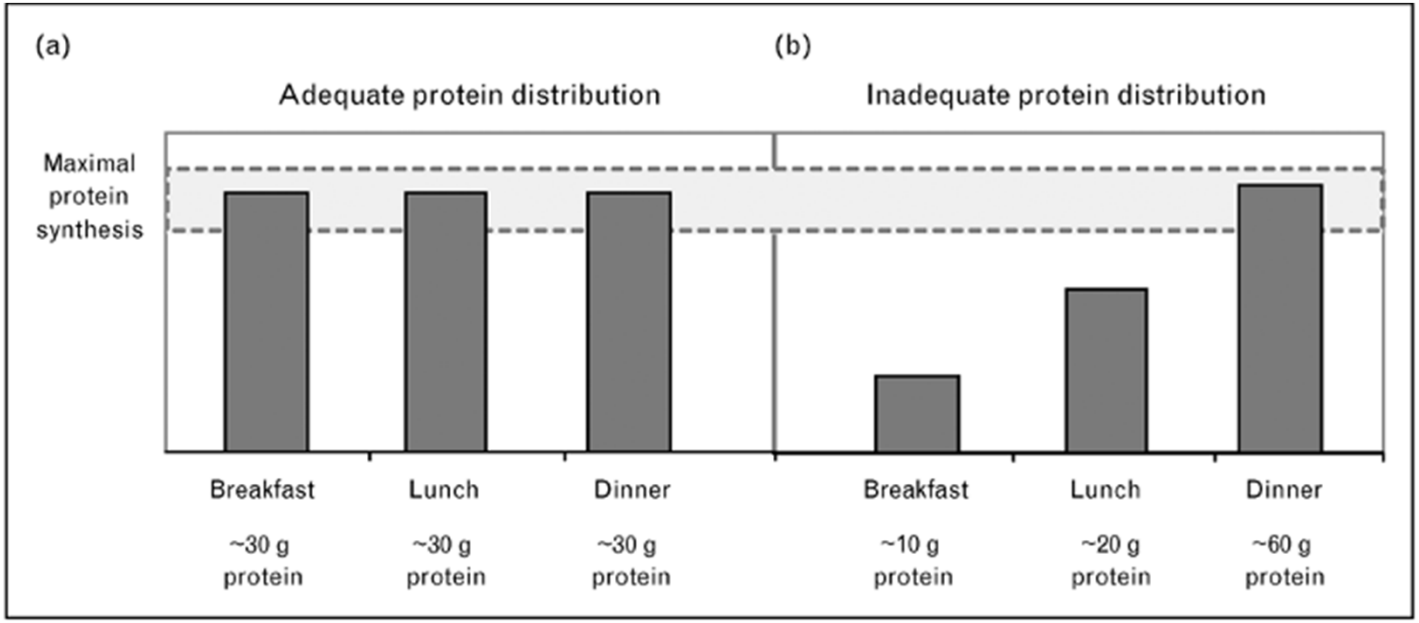
Optimal Protein intake in elderly

- Optimal protein intake remains virtually constant across all energy intakes. Thus, a reduced intake of food automatically is related to reduced of insufficient protein intake
- Efficiency of protein utilization decreases with age
- Elderly need 30 gram of protein/meal to have a fully stimulated skeletal muscle protein synthesis
- Optimal protein intake for elderly **1.5 gram / kg BW / day**
  - Positive effects calcium supplements when protein intake at least 1.2 gram/kg BW (protein ⇑ intestinal Ca-uptake and ⇑ bone matrix turnover)
  - Negative effect of this level of protein intake on renal function not observed

Layman. Nutrition and Metabolism 2009; 6: 12

Distribution of intake (1.5 g/kg BW/day)



(a) Ingestion of 90 g of protein, distributed evenly over 3 meals. (b) Ingestion of 90 g of protein unevenly distributed throughout the day. Stimulating muscle protein synthesis to a maximal extent during the meals shown in Fig. 1a is more likely to provide a greater 24 h protein anabolic response than an unequal protein distribution.

Breakfast is the most important meal for stimulation of muscle protein synthesis as the body comes from the overnight catabolic state

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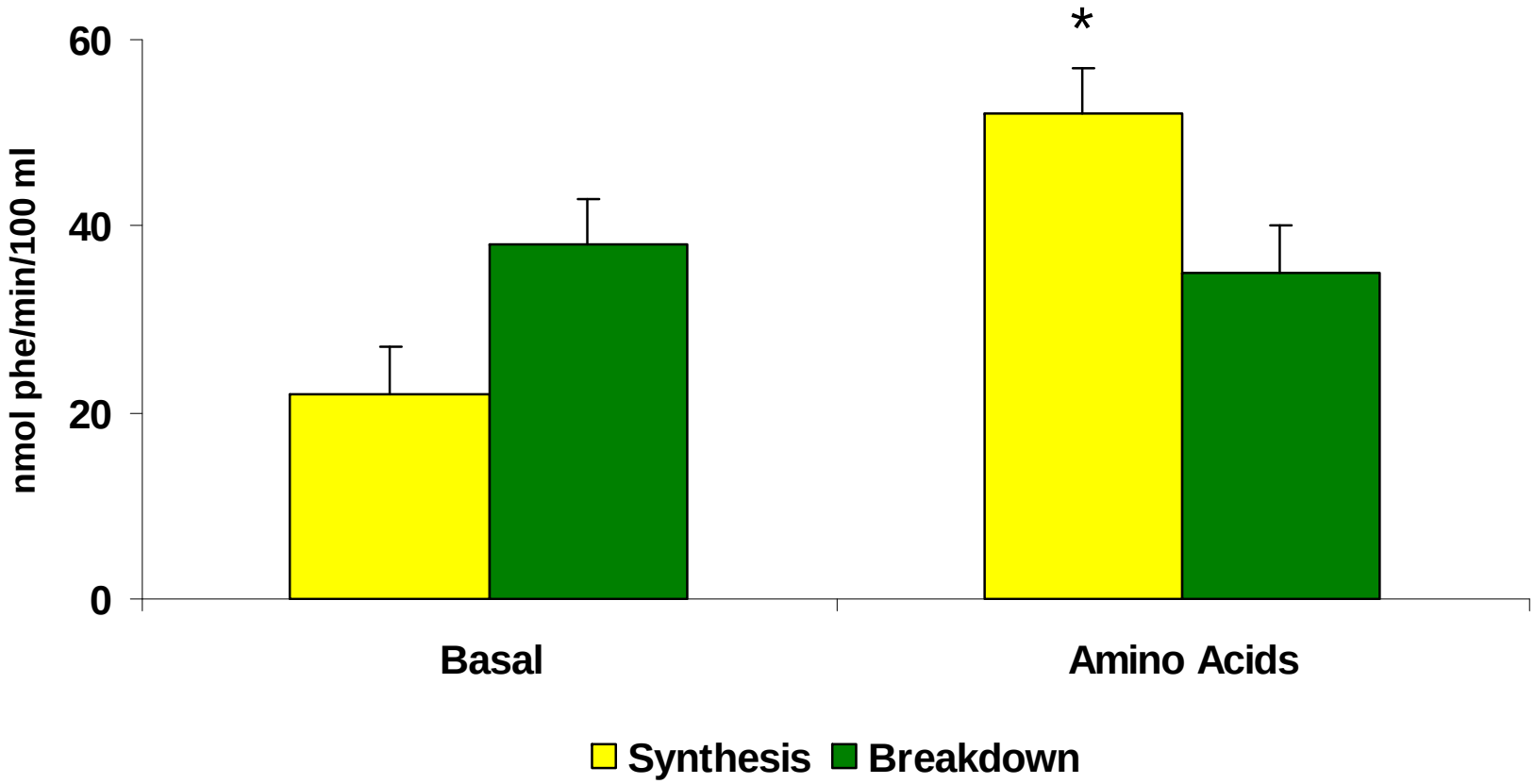
Paddon-Jones D and Rasmussen BB. Curr Opin Clin Nutr Metab Care 2009;12:86-90.

