



THE ROLE OF PROTEIN IN MUSCLE HEALTH

Module 3

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CELLULAR MECHANISMS BEHIND MUSCLE LOSS



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INTRODUCTION

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INTRODUCTION

Muscle protein turnover

- Skeletal muscle is a highly plastic tissue.¹
- Muscle proteins have a relatively slow turnover (1.5% per day).¹
- **Net protein balance (NPB)** is the difference between **muscle protein synthesis (MPS)** and **muscle protein breakdown (MPB)**.²
- Older adults lose up to 1% per year of muscle mass and up to 3% per year of muscle strength.³

DID YOU KNOW?

In an 80 kg adult, roughly 500 g of muscle tissue are broken down and rebuilt every day—thanks to a constant turnover daily rate of around 1.5%.



1. Janssen TAH, et al. From molecular to physical function: The aging trajectory. Curr Res Physiol. 2024 Dec 16;8:100138.
 2. McKendry J, et al. Resistance Exercise, Aging, Disuse, and Muscle Protein Metabolism. Compr Physiol. 2021 Jun 30;11(3):2249-2278.
 3. Breen L et al. Skeletal muscle protein metabolism in the elderly: Interventions to counteract the "anabolic resistance" of ageing. Nutr Metab (Lond). 2011;8(1):68.

INTRODUCTION

Key factors influencing muscle mass

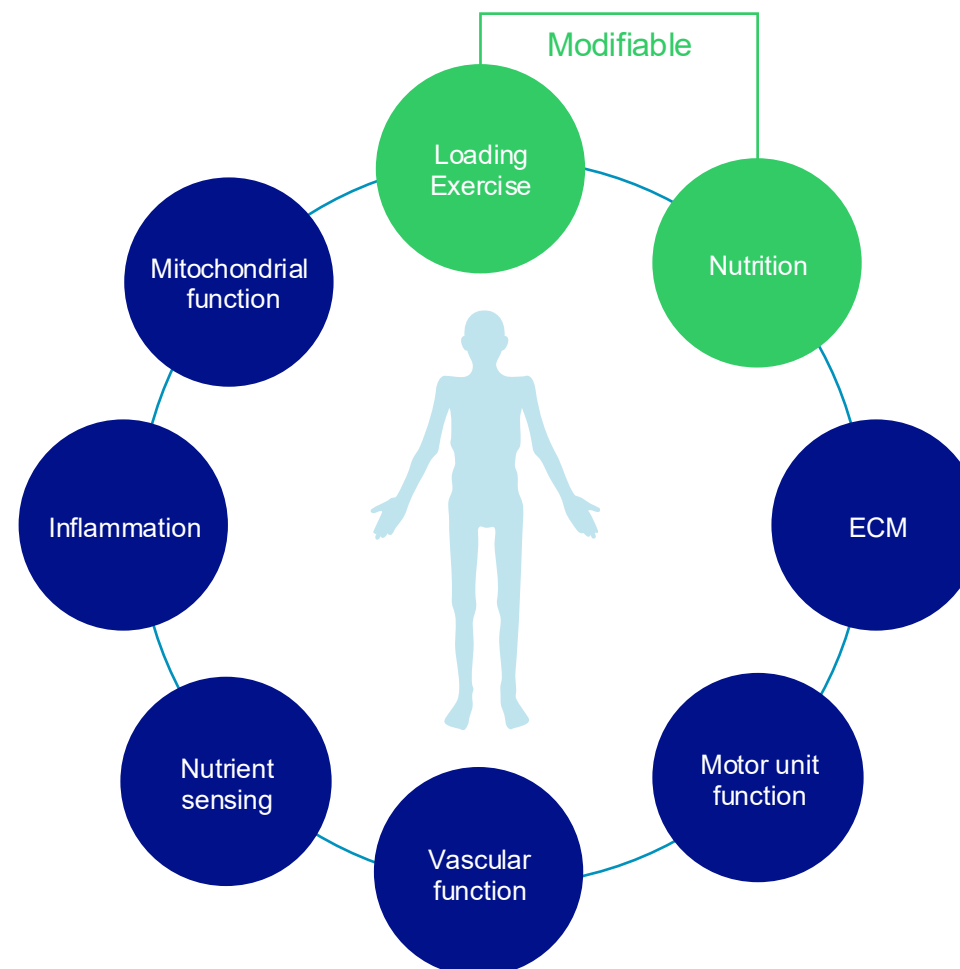
Muscle mass is regulated by the balance between anabolic and catabolic signals—while anabolic stimuli promote muscle growth and maintenance, catabolic signals drive muscle breakdown and atrophy.¹

ANABOLIC STIMULI

- Protein intake
- Exercise
- Hormones (e.g., Insulin, IGF-1)

CATABOLIC STIMULI

- Fasting/starvation
- Low carbohydrate availability
- Bed rest
- Hormones (e.g., cortisol)
- Sepsis and systemic inflammation



More information in Module 2.



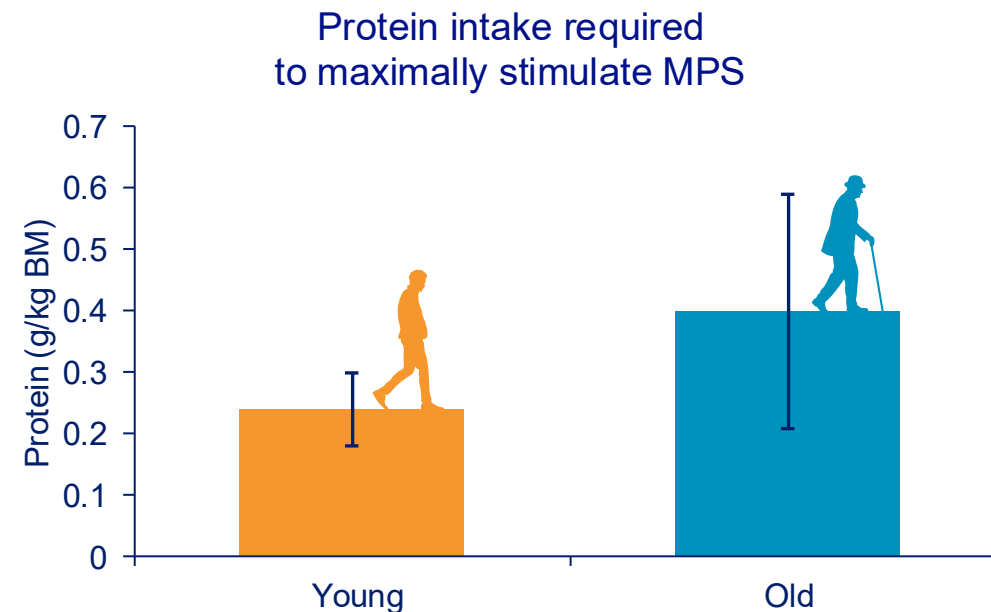
INTRODUCTION

Impact of anabolic resistance on protein requirements

Older adults require **higher per meal protein intakes** to effectively stimulate muscle protein synthesis (MPS) compared to younger individuals.¹

DID YOU KNOW?

Older adults need almost twice as much protein intake to achieve a comparable MPS response.¹



Representation of relative protein intake per kg body mass (BM) per meal required to maximally stimulate MPS in young individuals and older individuals. Mean $\pm$ CI. Figure based on data described in ¹

1. Moore DR, et al. Protein ingestion to stimulate myofibrillar protein synthesis requires greater relative protein intakes in healthy older versus younger men. J Gerontol A Biol Sci Med Sci. 2015 Jan;70(1):57-62.

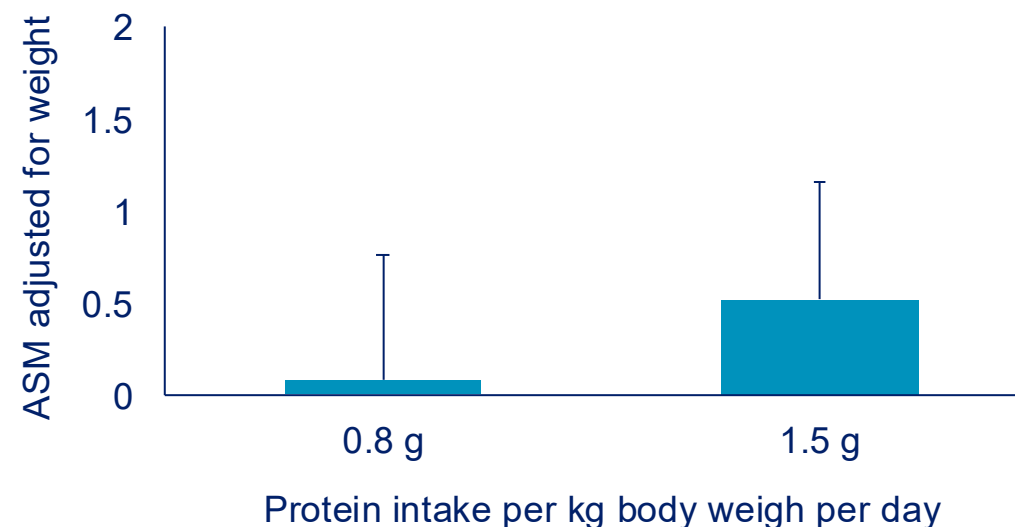
INTRODUCTION

Protein dose effect on muscle mass in older adults

Higher protein intake increases muscle mass gain and improves physical performance.¹

Elderly subjects supplemented with progressively higher protein doses (0.8, 1.2 or **1.5 g/kg/d**) showed significant **increases in muscle mass and gait speed** in the group receiving the highest dose.¹

Protein intake above ~1.6 g/kg/day during resistance training exercise does not yield additional improvements in muscle mass or strength in healthy adults.²



