Anabolic Resistance, the Leucine Threshold, and Protein Requirements Across the Adult Lifespan: Clinical Implications for Preventing Sarcopenia

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Anabolic resistance is now recognized as a central mechanism driving the age-related loss of skeletal muscle mass and function (*sarcopenia*). It describes the diminished stimulation of muscle protein synthesis (MPS) in response to normally anabolic stimuli, principally dietary protein intake and resistance exercise (Breen & Phillips, 2011; Hodson et al., 2019; Wall et al., 2015; Aragon et al., 2022). Over time, this attenuated MPS response to each meal or training bout leads to a cumulative, clinically significant decline in muscle tissue and strength, particularly when compounded by physical inactivity, inflammation, or chronic disease (Breen & Phillips, 2011; Deutz et al., 2014).

In this paper, we synthesize current evidence on anabolic resistance, the leucine *threshold* concept, and protein requirements across the adult lifespan, with emphasis on clinically actionable guidance for dietitians and other health professionals. The central questions addressed are: (1) when anabolic resistance tends to emerge; (2) how the leucine and protein dose–response relationships differ between younger and older adults; (3) why the conventional adult protein RDA of 0.8 $g \cdot kg^{-1} \cdot day^{-1}$ appears inadequate in later life; and (4) how protein and leucine provision might be titrated in clinical practice for individuals at 23, 40, and 57 years of age.

Anabolic Resistance and the Development of Sarcopenia

The concept of anabolic resistance emerged from tracer studies showing that older adults exhibit a diminished rise in MPS in response to amino acids and protein ingestion compared with younger adults, despite generally similar basal (fasted) MPS rates (Wall et al., 2015; Breen & Phillips, 2011). Wall and colleagues (2015) reported that older men (mean age ≈74 years) had approximately a 16 % lower post-prandial MPS response to protein ingestion than young men (mean age ≈22 years), even though basal MPS did not differ, leading the authors to describe "muscle anabolic inflexibility" with

aging (Wall et al., 2015). Similarly, older muscle shows impaired activation of mTORC1 signaling and its downstream targets (e.g., S6K1, 4EBP1) following protein ingestion or resistance exercise, consistent with reduced sensitivity of the translation-initiation machinery to anabolic cues (Hodson et al., 2019). This attenuated responsiveness, discussed later in the paper, has led investigators to focus on leucine, the principal amino-acid activator of mTORC1, as a potential key to overcoming age-related anabolic resistance.

Longitudinal data indicate that skeletal-muscle mass and strength begin to decline from approximately the fourth decade of life and accelerate with advancing age, particularly when compounded by reduced physical activity, inadequate protein intake, and chronic illness (Breen & Phillips, 2011; Deutz et al., 2014). However, current evidence does not support a discrete chronological "cut-off" at which an individual abruptly transitions from anabolic sensitivity (e.g., a healthy 23-year-old) to anabolic resistance (e.g., a frail 80-year-old). Rather, the shift appears gradual, heterogeneous, and strongly influenced by lifestyle and health status (Markofski et al., 2015; Wall et al., 2015; Hodson et al., 2019).

Markofski and colleagues (2015) examined basal muscle fractional-synthesis rates in a large cohort of young and older men and women and found no significant age-related differences in basal MPS, despite higher basal mTORC1 phosphorylation in the older participants. This pattern suggests a partial uncoupling between mTORC1 phosphorylation and actual protein-synthesis output, indicating that while basal signaling remains elevated, the capacity of the pathway to further activate in response to anabolic stimuli is reduced, a hallmark of anabolic inflexibility in aging muscle, or anabolic resistance (Breen & Phillips, 2011; Wall et al., 2015; Hodson et al., 2019).

Beyond these intracellular signaling changes, extrinsic lifestyle factors, particularly physical activity and muscle-loading patterns, play a decisive role in modulating the degree of anabolic resistance. While chronological aging creates a backdrop for diminished muscle-protein synthesis, the

emergence and magnitude of anabolic resistance are strongly modulated by physical-activity status. Short periods of muscle disuse, or chronic low-step counts, rapidly induce a blunted post-prandial MPS response, with reductions of >30 % in older women and ≈18 % in older men after only 7 days of unilateral limb suspension (Kilroe et al., 2025; Paulussen et al., 2021). Conversely, resistance-type exercise restores the muscle's sensitivity to amino acids and can shift the dose-response curve leftward, enabling a sub-maximal protein dose to elicit a young-adult-like MPS response. In young volunteers, a single bout of resistance exercise followed by a modest protein feed (≈15 g whey) increased myofibrillar MPS for up to 24 h, and this "exercise-sensitised" window was even more pronounced when the training set was performed to volitional failure (Moore et al., 2009; Atherton et al., 2010). In older adults, ingesting a leucine-rich whey bolus (≈40 g) after resistance training restored post-prandial MPS to levels comparable with younger subjects, demonstrating that the anabolic block is not immutable (Paulussen et al., 2021; Aragon et al., 2022). Moreover, longitudinal training studies show that regular resistance training (2–3 sessions /week) combined with protein intakes of ≥1.2 $g \cdot kg^{-1} \cdot day^{-1}$ markedly attenuates the age-related loss of lean mass and strength, even in frail or sarcopenic populations (Janssen et al., 2025; Kilroe et al., 2025). These data collectively indicate that anabolic resistance is a modifiable phenotype: inactivity and the absence of resistance-type loading accelerate the "dim-switch," whereas purposeful resistance training, performed at an appropriate intensity or to failure—re-sensitises the mTORC1 pathway and re-establishes robust MPS responses across the adult lifespan.