Effect of free Amino Acids on Muscle Protein Synthesis and Breakdown



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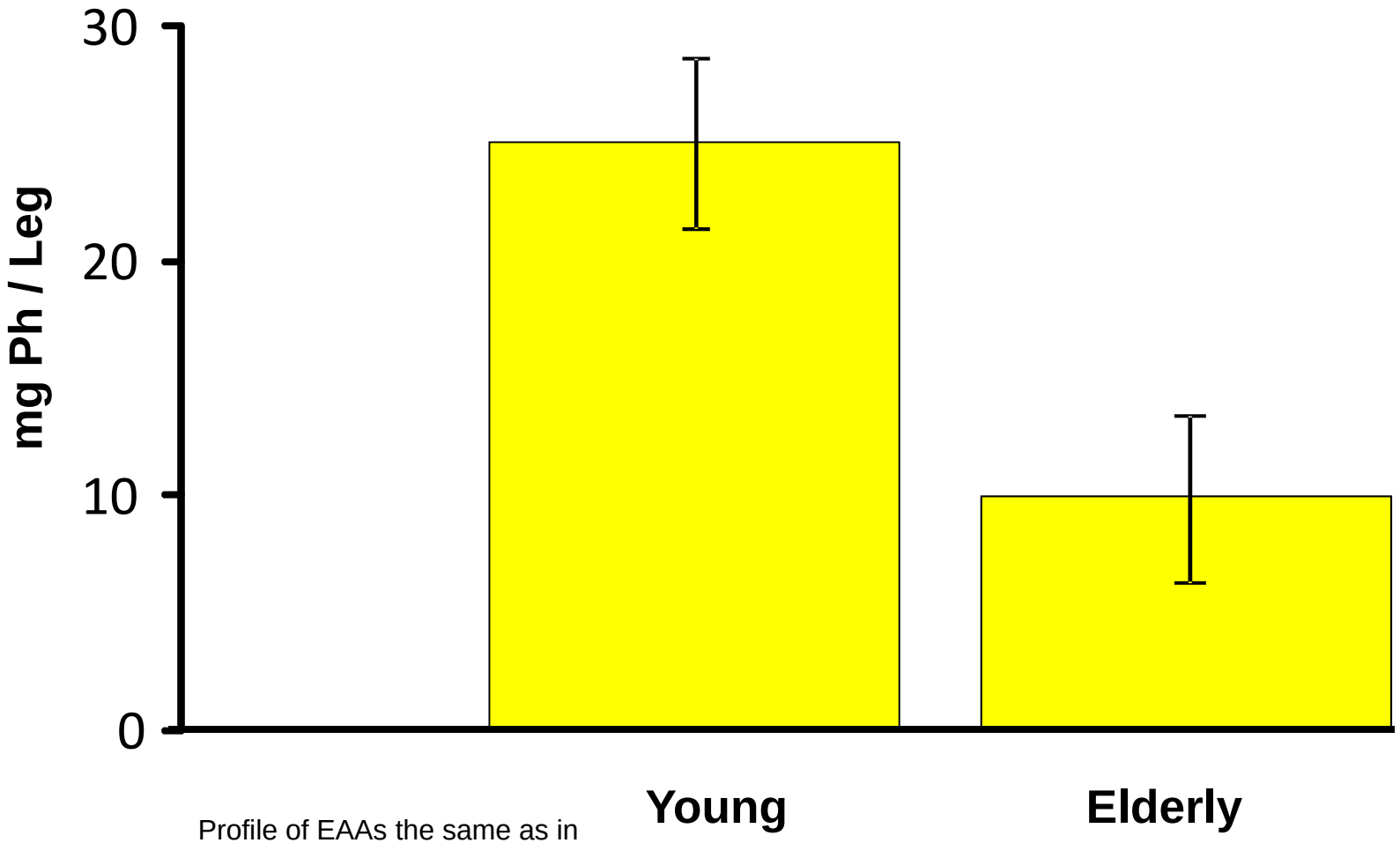
Biolo et al. Am J Physiol 1997; 273: E122-E129

Effect of Age on Anabolic Muscle Response to 7 gm of EAAs



Profile of EAAs the same as in whey protein

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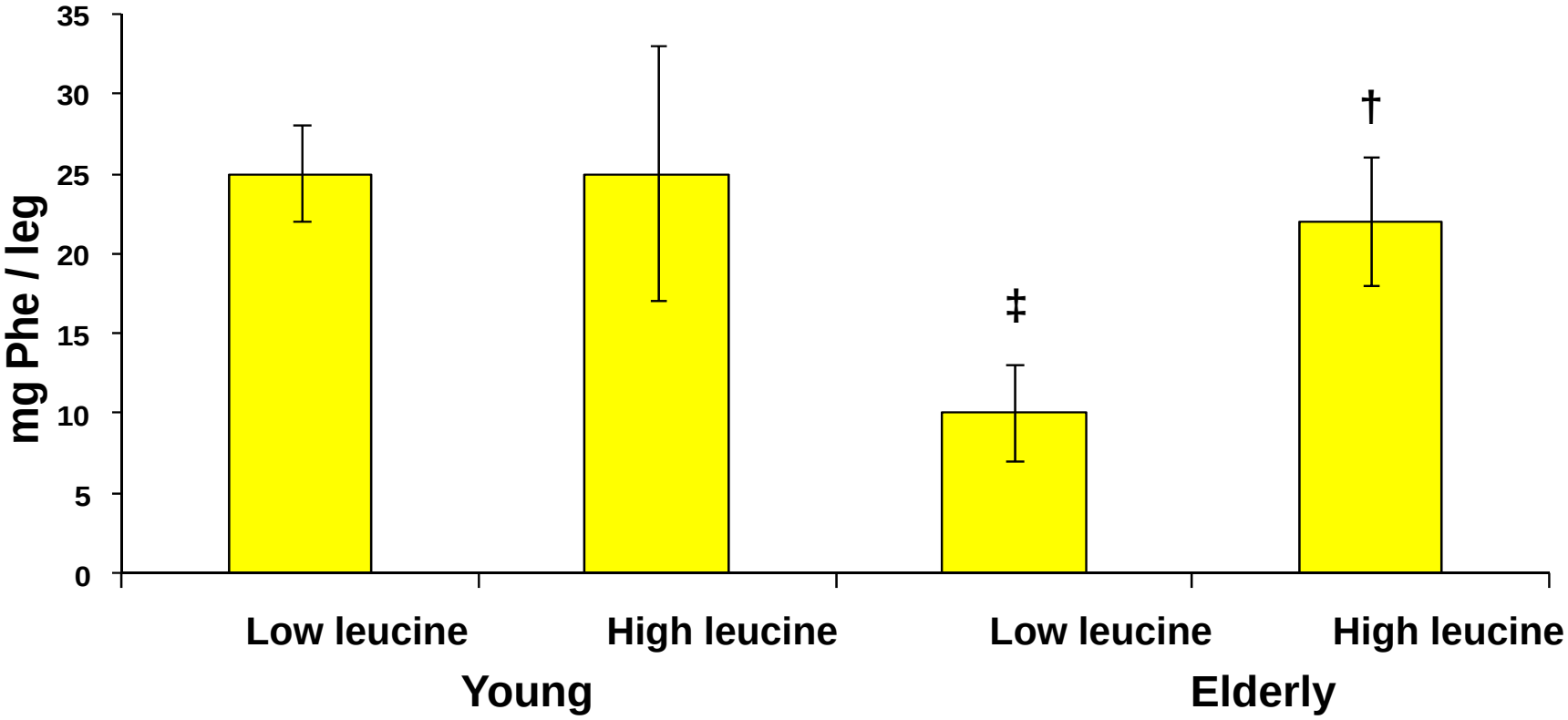
Katsanos CS et al. Am J Clin Nutr 82: 1065-73, 2005