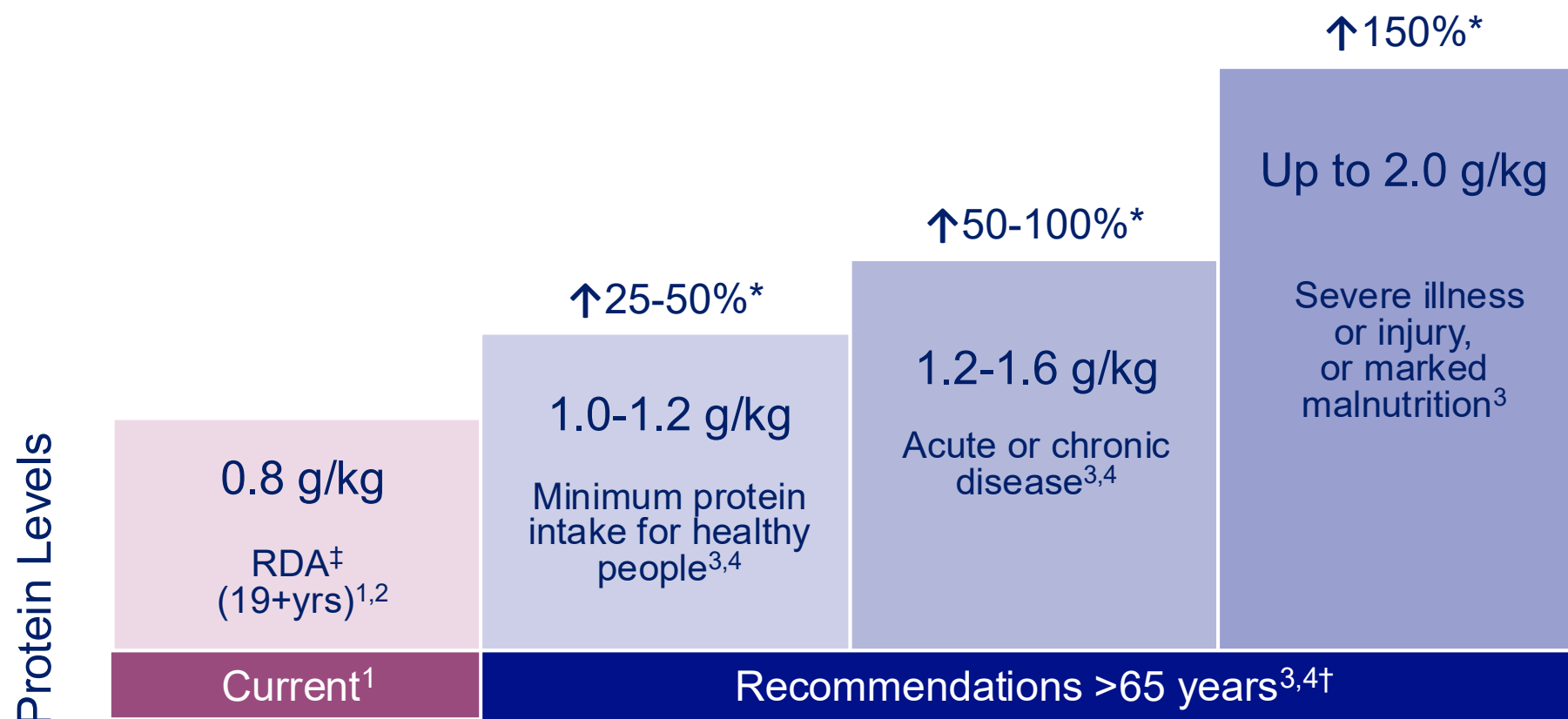
Impact of protein intake on appendicular skeletal muscle mass (ASM) in different groups after 12 weeks of intervention.
p=0.036. Figure based on data described in ¹



1. Park Y, et al. Protein supplementation improves muscle mass and physical performance in undernourished prefrail and frail elderly subjects: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr. 2018 Nov 1;108(5):1026-1033.
2. Morton RW, et al. A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. Br J Sports Med. 2018 Mar;52(6):376-384.

INTRODUCTION

Recommendations from working groups call for higher protein intakes in older adults



* Increased above current protein RDA.¹
 † Older people with severe kidney disease who are not on dialysis may need to limit protein intake.
 ‡ RDA: recommended dietary allowance.

1. DRIs for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). National Academy of Sciences. Institute of Medicine, 2005.
 2. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion on dietary reference values for protein. EFSA Journal. 2012 Feb;10(2):2557.
 3. Bauer J et al. Evidence-based Recommendations for Optimal Dietary Protein Intake in Older People: A Position Paper From the PROT-AGE Study Group. JAMDA. 2013;14:542-59.
 4. Deutz NEP et al. Protein intake and exercise for optimal muscle function with aging: Recommendations for the ESPEN Expert Group. Clinical Nutrition. Clin Nutr. 2014; 33(6): 929-36.

Summary



- ✓ Nutrition and exercise are modifiable life-style factors that significantly impact on muscle health.
- ✓ **Older adults require higher protein intake** than younger adults to effectively stimulate muscle protein synthesis (MPS).
- ✓ Higher protein intake in older adults supports muscle mass gain and improves physical performance.
- ✓ **ESPEN** recommendation: **1.2–1.5 g/kg body weight daily** for malnourished or at-risk older adults; higher intake recommended for severe illness or injury.



IMPORTANCE OF ESSENTIAL AMINO ACIDS AND LEUCINE IN MUSCLE CELLS

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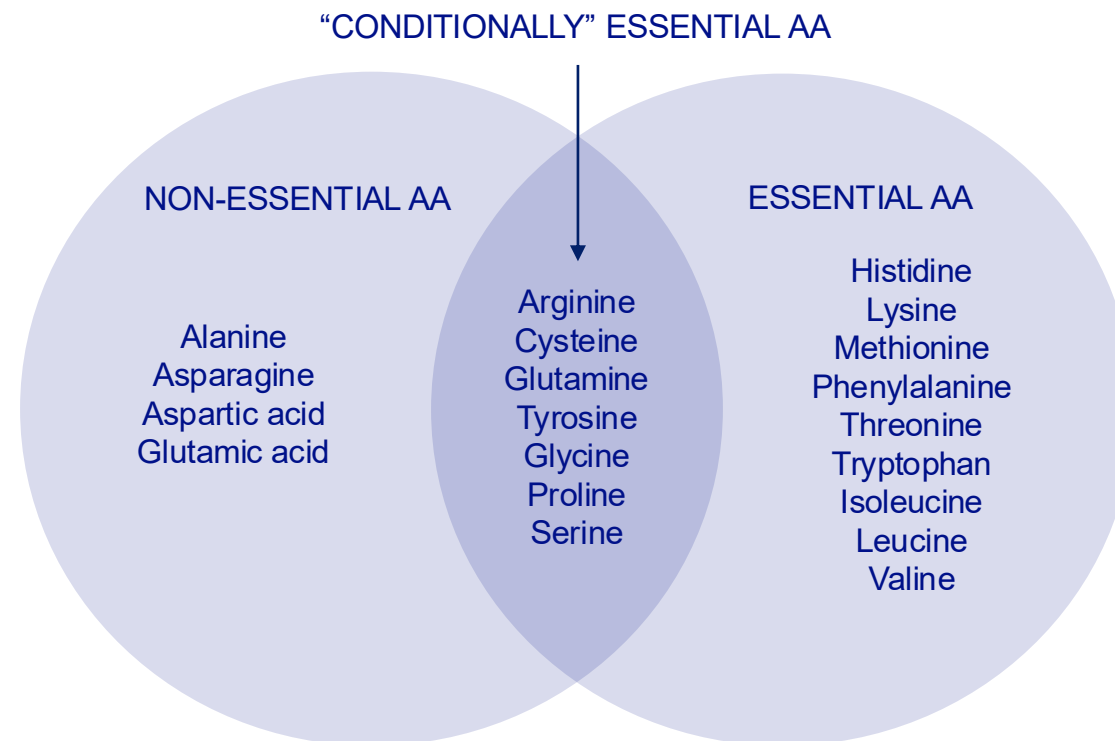
[2.8. Summary](#)



IMPORTANCE OF ESSENTIAL AMINO ACIDS AND LEUCINE IN MUSCLE CELLS

Essential vs. non-essential amino acids

- **Essential AA** are amino acids that the human body cannot synthesize on its own and must therefore be obtained through diet.¹
- **Non-essential AA** are amino acids that the body can synthesize on its own.¹
- **Conditionally essential AA** are non-essential amino acids that are hypothesized to become essential under specific conditions, such as during severe illness, injury, or infancy (rapid growth), because the body may be unable to produce enough to meet the increased demand.¹



Essential amino acids recommendation



- In 2007, the WHO offered specific recommendations for essential amino acids for **healthy adults**.¹
- These values are based on the assumption of a **normal nitrogen balance**, indicating that the intake of these amino acids is sufficient to meet the body's needs.¹

Amino acid protein	mg/kg per day
Histidine	10
Isoleucine	20
Leucine	39
Lysine	30
Methionine + cysteine	15
Methionine	10
Cysteine	4
Phenylalanine + tyrosine	25
Threonine	15
Tryptophan	4
Valine	26
Total essential amino acids	184

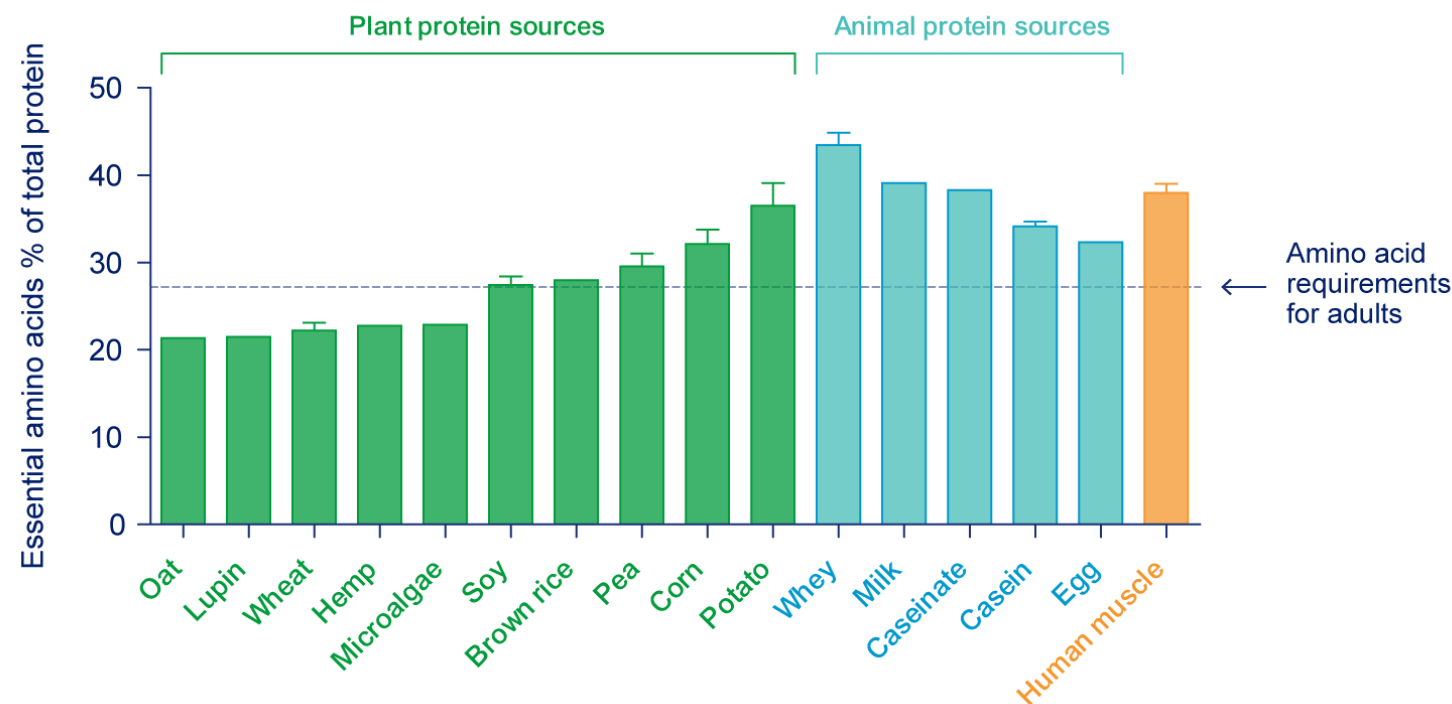


1. Joint FAO/WHO/UNU Expert Consultation on Protein and Amino Acid Requirements in Human Nutrition (2002 : Geneva, Switzerland), Food and Agriculture Organization of the United Nations, World Health Organization & United Nations University. (2007). Protein and amino acid requirements in human nutrition : report of a joint FAO/WHO/UNU expert consultation. World Health Organization.