Specific Role of Leucine as a Stimulator of Muscle Protein Synthesis

Composition of EAA Mixture: Effect on Muscle Protein Synthesis



Dosage = 7 gm of each mixture; low leucine = 26% leucine; high leucine = 40% leucine.

† Significant difference from low leucine (Elderly) ($p<0.05$)

‡ Different from low leucine (Young)

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

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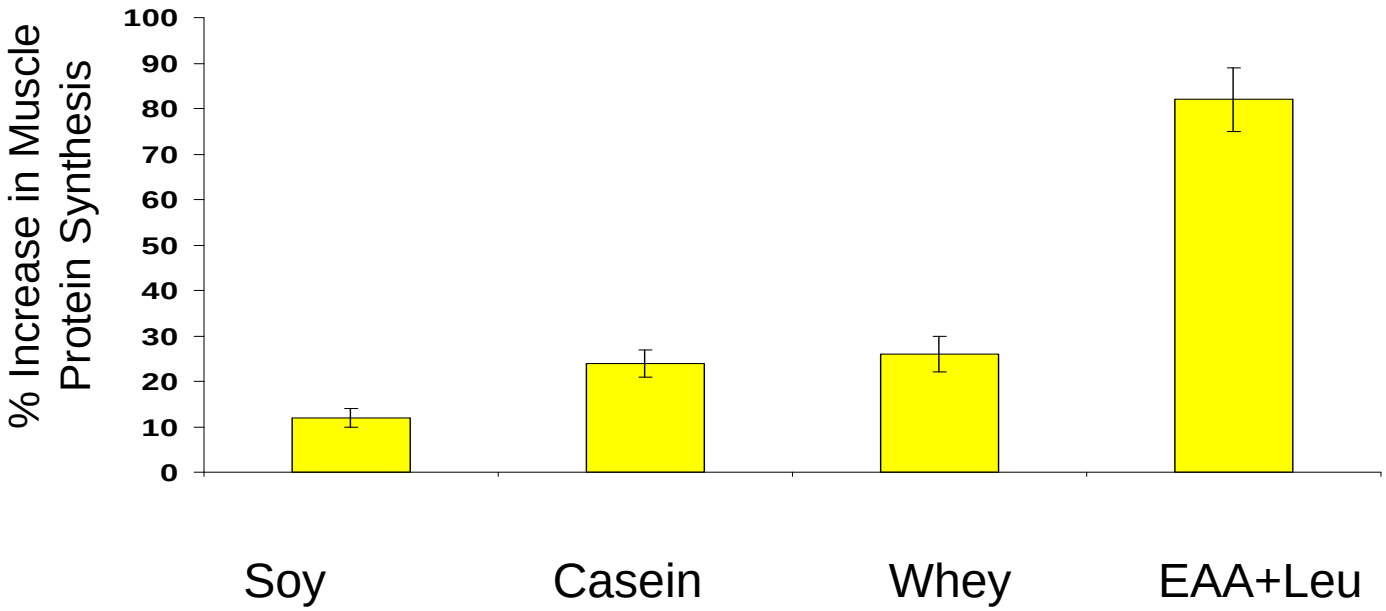
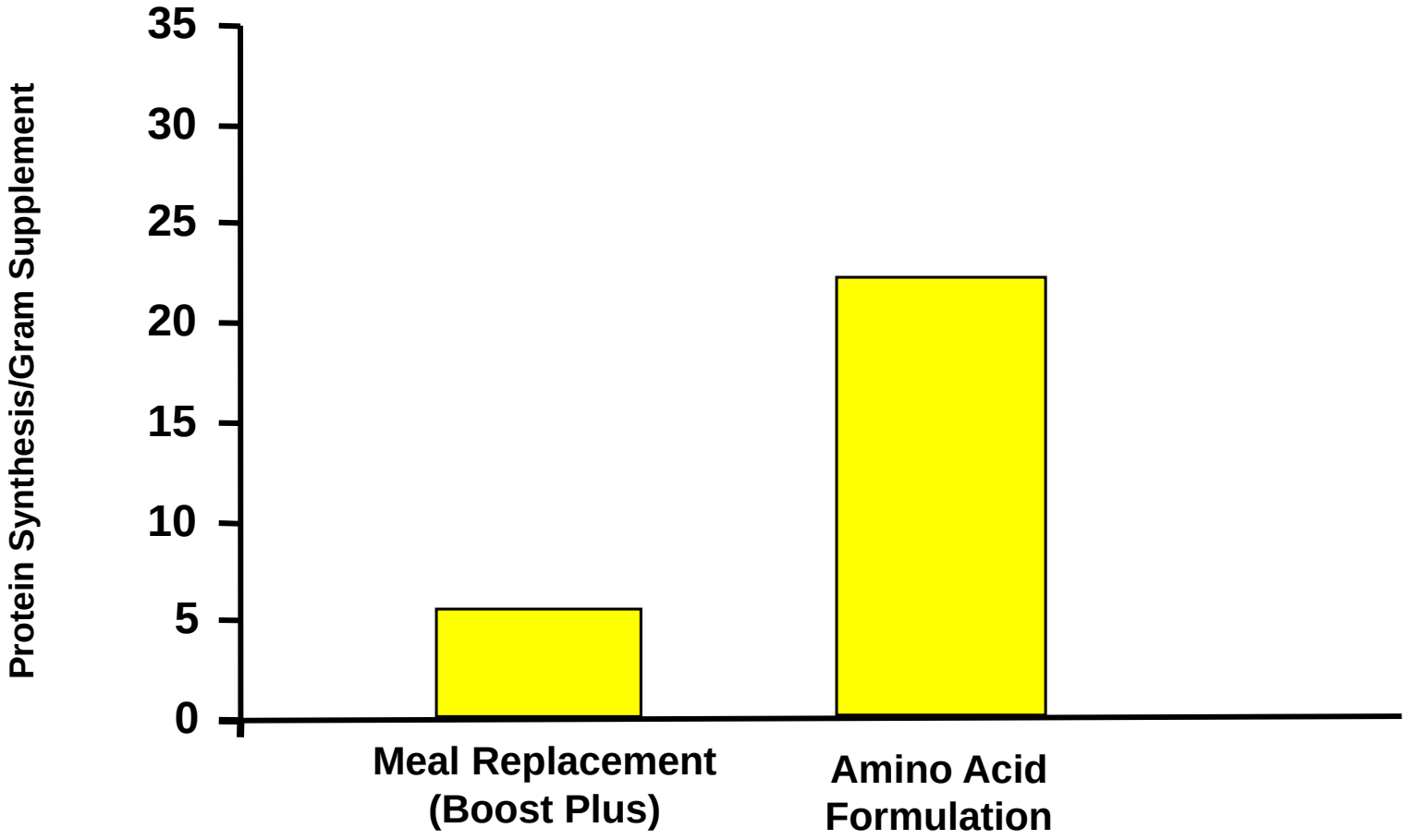
Comparing Anabolic Stimulus (15g)



Amino Acids vs Meal Replacement in the anabolic response of muscle



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Paddon Jones et al. Am J Physiol 2004;286:E321-E325. Am J Physiol 2005;288:E761-E767

Can Supplementation of the Diet with Optimal Profile and dose of EAAs Increase Muscle Mass and Strength in the Eldery?

EAAs Maintain 24 Hour Muscle Protein Synthesis After 10 Days of Bed Rest in Elderly

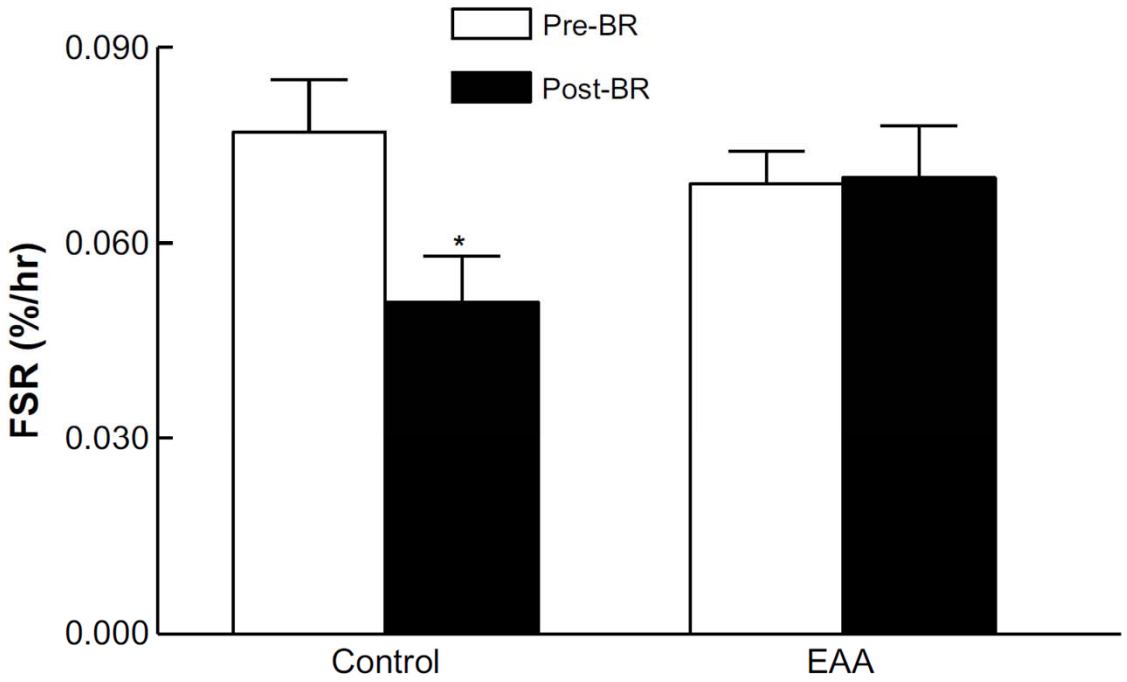

Fig. 1. Twenty-four hour muscle protein synthesis (fractional synthetic rate; FSR) before and after 10 d of bed rest in elderly subjects. Control – ($n = 1110$; placebo drink of non-caloric diet soda); EAA – ($n = 87$; 3 drinks of 15 g/d of amino acids (listed in Table 1)). There were no significant pre-bed rest differences between groups by *t*-test.

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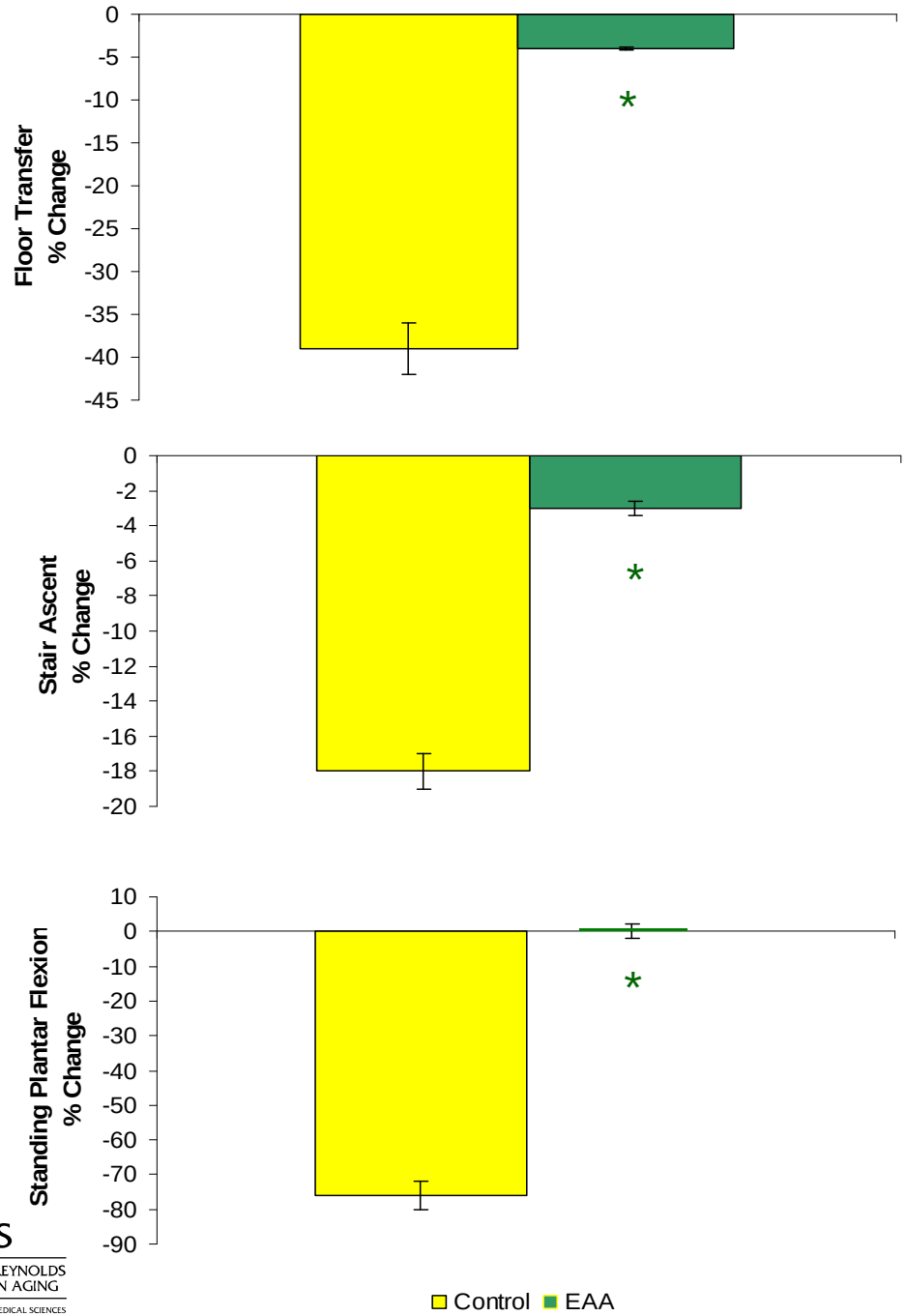
Ferrando et al., Clinical Nutrition 2009; In press.