IMPORTANCE OF ESSENTIAL AMINO ACIDS AND LEUCINE IN MUSCLE CELLS

Essential amino acid content of different proteins

- All animal-based proteins exceed the WHO/FAO/UNU essential amino acid (EAA) requirements.¹
- **Whey protein has the highest EAA content** among all protein sources analyzed: 43% of total protein.¹
- Plant-based proteins generally have lower EAA contents.¹



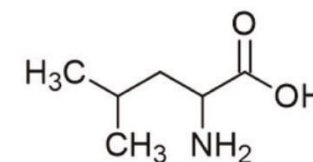
Essential amino acid contents of different protein sources.¹

1. Gorissen SHM, et al. Protein content and amino acid composition of commercially available plant-based protein isolates. Amino Acids. 2018 Dec;50(12):1685-1695.



Impact of essential amino acids on muscle protein synthesis

- Not all amino acids foster muscle protein synthesis (**MPS**) in the same way.
- **Essential amino acids** can **stimulate MPS** while nonessential amino acids cannot.¹
- Among EAAs, branched chain amino acids (**BCAAs**) i.e., leucine, isoleucine and valine, leucine is the key AA that is capable of **activating molecular pathways** that promote MPS.²



Leucine

Molecular structure of leucine.³



1. Smith K, et al. Effects of flooding amino acids on incorporation of labeled amino acids into human muscle protein. Am J Physiol. 1998 Jul;275(1):E73-8.

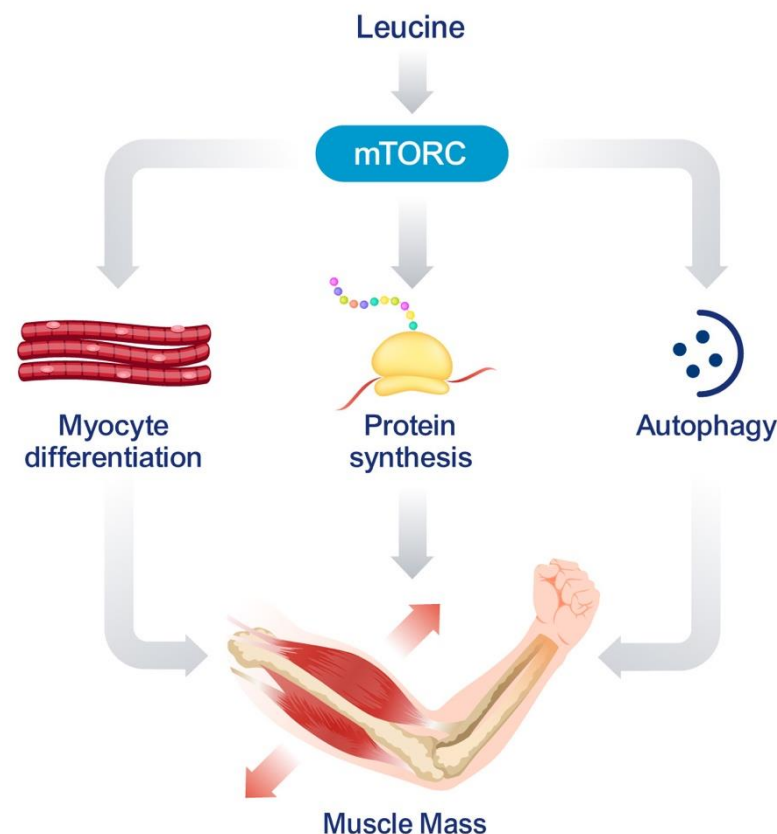
2. Kaspy MS, et al. The effects of branched-chain amino acids on muscle protein synthesis, muscle protein breakdown and associated molecular signalling responses in humans: an update. Nutr Res Rev. 2024 Dec;37(2):273-286.

3. Choi BH, et al. The role of BCAA metabolism in metabolic health and disease. Exp Mol Med. 2024 Jul;56(7):1552-1559. doi: 10.1038/s12276-024-01263-6. Epub 2024 Jul 2.

IMPORTANCE OF ESSENTIAL AMINO ACIDS AND LEUCINE IN MUSCLE CELLS

Impact of leucine in muscle protein synthesis

- Among BCAAs, **leucine** is the **most potent** stimulator of MPS.¹
- Leucine activates the mTOR synthesis pathway that in turn **stimulates anabolic processes** and inhibits catabolic ones, like autophagy, resulting in **increased muscle mass**.²



Leucine supplementation induce muscle growth through mTOR pathway. Figure based on data described in ³



1. Ely JA, et al. A focus on leucine in the nutritional regulation of human skeletal muscle metabolism in ageing, exercise and unloading states. Clin Nutr. 2023 Oct;42(10):1849-1865.

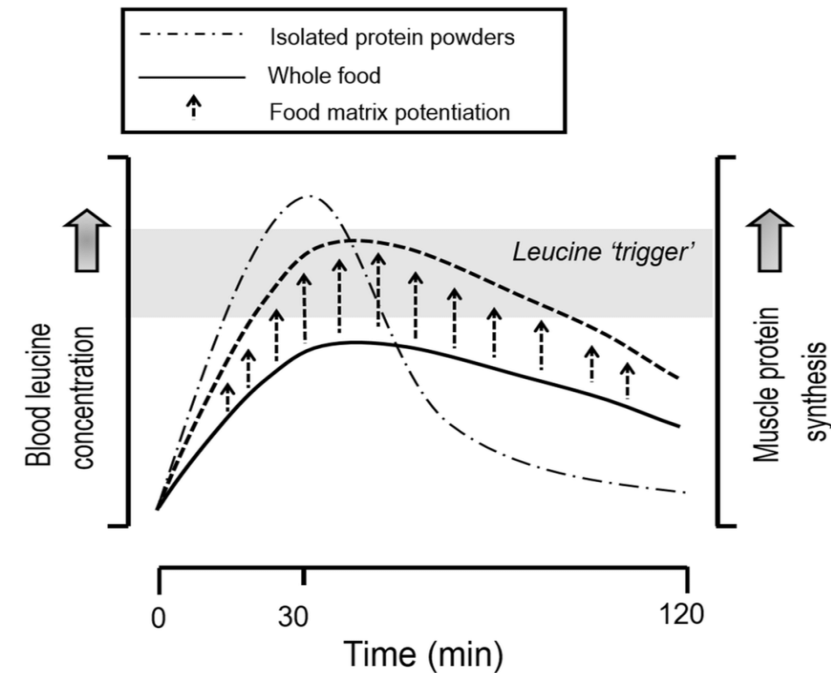
2. Wolfson RL et al. The Dawn of the Age of Amino Acid Sensors for the mTORC1 Pathway. Cell Metab. 2017;26(2):301-9.

3. Torre-Villalvazo I, et al. Protein intake and amino acid supplementation regulate exercise recovery and performance through the modulation of mTOR, AMPK, FGF21, and immunity. Nutr Res. 2019 Dec;72:1-17.

IMPORTANCE OF ESSENTIAL AMINO ACIDS AND LEUCINE IN MUSCLE CELLS

“Leucine trigger” hypothesis

- Intracellular leucine levels in muscle must reach a certain threshold to activate muscle protein synthesis.¹
- Leucine acts as a "switch" that triggers the process of muscle protein synthesis.¹
- High quality proteins rich in leucine such as **whey protein** are more effective in stimulating muscle protein synthesis because they reach the trigger threshold.¹
- Proteins with lower leucine content may not effectively activate muscle protein synthesis.¹



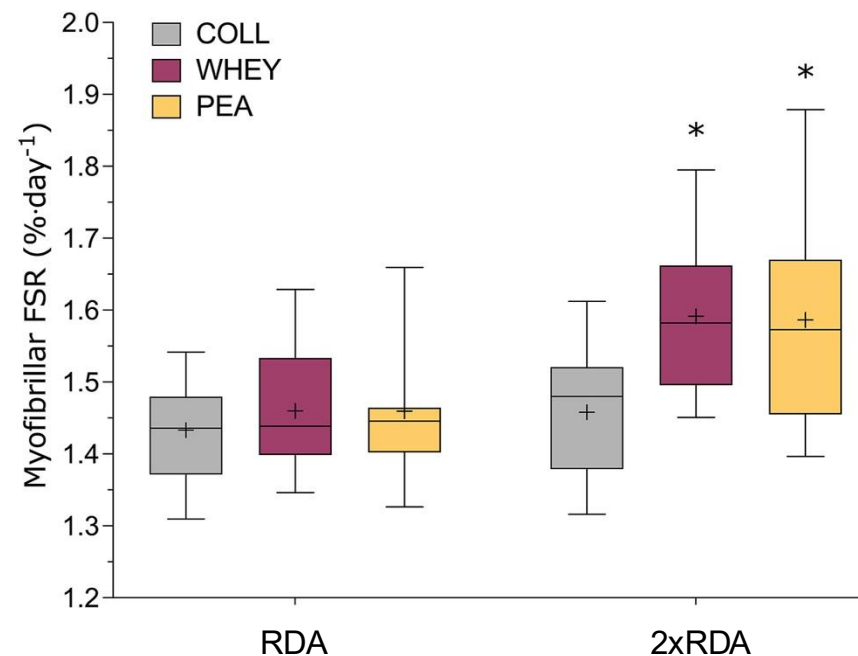
The “leucine trigger” hypothesis.¹

1. Burd NA, et al. Food-First Approach to Enhance the Regulation of Post-exercise Skeletal Muscle Protein Synthesis and Remodeling. Sports Med. 2019 Feb;49(Suppl 1):59-68.

IMPORTANCE OF ESSENTIAL AMINO ACIDS AND LEUCINE IN MUSCLE CELLS

Whey Protein and MPS in Older Adults

- In older adults, the MPS response to protein intake is reduced.¹
- High-quality protein supplements, such as whey and pea protein, stimulate MPS rates in older adults more than recommended daily protein intake (0.8 g/kg/d)² or protein supplements with low leucine content (collagen).¹



Myofibrillar fractional synthetic rate.
 COLL: collagen, RDA: recommended daily allowance. Modified from ¹

1. McKendry J, et al. The effects of whey, pea, and collagen protein supplementation beyond the recommended dietary allowance on integrated myofibrillar protein synthetic rates in older males: a randomized controlled trial. Am J Clin Nutr. 2024 Jul;120(1):34-46.
 2. Rand WM, et al. Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults. Am J Clin Nutr. 2003 Jan;77(1):109-27.