EAAs Ameliorate the Effect of Bed Rest on Functional Tests in Elderly

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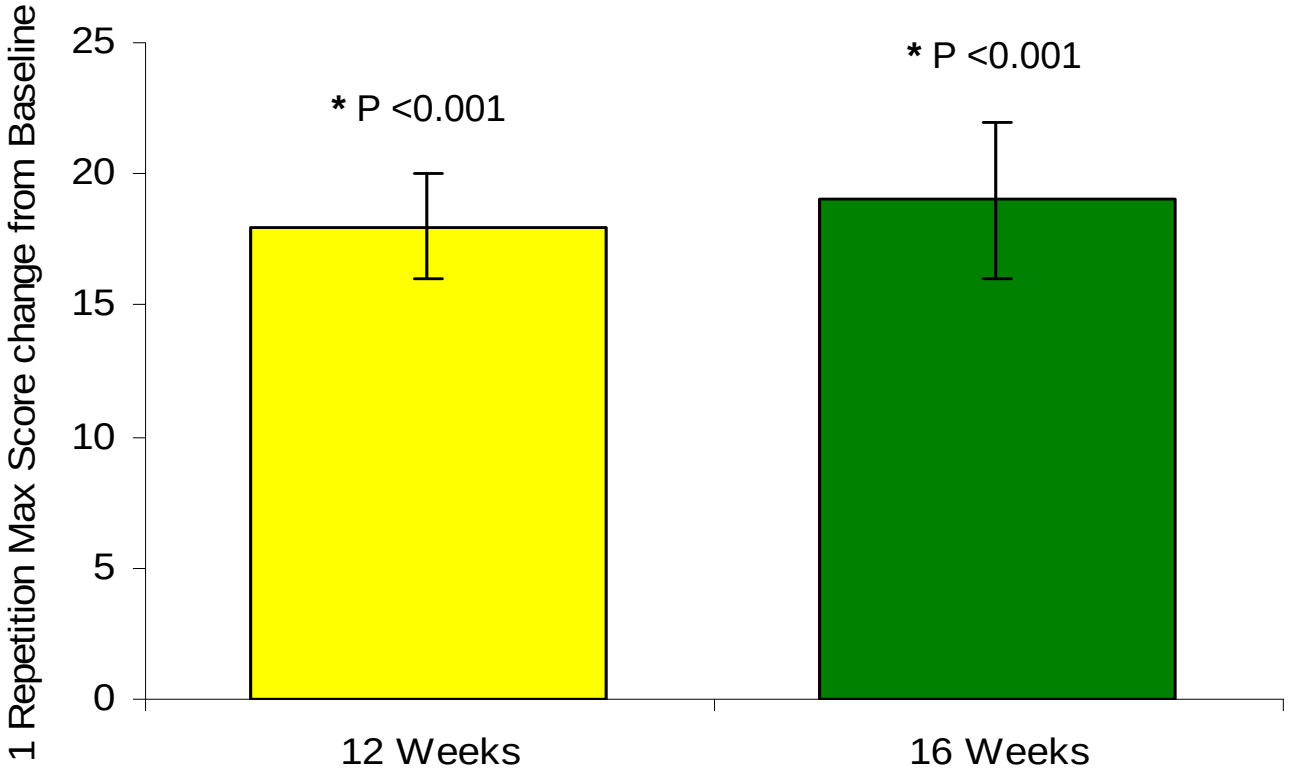
Ferrando et al., Clinical Nutrition 2009; In press.

Effect of EAA Supplementation on Leg Strength in the elderly



Response to 16 Weeks Supplementation with EAAS in Healthy Elderly. 2 x 11 g Between Meals

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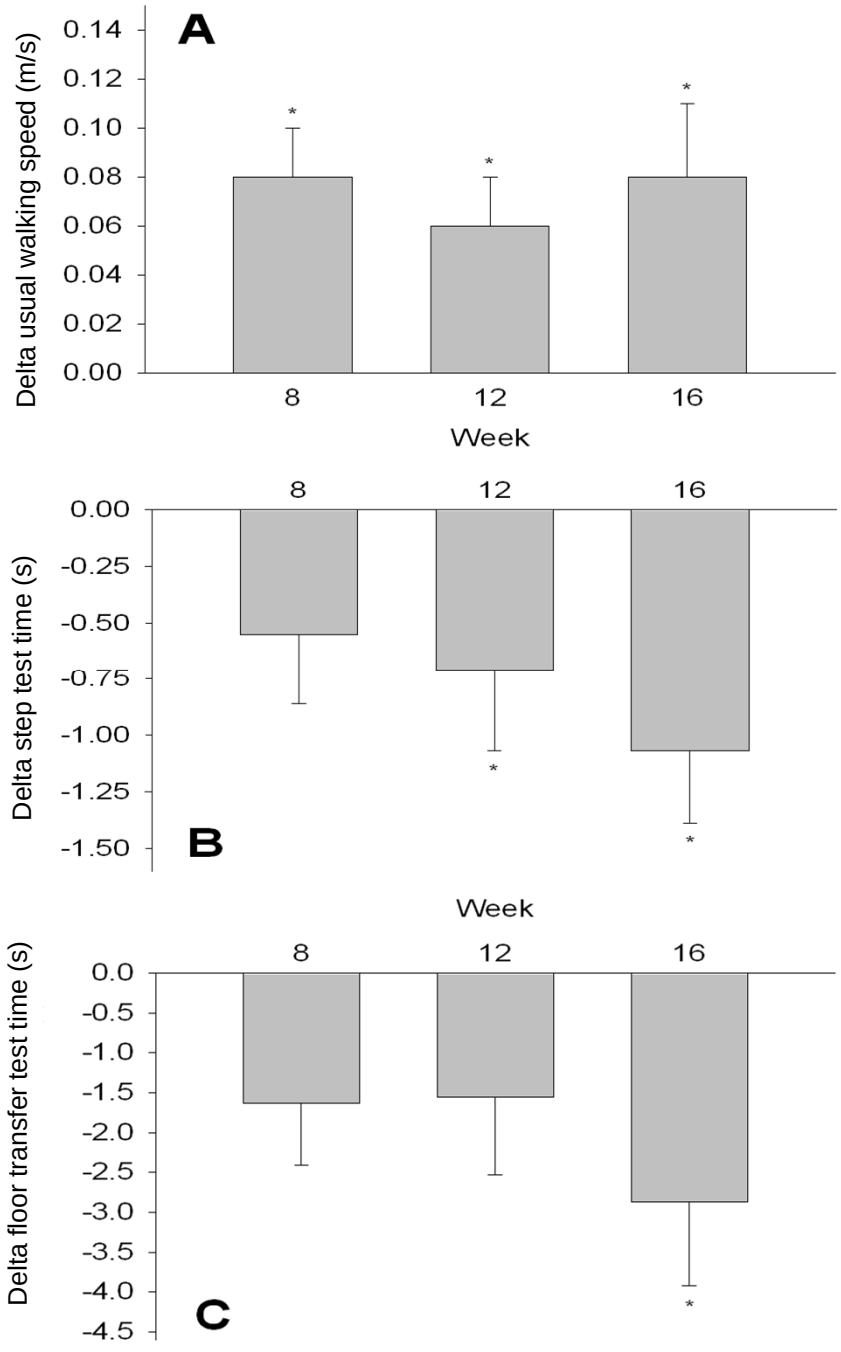
Borsheim et al. Clin Nutr 27:189-195, 2008



Effect of EAA Supplement on Functional Tests

Borsheim et al. Clin Nutr 27:189-195, 2008

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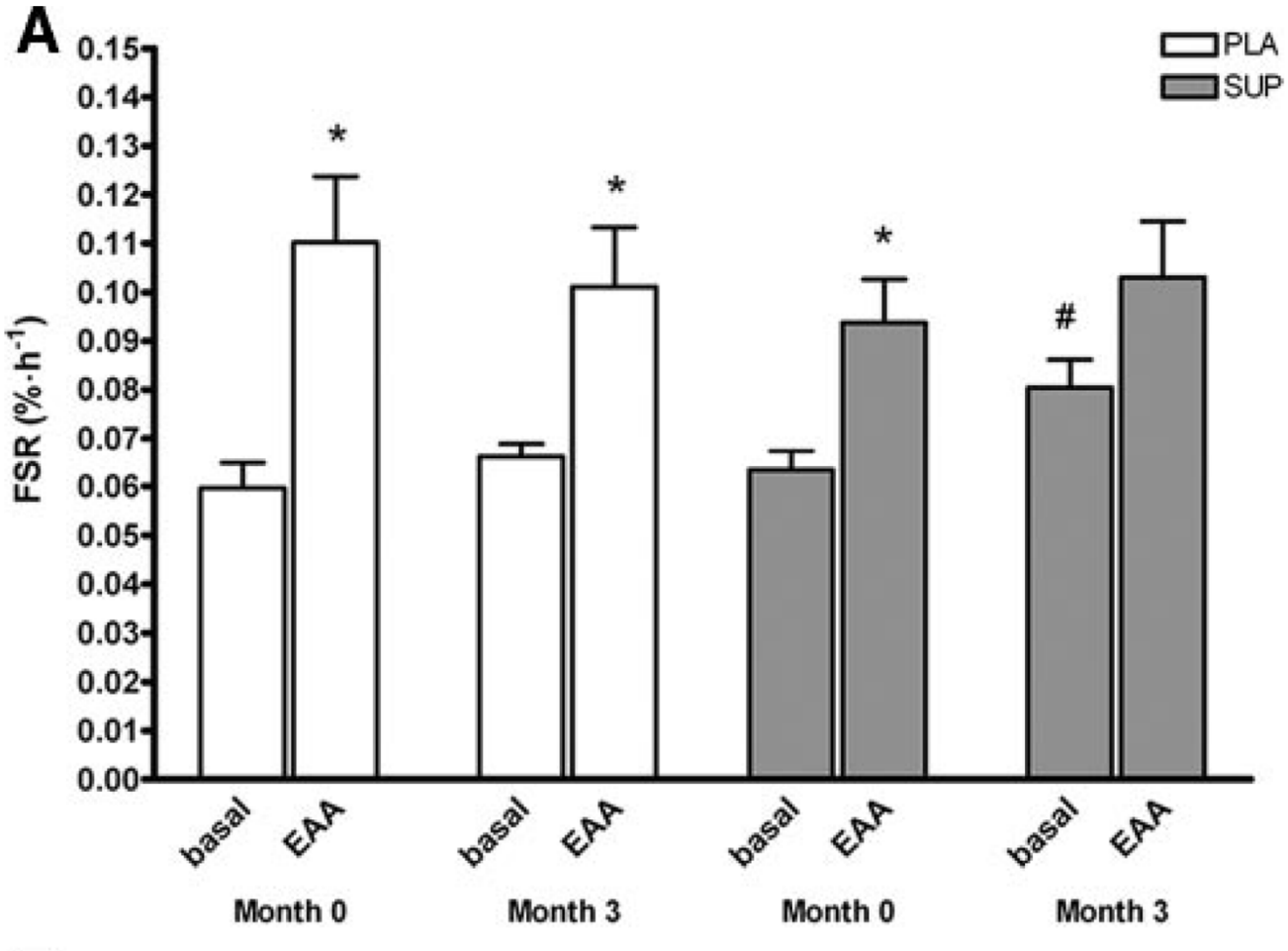
EAA intake and muscle protein synthesis



15 gram EAA supplement daily for 3 months

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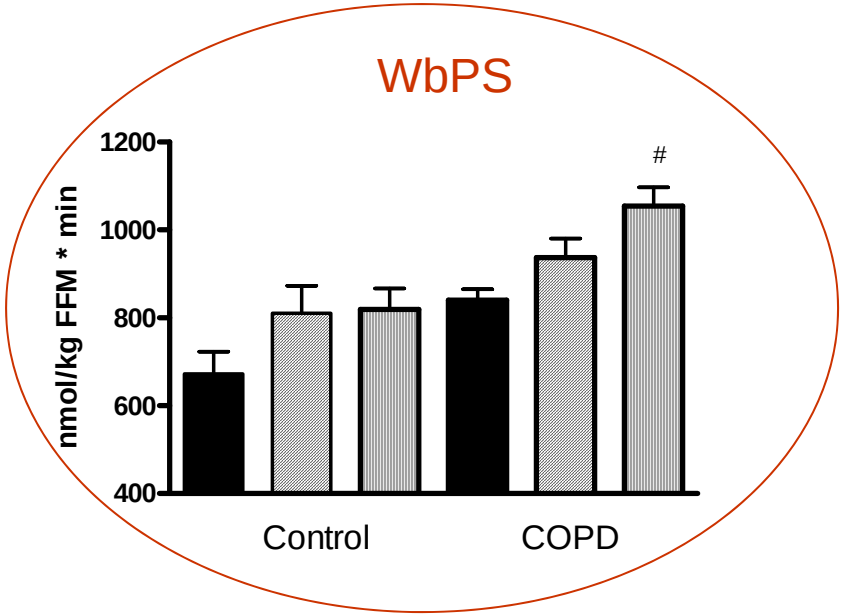
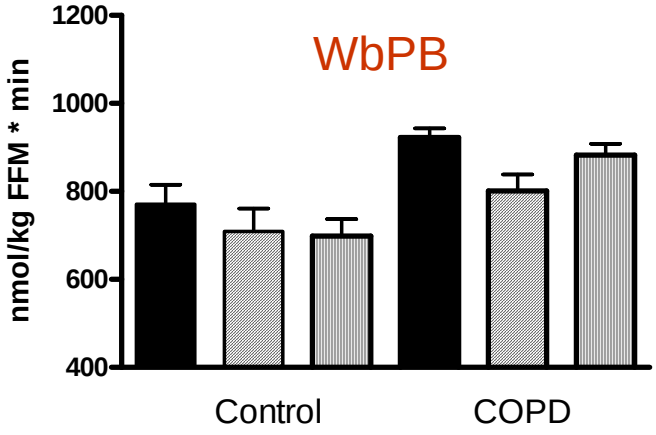
Dillon EL et al J Clin Endocrinol Metab 2009;94:1630-7