IMPORTANCE OF ESSENTIAL AMINO ACIDS AND LEUCINE IN MUSCLE CELLS

Summary

- ✓ Essential amino acids (EAAs): must be obtained through diet because the body cannot synthesize them.
- ✓ Not all amino acids stimulate muscle protein synthesis (MPS) equally:
 - Branched-chain amino acids (BCAAs) — leucine, isoleucine, valine — activate pathways that promote MPS.
 - **Leucine** is the **most potent** BCAA for **stimulating MPS**.
- ✓ Intracellular leucine must reach a **threshold to trigger MPS** — it acts as a molecular “switch.”
- ✓ Proteins high in leucine (e.g., whey, protein isolates) are more effective at triggering MPS than proteins with lower leucine content.





RELEVANCE OF PROTEIN QUALITY ON MUSCLE HEALTH

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RELEVANCE OF PROTEIN QUALITY ON MUSCLE HEALTH

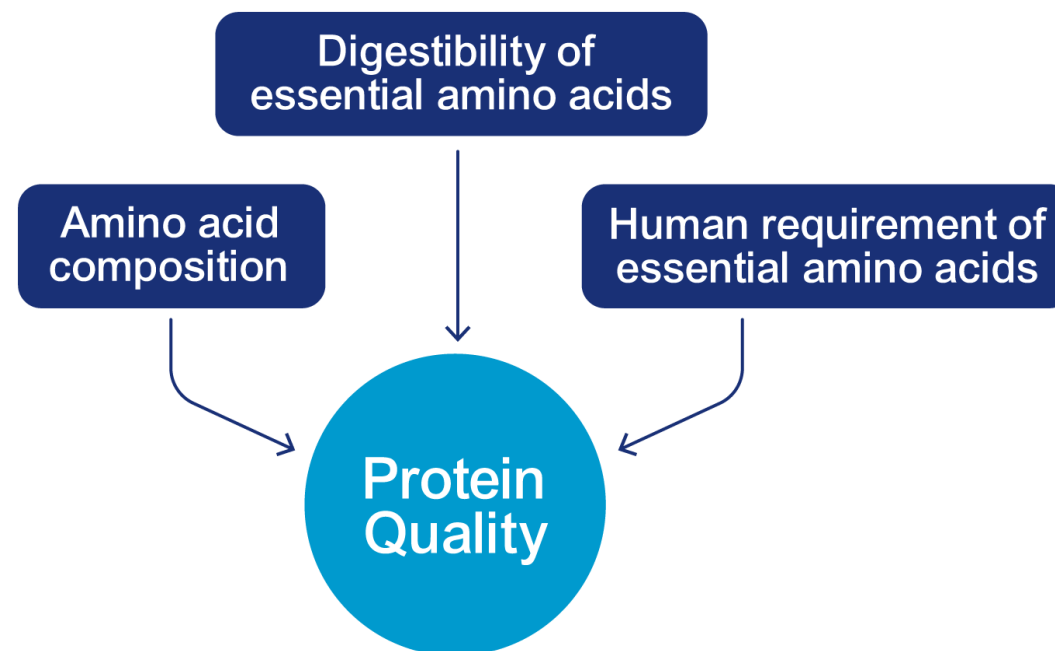
Introduction to protein quality

Protein quality reflects the ability of a protein source to supply **sufficient nitrogen** and all **9 EAAs** required to support various physiological functions in humans.¹

Protein quality is assessed by a protein's ability to supply **EAA**.²

Protein requirements = Quantity (total protein intake) + Quality (EAA content)

Protein quality varies widely among foods, with some lacking sufficient levels of digestible EAAs to fully meet nutritional needs.²



Key determinants of protein quality.²



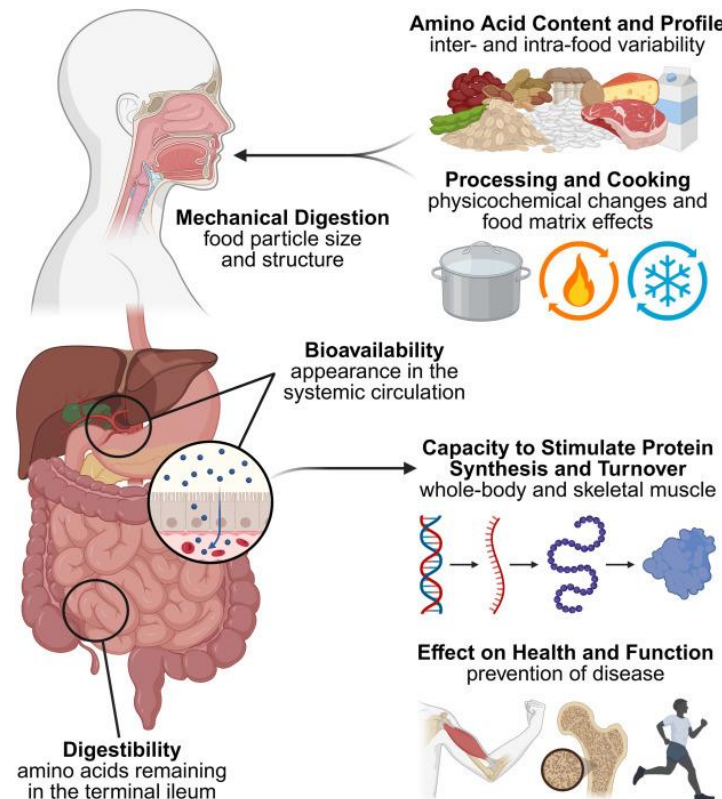
1. Calvez J. Protein quality, nutrition and health. Front Nutr. 2024 May 28;11:1406618.

2. Adhikari S, et al. Protein Quality in Perspective: A Review of Protein Quality Metrics and Their Applications. Nutrients. 2022 Feb 23;14(5):947.

RELEVANCE OF PROTEIN QUALITY ON MUSCLE HEALTH

Protein absorption as a determinant of protein quality

- A high-quality protein is not just rich in essential amino acids—it must also be **easily digested and absorbed**.¹
- Most **protein digestion and absorption** takes place in the **small intestine**, where AA and peptides are efficiently taken up.¹
- The **digestibility** of a protein—how completely and efficiently it is broken down and absorbed—directly impacts its **quality**.¹
- **Food processing can alter protein digestion and absorption**. High heat, alkaline pH or reducing sugars may modify amino acid side chains reducing its bioavailability.²



Factors influencing the quality of dietary protein.³

1. Adhikari S, et al. Protein Quality in Perspective: A Review of Protein Quality Metrics and Their Applications. *Nutrients*. 2022 Feb 23;14(5):947.

2. Loveday SM. Protein digestion and absorption: the influence of food processing. *Nutr Res Rev*. 2023 Dec;36(2):544-559.

3. Matthews JJ, et al. Understanding Dietary Protein Quality: Digestible Indispensable Amino Acid Score and Beyond. *J Nutr*. 2025 Jul 15:S0022-3166(25)00428-6.

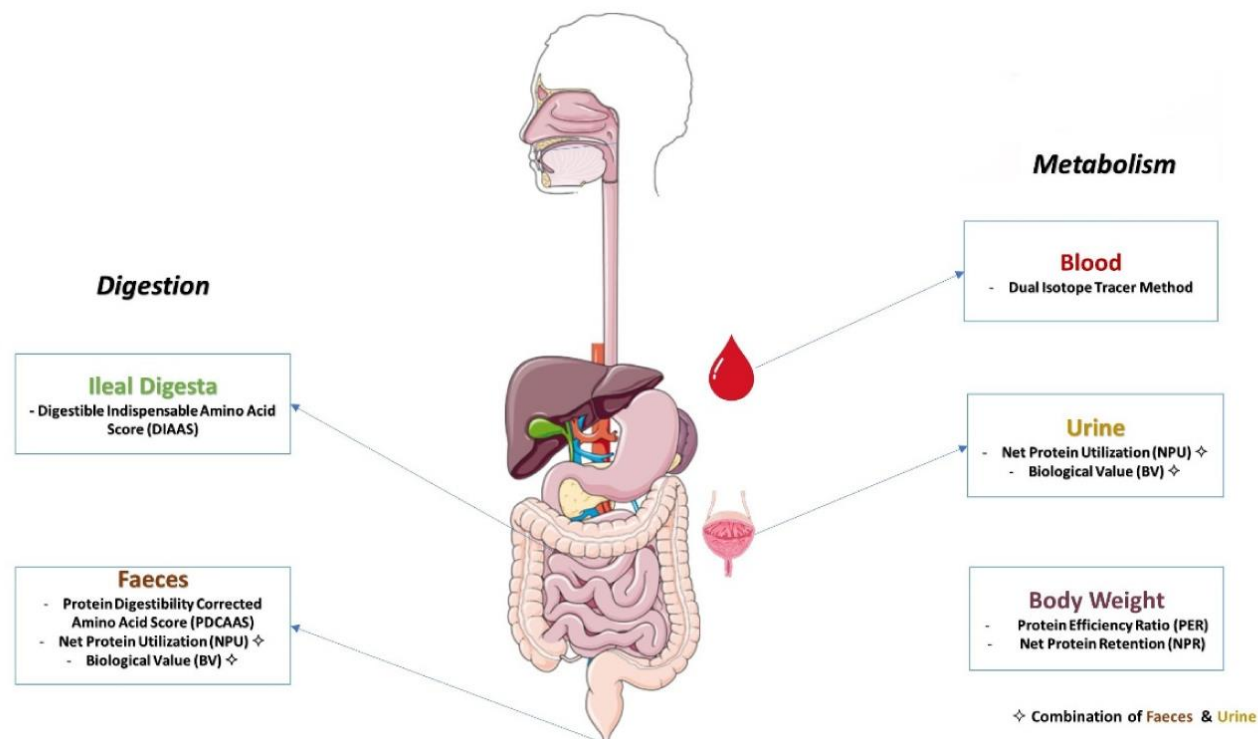
RELEVANCE OF PROTEIN QUALITY ON MUSCLE HEALTH

Methods used to evaluate protein quality

Measurement Principle:¹

DIAAS (Digestible Indispensable Amino Acid Score): Ratio of IAA_{lim} in test protein compared to reference protein (often casein) corrected for ileal digestibility of IAA_{lim}

PDCAAS (Protein Digestibility-Corrected Amino Acid Score): Ratio of IAA_{lim} in test protein compared to reference protein corrected for **fecal** protein digestibility



Anatomic locations for different in vivo assessments of protein quality.¹

IAA_{lim}: first limiting indispensable amino acid

RELEVANCE OF PROTEIN QUALITY ON MUSCLE HEALTH

Methods used to evaluate protein quality - PDCAAS

The **PDCAAS** - Introduced by the FAO/WHO in 1991.¹ considers both the **EAA** profile of a protein and its **fecal digestibility**.