Co-ingestion of BCAA and protein increases Protein synthesis only in COPD

- Postabs Control
- Soy control
- Soy + BCAA control
- Postabs COPD
- Soy COPD
- Soy BCAA



Sign group-by-protein interaction for the change in WbPS ($p<0.05$)



Group-by-protein interaction for the change in WbPb ($P=0.07$)

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Engelen MP et al. Am J Clin Nutr 2007;85:431-9

EPA+DHA supplementation on muscle function in elderly with COPD

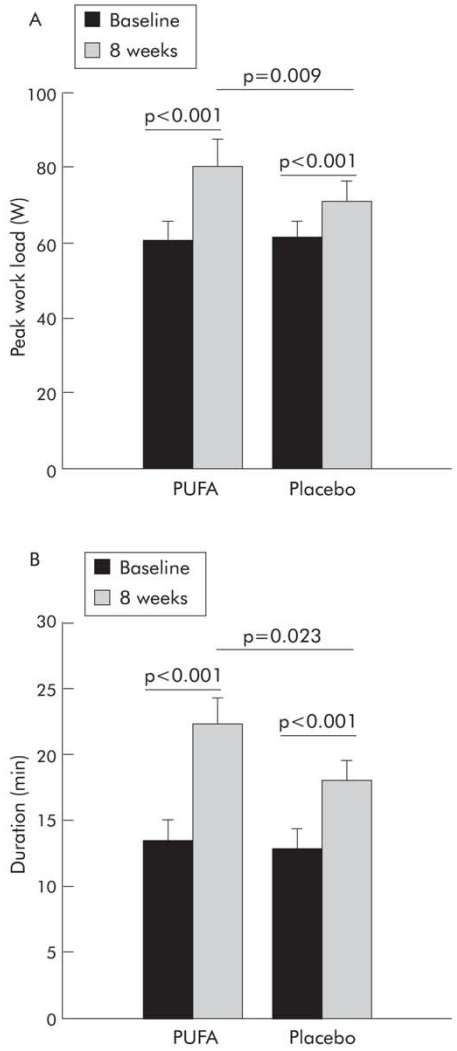

Figure 2 (A) Peak workload. The increase in peak workload during the incremental bicycle ergometry test was higher in patients receiving PUFA than in patients receiving placebo during an 8 week rehabilitation programme (mean difference 9.7 W (95% CI 2.5 to 17.0), p=0.009). (B) Duration. The increase in duration of the submaximal bicycle ergometry test was higher in patients receiving PUFA than in patients receiving placebo during an 8 week rehabilitation programme (mean difference 4.3 min (95% CI 0.6 to 7.9); p=0.023). Data are presented as mean (SE). Within group changes were tested with the paired *t* test between groups by linear regression (p<0.05).

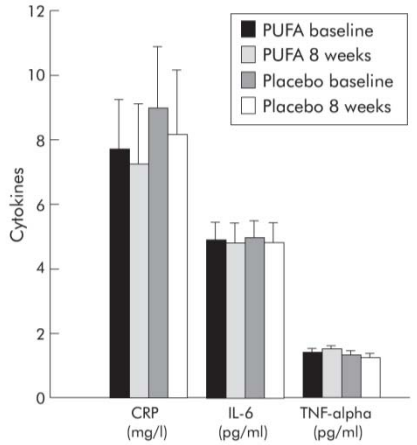

Figure 3 Inflammatory markers. No changes were seen in C-reactive protein (CRP), interleukin-6 (IL-6), or tumour necrosis factor-α (TNF-α) after 8 weeks of either PUFA or placebo in combination with rehabilitation. Data are presented as mean (SE) change. Within group changes were tested with the paired *t* test, between groups by linear regression (p<0.05).

No change in inflammatory markers!

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Broekhuizen R et al. Thorax 2005;60:376-82

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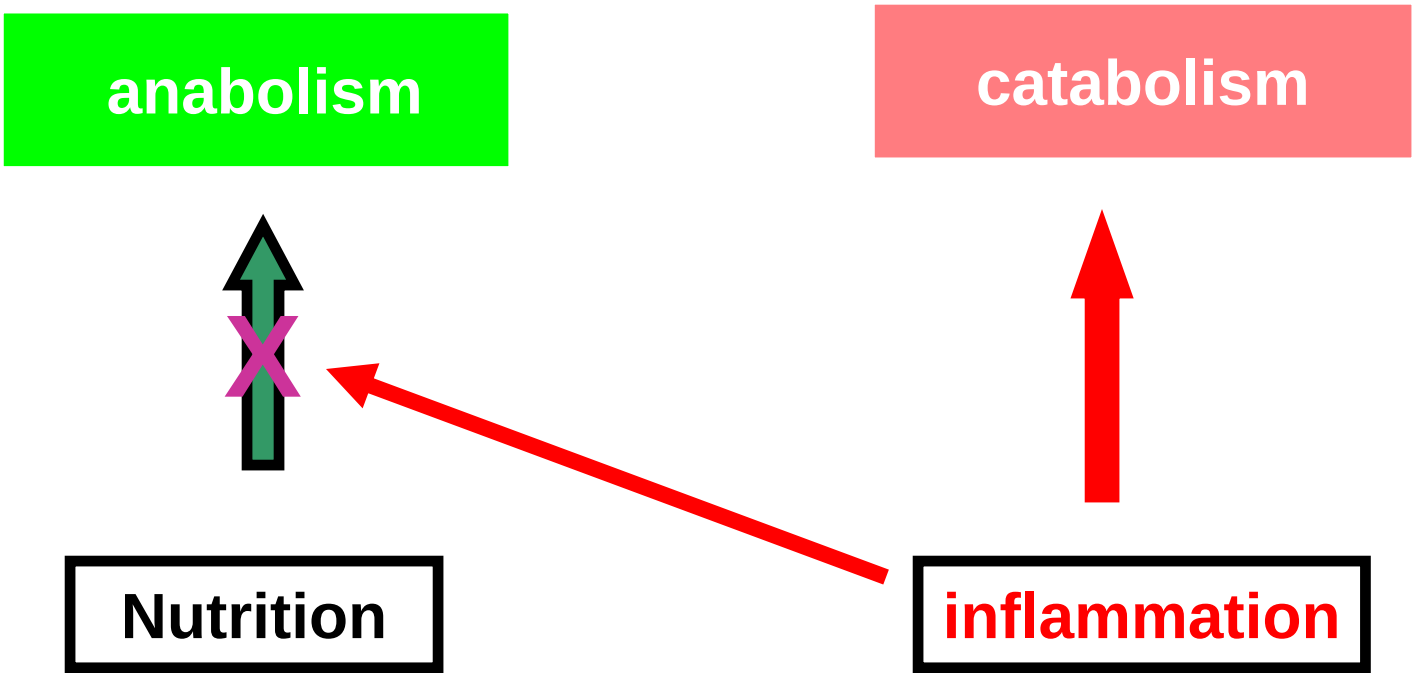
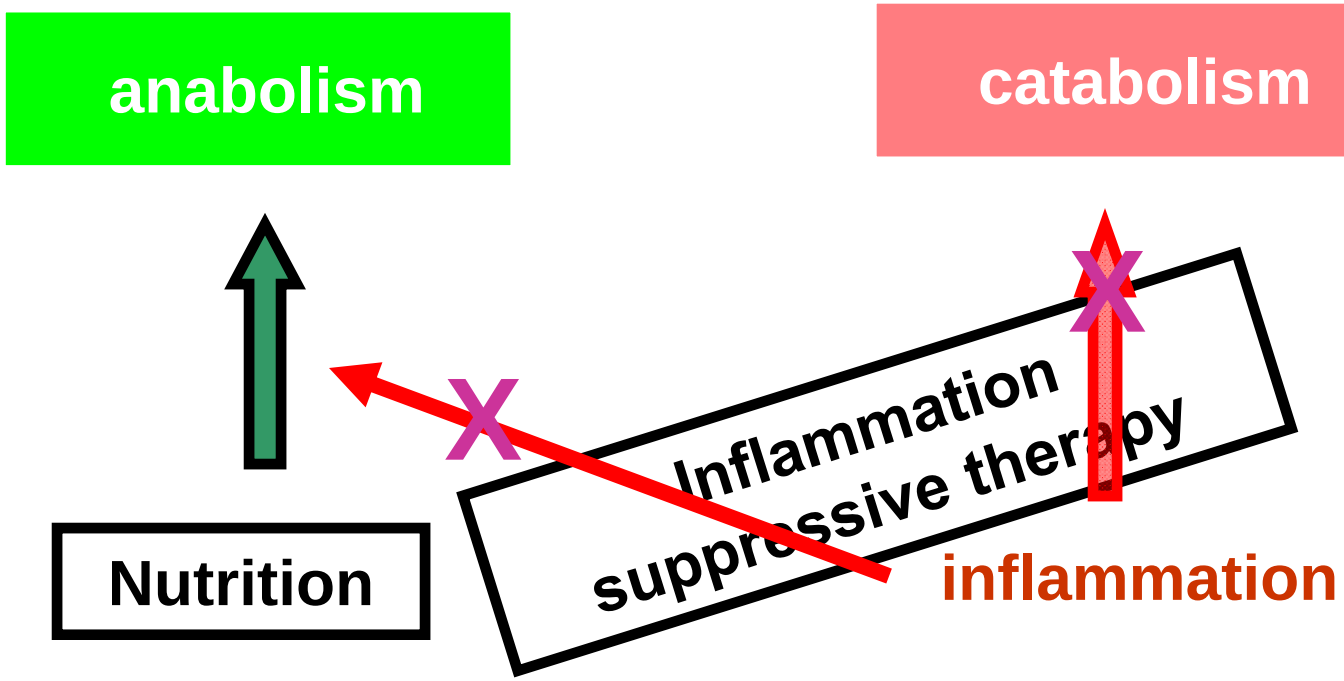
Hypothesis: Non-response to feeding when inflammation is present