PDCAAS = ((mg of limiting amino acid in 1g of test protein)/(mg of same amino acid in 1 g of reference protein or requirement pattern)) x true fecal digestibility (%) x 100.²

Scores range from **0 to 1.0% (100%)**

LIMITATIONS:

- Based on fecal digestibility
- Caps scores at 1.0, possibly underestimating superior proteins

Protein source	PDCAAS values
Whey	1.00
Casein	1.00
Egg white	1.00
Soy protein concentrate	0.99
Rapeseed protein concentrate	0.93
Soy protein isolate	0.92
Kidney beans	0.68
Peas	0.61-0.68
Peanuts	0.52
Lentils	0.51-0.52
Whole wheat	0.40
Wheat gluten	0.25

PDCAAS values of common dietary protein sources. ^{1,3}



1. FAO/WHO Expert Consultation (1991) Protein quality evaluation. Food and Agricultural organization of the United Nations, FAO Food and Nutrition Paper no. 51, Rome.
 2. Boye J, et al. Protein quality evaluation twenty years after the introduction of the protein digestibility corrected amino acid score method. Br J Nutr. 2012 Aug;108 Suppl 2:S183-211.
 3. Phillips SM. The impact of protein quality on the promotion of resistance exercise-induced changes in muscle mass. Nutr Metab (Lond). 2016 Sep 29;13:64.

RELEVANCE OF PROTEIN QUALITY ON MUSCLE HEALTH

Methods used to evaluate protein quality - DIAAS

DIAAS - Introduced by the FAO 2013.¹

Measures ileal digestibility of each essential amino acid. → More accurate and biologically relevant.¹

Scores are not capped—can exceed 100%.¹

DIAAS = ((mg of digestible dietary EAA in 1g of test protein)/(mg of same EAA in 1 g of reference protein)) x 100.¹

ADVANTAGES:¹

- Reflects true amino acid absorption.
- Differentiates high-quality proteins more precisely.

Food Item	DIAAS Value (%)	IAA _{lim}
Dry milk	144	SAA
Bacon (smoked-cooked)	142	Valine
Milk protein concentrate	141	SAA
Pork loin (medium)	139	Valine
Whey protein concentrate	133	Histidine
Ham (alternatively-cured)	133	Valine
Ribeye (roast, medium)	130	Valine
Bologna	128	Leucine
Ham (conventionally-cured)	126	Valine
Whey protein isolate	125	Histidine

Overview of DIAAS value, including the first limiting indispensable amino acid (IAA_{lim}).²

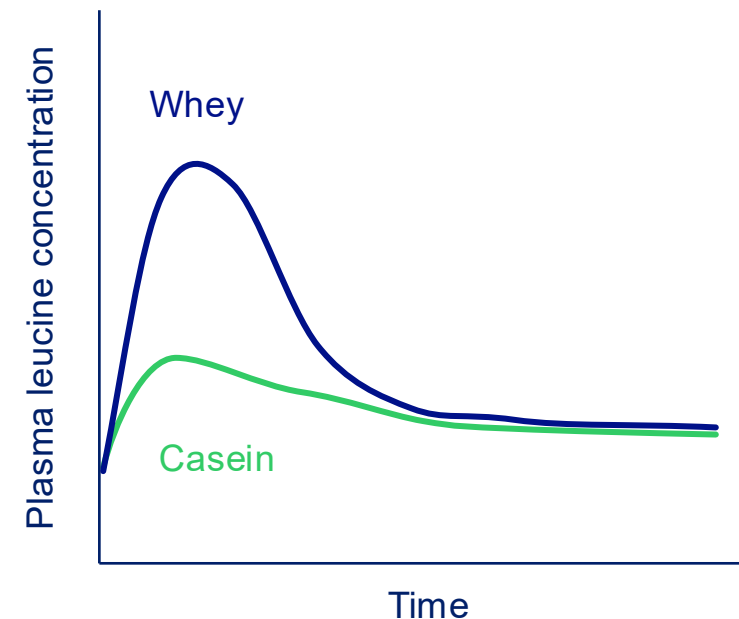


RELEVANCE OF PROTEIN QUALITY ON MUSCLE HEALTH

Casein vs Whey

- **Whey protein: Fast-digesting protein.** Causes a rapid increase in blood leucine levels and maximally stimulates MPS.¹
- **Casein: Slow-digesting protein.** Sustains amino acid availability over time and supports a prolonged MPS response.¹

A balance of fast and slow proteins (e.g., whey + casein) may enhance the efficacy and duration of MPS.²



Postprandial leucine concentration following ingestion of whey and casein. Figure based on data described in ¹



1. Pennings B, et al. Whey protein stimulates postprandial muscle protein accretion more effectively than do casein and casein hydrolysate in older men. Am J Clin Nutr. 2011 May;93(5):997-1005.
 2. Kanda A, et al. Effects of Whey, Caseinate, or Milk Protein Ingestion on Muscle Protein Synthesis after Exercise. Nutrients. 2016 Jun 3;8(6):339.

RELEVANCE OF PROTEIN QUALITY ON MUSCLE HEALTH

Summary

- ✓ Protein quality reflects a protein's ability to supply sufficient nitrogen and all 9 essential amino acids (EAAs) to meet human physiological needs.
- ✓ A **protein's quality** depends on both its **EAA content** and its **digestibility** and absorption in the small intestine.
- ✓ Protein quality is assessed using two main methods:
- ✓ **PDCAAS**, combines the essential amino acid profile with fecal digestibility
- ✓ **DIAAS** uses ileal digestibility of each EAA, providing a **more accurate**, uncapped score that better distinguishes high-quality proteins.
- ✓ Examples of protein quality & digestion:
 - ✓ **Whey protein:** Fast-digesting → rapid rise in blood leucine → **maximally stimulates MPS**.
 - ✓ **Casein:** Slow-digesting → sustained amino acid release → **prolonged MPS response**.





PLANT-BASED PROTEINS

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PLANT-BASED PROTEINS

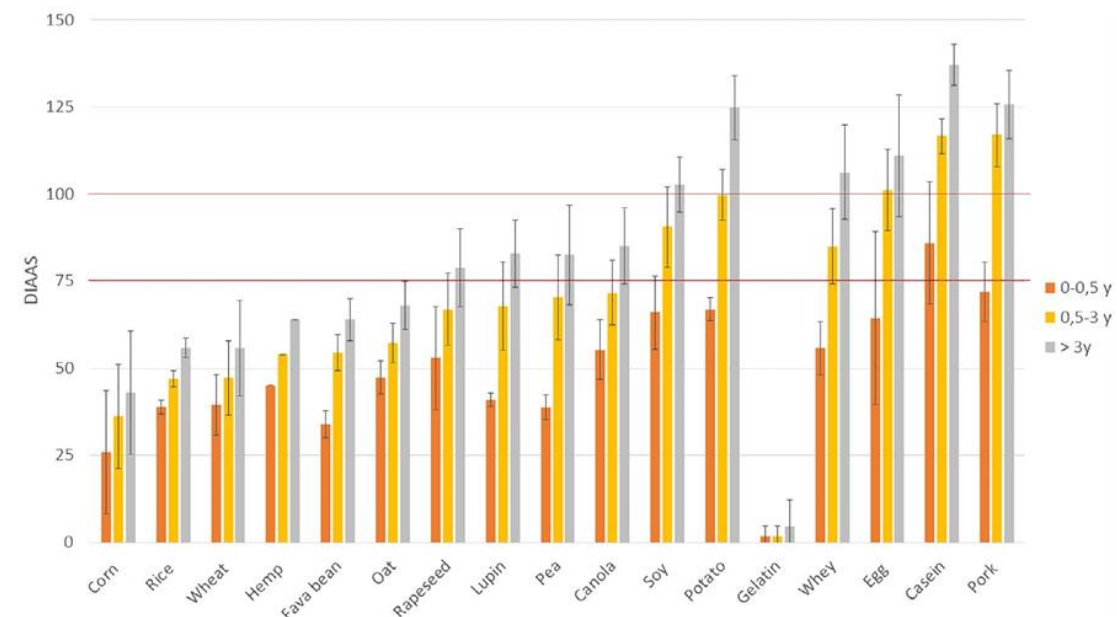
Animal vs. plant protein quality

Quality differences

Animal proteins (e.g., whey, egg) have higher digestibility scores, richer essential amino acid (EAA) profiles, and faster absorption than most plant proteins.¹

Lower digestibility

Plant proteins often contain **antinutritional factors** (e.g., phytates, trypsin inhibitors), which can impede amino acid absorption.¹



Digestible indispensable amino acid score (DIAAS) of various protein sources by age group. Infant (0–0.5 years), children (0.5–3 years), and children older than 3 years, adolescents, and adults.²

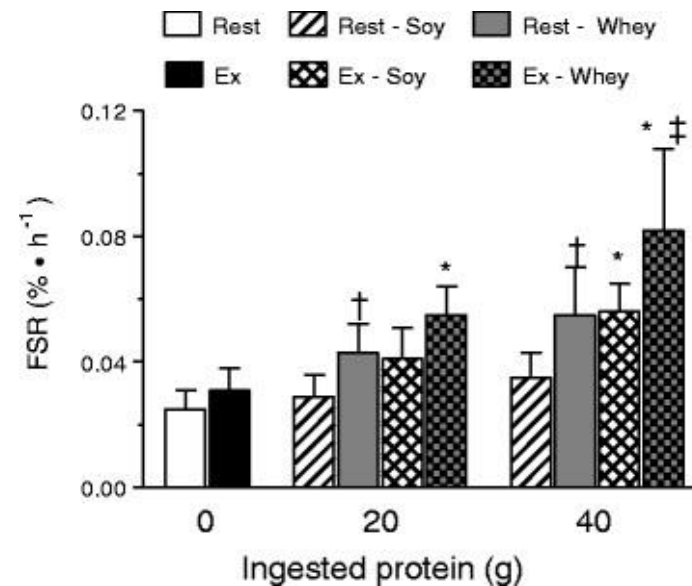
1. Putra C, et al. Protein Source and Muscle Health in Older Adults: A Literature Review. *Nutrients*. 2021 Feb 26;13(3):743

2. Herreman L, et al. Comprehensive overview of the quality of plant- And animal-sourced proteins based on the digestible indispensable amino acid score. *Food Sci Nutr*. 2020 Aug 25;8(10):5379-5391.

PLANT-BASED PROTEINS

Plant based protein impact on muscle protein synthesis

- Plant-based dietary patterns showed positive overall associations with muscle strength, a negative link with body composition, and unclear effects on muscle function.¹
- Whey typically triggers higher MPS than soy at moderate doses, both at rest and after exercise in elderly men.²



Fractional synthetic rate (FSR) response to soy and whey protein ingestion at rest (Rest) and after exercise (Ex) in elderly men.²

PLANT-BASED PROTEINS

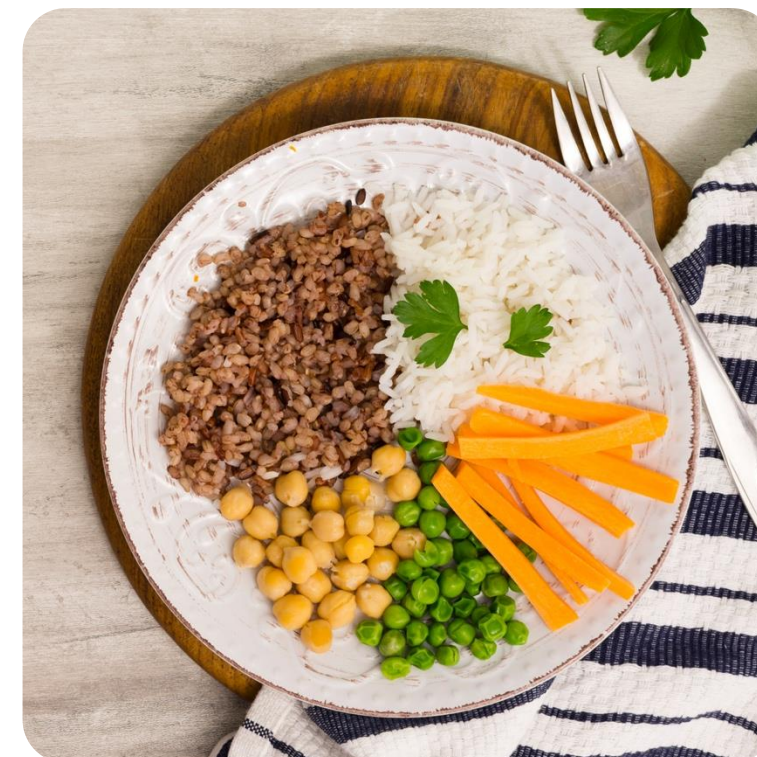
Strategies with plant-based proteins

Most plant protein lack or are low in one or more EAAs.¹

- Grains (rice, corn) are low in the amino acid lysine and isoleucine
- Beans (legumes) are low in the amino acid methionine

	Limiting amino acid			
	Isoleucine	Lysine	Methionine	Tryptophan
Legumes	✓	✓	✗	✗
Grains	✗	✗	✓	✓
Together	✓	✓	✓	✓

Pairing (complementing) them makes a higher quality protein.¹

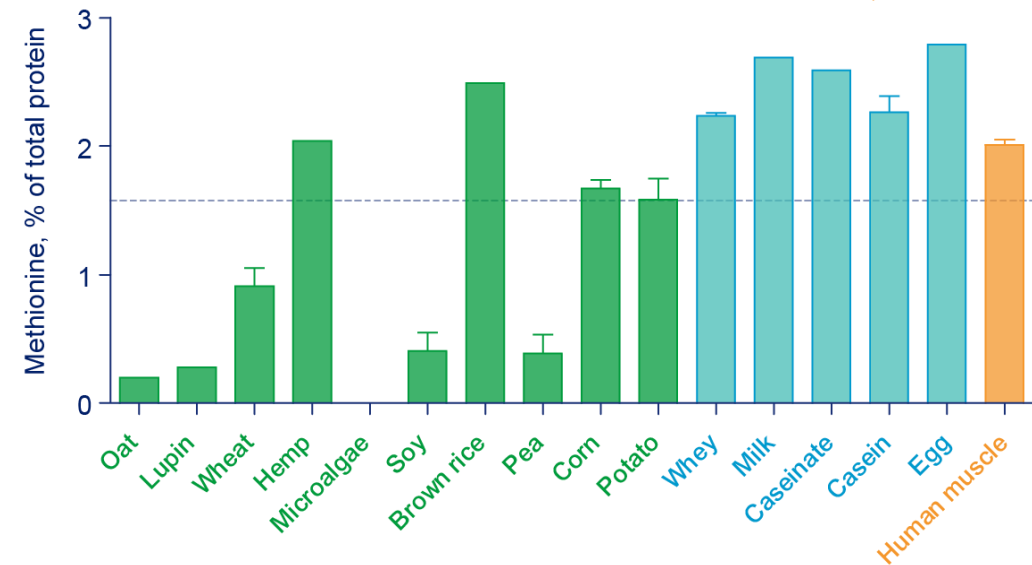
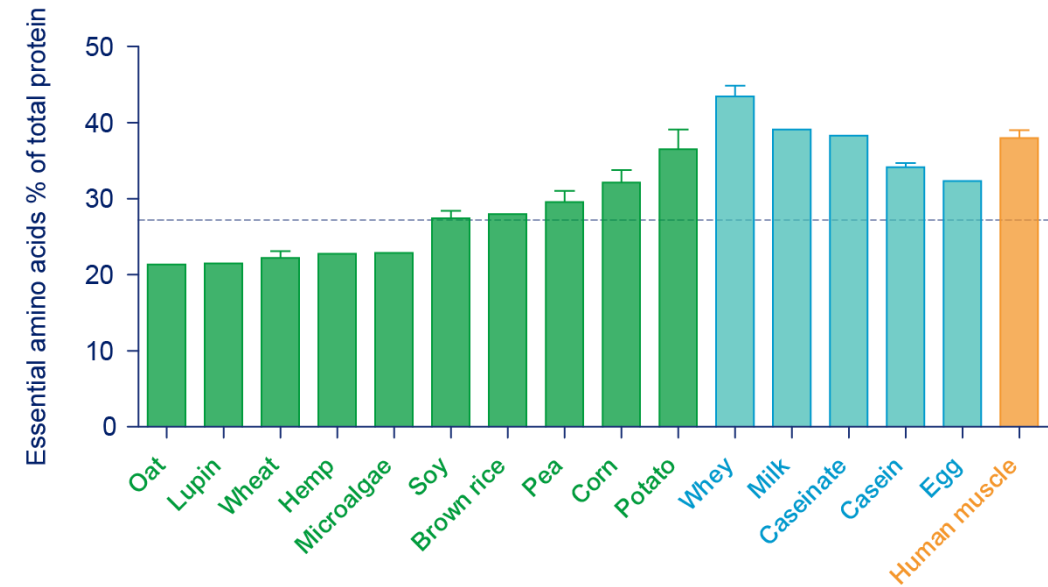
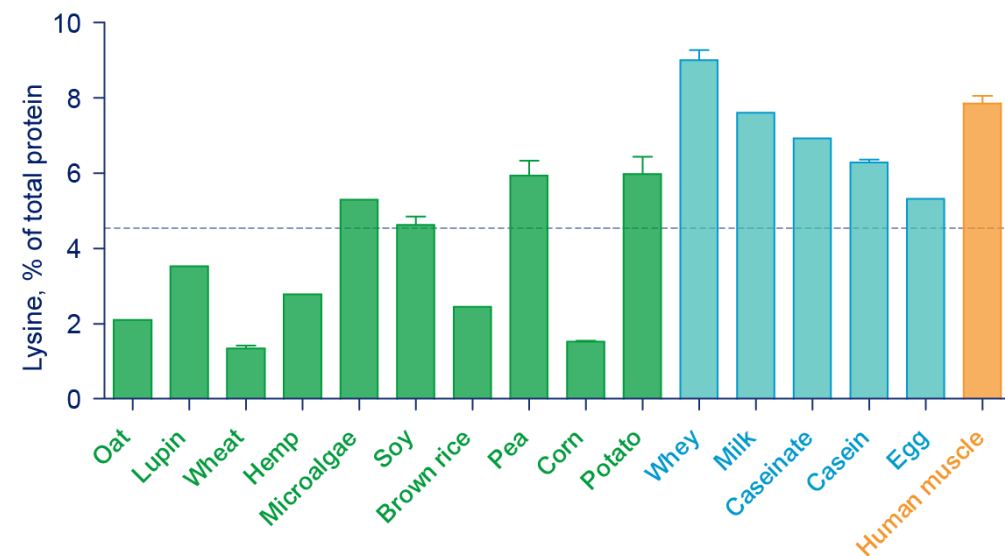


Click here for amino acid content of different proteins



Amino acid content of various protein sources

1. Gorissen SHM, et al. Protein content and amino acid composition of commercially available plant-based protein isolates. Amino Acids. 2018 Dec;50(12):1685-1695.

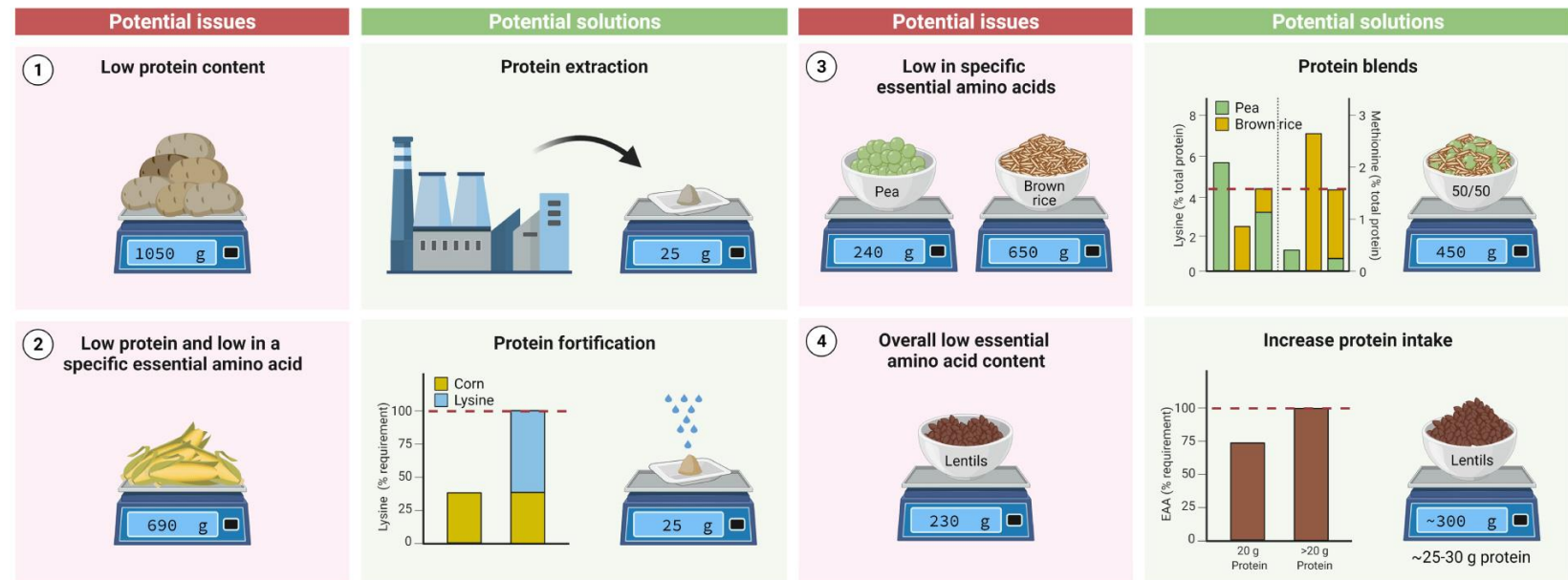


PLANT-BASED PROTEINS

Optimizing the anabolic response to plant proteins: challenges & solutions

To enhance the quality and muscle-stimulating properties of plant proteins:¹

- Complementation – globally recognized as important
- Protein fortification with limiting essential amino acids or leucine to meet the threshold for stimulation of muscle protein synthesis
- Consume more protein!