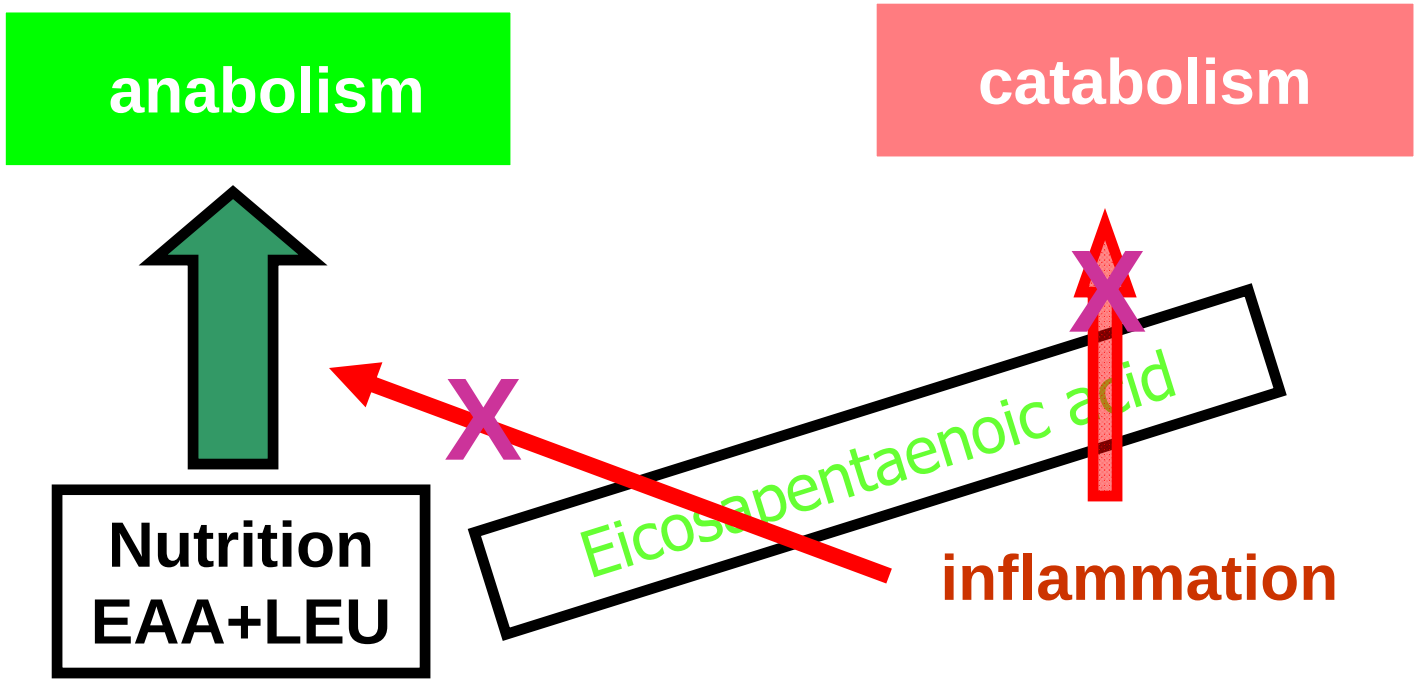


Non-response to feeding when inflammation is present: Hypothesis



Stimulation of PS + attenuation of PB needs to be obtained simultaneously before protein anabolism and thus gain in muscle mass will be achieved !!

Non-response to feeding when inflammation is present: Hypothesis



Stimulation of PS + attenuation of PB needs to be obtained simultaneously before protein anabolism and thus gain in muscle mass will be achieved !!

Eicosapentaenoic acid (EPA)

- Eicosapentanoic acid (EPA) is one of the few agents capable to suppress the generation of pro-inflammatory cytokines
  - one of the primary ω-3 fatty acids found in fish oils
  - is able to attenuate protein degradation in cancer cachexia by decreasing the acute phase response

Mayer, AJRCCM 2003. Wigmore, Clin Sci 1997

Amino Acids Supplements

- To preserve / gain peripheral muscle mass
  - Protein intake and source needs to be optimal (1.5 - 2 ?? g/kg bw)
  - Essential Amino acid supplementation with high Leucine or comparable composition
- Combination therapy to simultaneously attenuate muscle protein degradation and stimulate protein synthesis
  - Optimal level and composition of
    - protein and amino acids (ie high LEU)
    - Anti-inflammation agents (ie EPA at least 2000 mg/day)