Optimising the anabolic response to plant-based proteins: challenges and solutions. Modified from¹

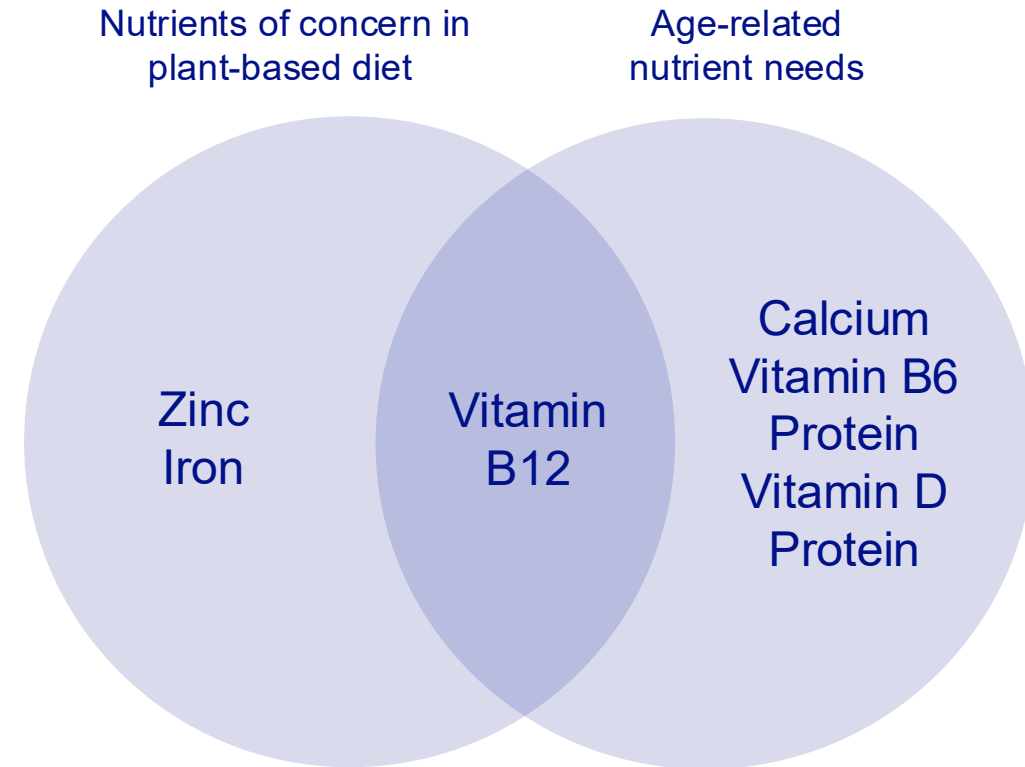
1. Pinckaers PJM, Trommelen J, Snijders T, van Loon LJC. The Anabolic Response to Plant-Based Protein Ingestion. Sports Med. 2021 Sep;51(Suppl 1):59-74.

Recommendations for older adults on plant-based diets

Older vegetarians tend to have **nutrient intakes similar to or better than nonvegetarians**, although they may be at risk for **lower zinc, iron status and vitamin B12**.^{1,2}

Higher intakes are recommended in the older adults:¹

- Protein
- Calcium
- Vitamin B6
- Protein
- Vitamin D



Summary

- ✓ Animal proteins (e.g., whey, egg) are highly digestible, EAA-rich, and rapidly absorbed.
- ✓ Plant proteins have lower digestibility due to antinutritional factors like phytates and trypsin inhibitors.
- ✓ Most plant proteins are low or lacking in one or more EAAs.
- ✓ Combining plant proteins (e.g., legumes + grains) can provide a complete EAA profile.
- ✓ Whey stimulates higher muscle protein synthesis than soy at moderate doses in older adults; higher doses may reduce these differences.
- ✓ Recognize that aging is associated with anabolic resistance and an increased need for protein
- ✓ Older vegetarians generally have adequate nutrient intakes but may need more protein, zinc, iron and vitamin B12.





HMB VS. PROTEIN INTAKE: CONTROVERSY & EVIDENCE

[5.1. \$\beta\$ -Hydroxy- \$\beta\$ -methylbutyrate](#)

[5.2. HMB metabolic pathway](#)

[5.3. Evidence and controversy of the HMB](#)

[5.4. An umbrella review of systematic reviews of
 \$\beta\$ -HMB supplementation in ageing and clinical practice](#)

[5.5. Summary](#)



HMB VS. PROTEIN INTAKE: CONTROVERSY & EVIDENCE

β -Hydroxy- β -methylbutyrate

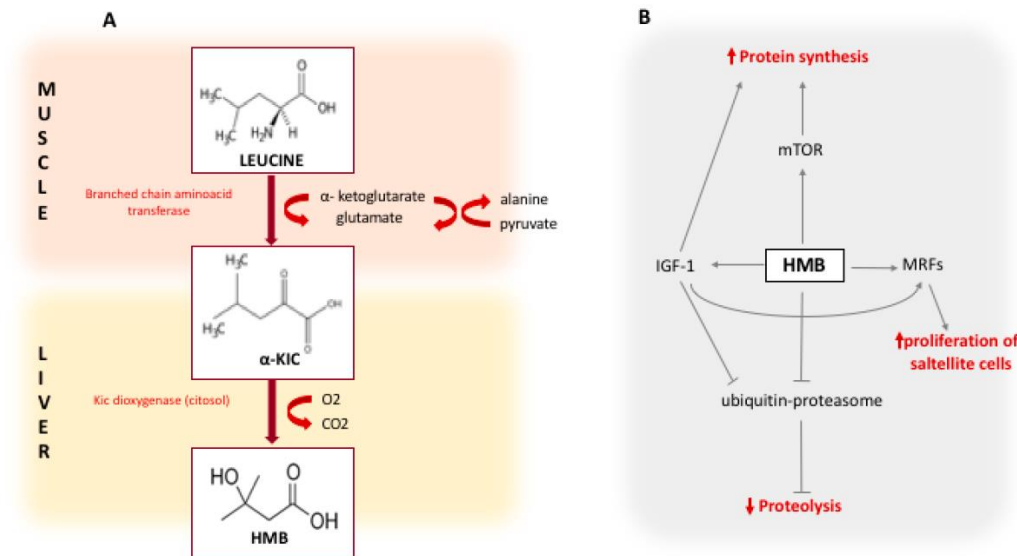
β -Hydroxy- β -methylbutyrate (HMB) is derived from leucine metabolism¹ and not essential for muscle protein synthesis.

HMB is believed to support muscle health by:^{2,3}

- Activating mTOR pathway $\rightarrow$ $\uparrow$ MPS
- Inhibiting the proteasome pathway $\rightarrow$ $\downarrow$ MPB

Main sources of HMB:

- Endogenous production from leucine metabolism¹
- From diet **1–5 nmol/g** in fruits and vegetables and **15–25 nmol/g** in meats⁴



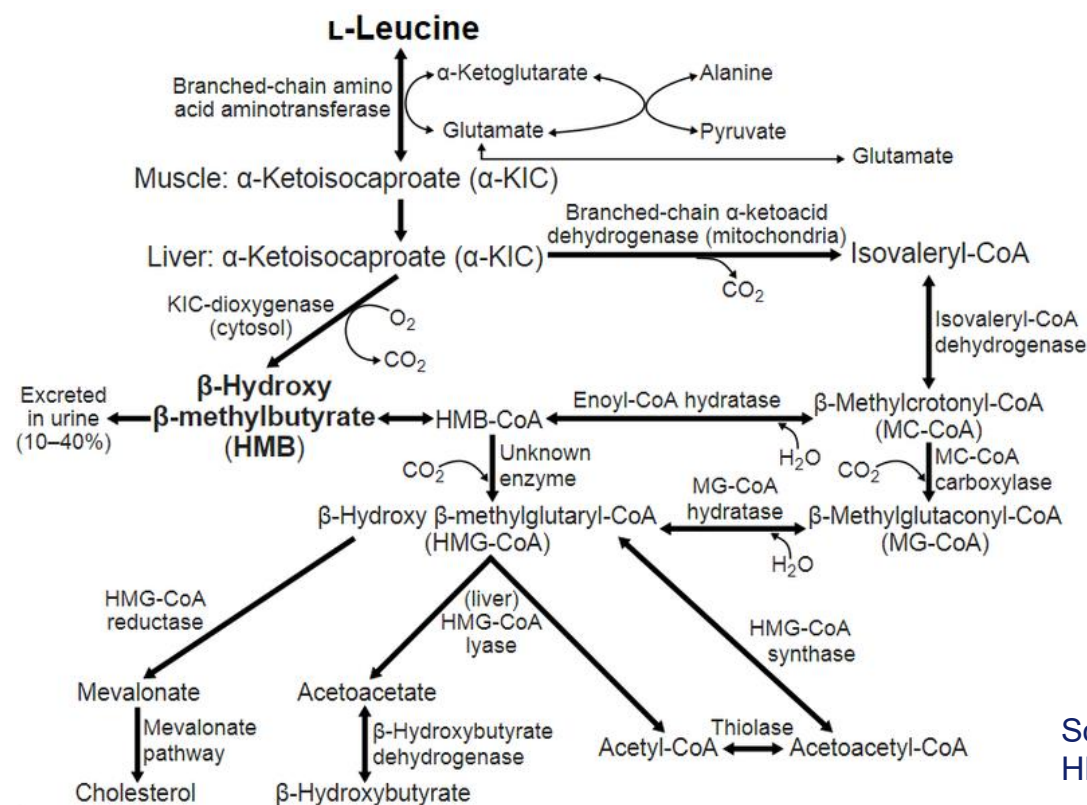
HMB- Metabolic pathway from leucine and its role in muscle protein balance.³

1. Nissen SL, et al. Nutritional role of the leucine metabolite β -hydroxy β -methylbutyrate (HMB). J Nutr Biochem. 1997;8(6):300-311.
 2. Bear DE, et al. β -Hydroxy- β -methylbutyrate and its impact on skeletal muscle mass and physical function in clinical practice: a systematic review and meta-analysis. Am J Clin Nutr. 2019 Apr 1;109(4):1119-1132.
 3. Lattanzi B, et al. The Effect of 12 Weeks of β -Hydroxy- β -Methyl-Butyrate Supplementation after Liver Transplantation: A Pilot Randomized Controlled Study. Nutrients. 2019 Sep 19;11(9):2259.
 4. Tata MR. Neonatal programming of skeletal development in sheep is mediated by somatotrophic axis function. Exp Physiol. 2008 Jun;93(6):763-72.

HMB VS. PROTEIN INTAKE: CONTROVERSY & EVIDENCE

HMB metabolic pathway

- The **endogenous conversion of leucine to HMB is low**, with only **2-10%** of leucine being converted to HMB.¹
- 10-40% of HMB is lost in the urine.¹
- HMB metabolism also results in cholesterol synthesis.¹
- When HMB is taken regularly in high doses it might be prudent to monitor lipid profiles to assess any potential cardiovascular impact.



Schematic representation of HMB metabolism.²



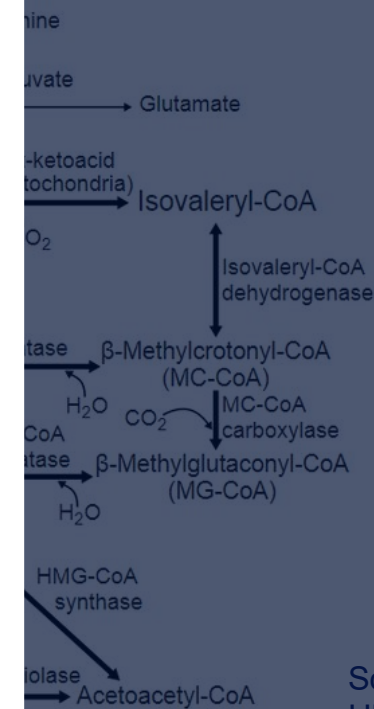
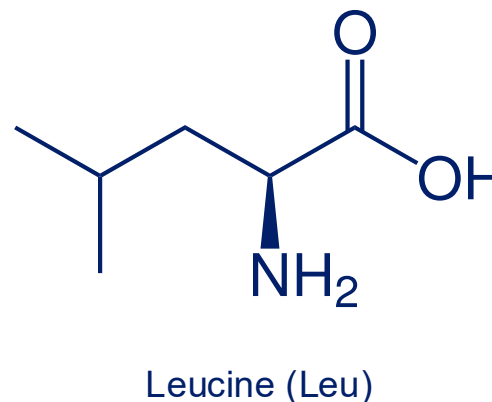
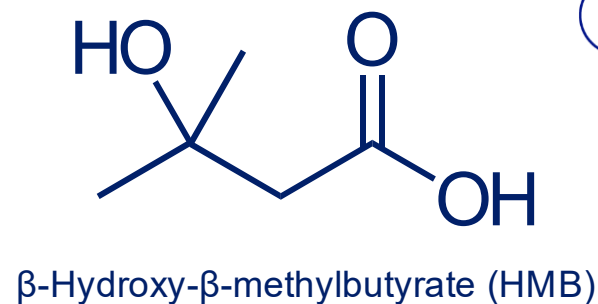
Click here to compare leucine and HMB formula

1. Nissen SL et al. Nutritional role of the leucine metabolite β-hydroxy β-methylbutyrate (HMB). J Nutr Biochem. 1997;8(6):300-11.

2. Wikimedia commons. File: HMB biosynthesis and metabolism. Available from: https://commons.wikimedia.org/wiki/File:HMB_biosynthesis_and_metabolism_diagram.png [Accessed 22-08-2025].

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[Click here to compare leucine and HMB formula](#)



Schematic representation of HMB metabolism.²

HMB VS. PROTEIN INTAKE: CONTROVERSY & EVIDENCE

Evidence and controversy of the HMB



- So far, no meta-analyses have clearly demonstrated that HMB alone benefits frail elderly individuals.
- According to Courel-Ibañez, HMB supplementation does not appear to provide additional gains in physical performance, strength, or body composition in adults aged 50–80.¹
- Furthermore, a recent umbrella review of 15 systematic reviews found no evidence that HMB improves physical function in older adults or supports its use in clinical practice.²
- Many experts expressed the need for **well-designed studies** to better evaluate whether HMB is effective for managing frailty or sarcopenia in older adults.^{1,3-5}

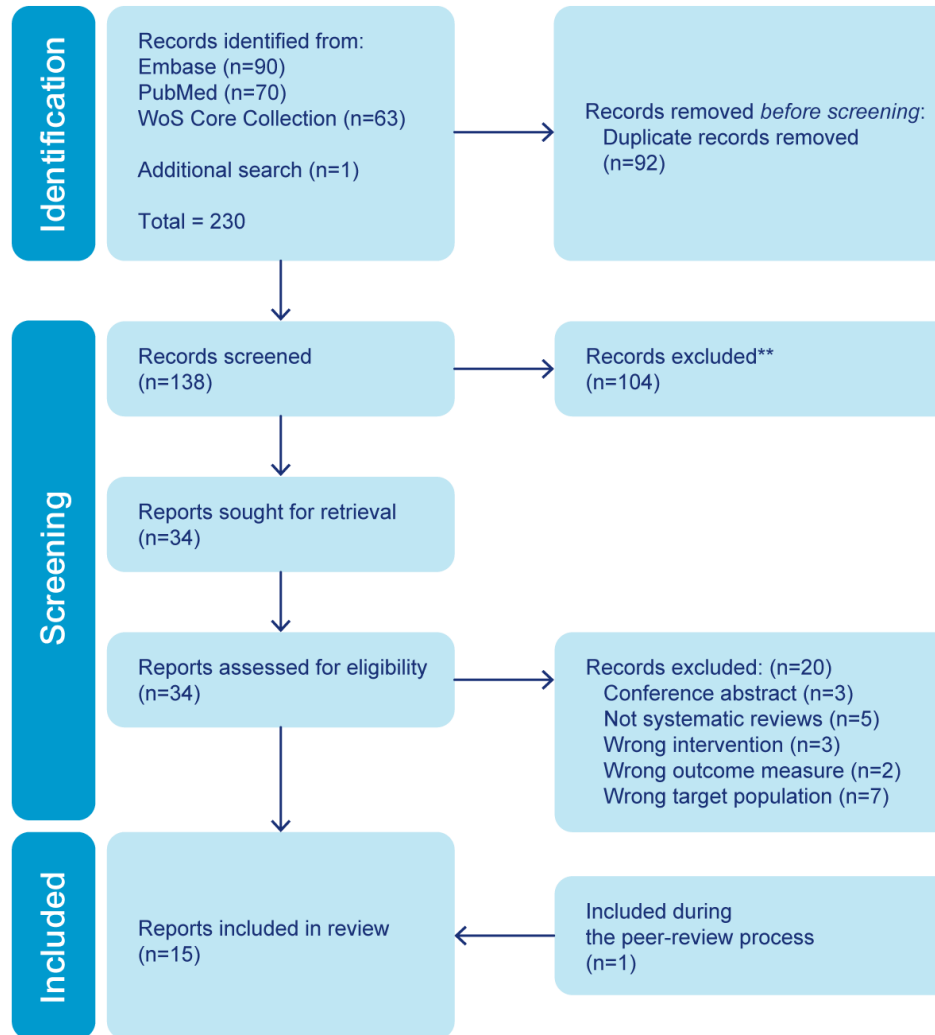


[Click here for study design](#)

1. Courel-Ibañez J et al. Health Benefits of β -Hydroxy- β -Methylbutyrate (HMB) Supplementation in Addition to Physical Exercise in Older Adults: A Systematic Review with Meta-Analysis. *Nutrients*. 2019;11(9):2082.
 2. Phillips SM, et al. An umbrella review of systematic reviews of β -hydroxy- β -methyl butyrate supplementation in ageing and clinical practice. *J Cachexia Sarcopenia Muscle*. 2022 Oct;13(5):2265-2275.
 3. Cruz-Jentoft AJ et al. Beta-Hydroxy-Beta-Methyl Butyrate (HMB): From Experimental Data to Clinical Evidence in Sarcopenia. *Curr Protein Pept Sci*. 2018;19(7):668–72.
 4. Bear DE et al. β -hydroxy- β -methylbutyrate supplementation in older persons – an update. *Curr Opin Clin Nutr Metab Care*. 2021;24(1):48–52.
 5. Gu WT, et al. The effects of β -hydroxy- β -methylbutyrate supplementation in patients with sarcopenia: A systematic review and meta-analysis. *Maturitas*. 2025 Apr;195:108219.

Evidence

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- Furthermore, a re
- Many experts exp



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gains in physical performance,

MB improves physical function

HMB is effective for managing



Click here for study design

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2. Phillips SM, et al. An umbrella review of systematic reviews of β -hydroxy- β -methyl butyrate supplementation in ageing and clinical practice. J Cachexia Sarcopenia Muscle. 2022 Oct;13(5):2265-2275.
3. Cruz-Jentoft AJ et al. Beta-Hydroxy-Beta-Methylbutyrate Supplementation in Older Persons – an update. Clin Opin Clin Nutr Metab Care. 2021;24(1):46-52.
4. Bear DE et al. β -hydroxy- β -methylbutyrate supplementation in older persons – an update. Clin Opin Clin Nutr Metab Care. 2021;24(1):46-52.
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2082.

HMB VS. PROTEIN INTAKE: CONTROVERSY & EVIDENCE

An umbrella review of systematic reviews of β -HMB supplementation in ageing and clinical practice

- Most reviews concluded that HMB supplementation did not affect strength outcome measures or studies were inconclusive.¹
- The current evidence is insufficient to assess the impact of HMB supplementation on functional outcome measures.¹
- Inconsistent support for HMB as part of an oral nutritional supplement or as a stand-alone supplement (or combined with other amino acids) to increase or promote retention of:¹
 - Lean soft-tissue mass (LSTM) – often incorrectly labelled as muscle
 - Improve strength
 - No evidence that it improves physical function in older persons or clinical populations



HMB VS. PROTEIN INTAKE: CONTROVERSY & EVIDENCE

Summary

- ✓ HMB is a metabolite of leucine that may support muscle health.
- ✓ Proposed actions: Activates mTOR → ↑ MPS; inhibits proteasome → ↓ MPB.
- ✓ Sources: mainly made in the body from leucine; small amounts in fruits, vegetables, and meats.
- ✓ HMB metabolism also contributes to cholesterol synthesis — monitor lipids with high doses.
- ✓ Some studies show modest effects on muscle mass in older adults; impact on strength or function is unclear.
- ✓ **Evidence for HMB alone is limited** — many trials use it with other nutrients.
- ✓ No evidence for HMB efficacy in improving lean tissue mass, function or mobility in older persons with or without sarcopenia.





CONCLUSIONS

CONCLUSIONS



- ✓ Nutrition & exercise are modifiable factors that strongly influence muscle health.
- ✓ **Older adults** have anabolic resistance → **need higher protein intake to stimulate muscle protein synthesis (MPS).**
- ✓ ESPEN: 1.2–1.5 g/kg/day for malnourished/at-risk older adults; more for severe illness.
- ✓ Not all AAs stimulate MPS equally. Leucine is the most potent “switch.” High-leucine proteins (e.g., whey) trigger MPS more effectively than low-leucine sources.
- ✓ Protein quality depends on EAA content, digestibility, and absorption. PDCAAS (fecal digestibility) and DIAAS (ileal digestibility) measure protein quality.
- ✓ **Whey: fast-digesting → rapid MPS; Casein: slow-digesting → sustained MPS.**
- ✓ Animal proteins are more digestible and EAA-rich than most plant proteins.
- ✓ Plant proteins are lower in some EAAs; combining sources (legumes + grains) helps.

This training material has been reviewed for scientific accuracy and relevance by Stuart Phillips – McMaster Experts. It is intended for educational purposes only and does not replace clinical judgment or institutional guidelines.



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- **Director** of the physical activity center of excellence (**PACE**) and the Mc Master center for nutrition, exercise and health research
- Leads the exercise metabolism research group.
- His academic work primarily investigates how **nutrition** and **physical activity** influence skeletal muscle in humans.

Thank you!