In practice, this implies that with advancing age, and especially in the context of inactivity or comorbidities, typical meals and habitual physical-activity levels may be insufficient to preserve muscle mass and function unless the anabolic stimulus is intensified through higher-protein, leucine-rich meals and regular resistance training.

Young versus Older Adults: Evidence from Stable-Isotope Studies

Stable-isotope tracer studies have traditionally compared “young” adults, typically in their late teens to early thirties, with “older” adults in their mid-sixties and beyond. Using primed, continuous amino-acid infusions and serial muscle biopsies, these studies consistently demonstrate that exogenous amino acids or intact proteins elicit smaller anabolic responses in older compared with younger individuals when standard doses are provided (Wall et al., 2015; Breen & Phillips, 2011). For example, Volpi et al. (2003) showed that essential-amino-acid (EAA) ingestion stimulated net muscle-protein synthesis (MPS) in older adults, but the magnitude of this response was attenuated relative to younger adults even when amino-acid and insulin concentrations were matched—evidence of reduced anabolic sensitivity (Breen & Phillips, 2011). Similarly, Cuthbertson and colleagues found that a 10 g EAA bolus robustly stimulated MPS in young men but failed to produce a comparable response in older men, even at higher doses, consistent with an age-related upward shift in the amino-acid dose–response curve (Breen & Phillips, 2011).

Despite these age-related differences in anabolic sensitivity, several investigations demonstrate that when protein intake is optimized and resistance exercise is performed, healthy, physically active older adults can mount MPS responses comparable in magnitude to those of younger adults (Breen & Phillips, 2011; Hodson et al., 2019). For instance, in older men ingesting rapidly digested, leucine-rich whey protein following resistance exercise, myofibrillar MPS increased substantially over the ensuing hours, mirroring the response of younger cohorts under matched conditions (Breen & Phillips, 2011; Yang et al., 2012). Collectively, these data reinforce that chronological age alone does not confer irreversible anabolic resistance; rather, the phenotype is strongly modifiable through physical activity, adequate protein quantity and quality, and overall metabolic health (Hodson et al., 2019; Aragon et al., 2022). Figure 1 summarizes does response to protein intake of MPS.

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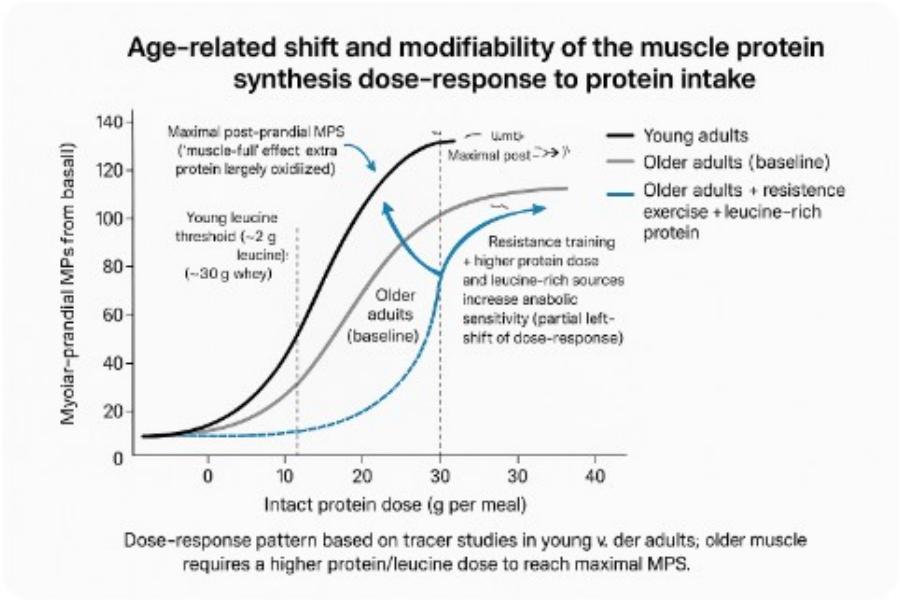

Figure 1.

Stable-isotope tracer studies demonstrate that younger adults (black curve) achieve near-maximal myofibrillar MPS at ≈ 20 g of high-quality protein (≈ 2–2.5 g leucine), whereas older adults (dark-gray curve) require a higher per-meal protein dose (≈ 30–40 g; ≈ 2.8–3 g leucine) to elicit a comparable anabolic response—a right-shift of the dose–response relationship characteristic of anabolic resistance. When resistance exercise is combined with leucine-rich protein sources (blue curve), anabolic sensitivity partially recovers, producing a left-shift toward the young pattern. Vertical dashed lines denote the approximate leucine thresholds for young and older adults. In both populations, MPS exhibits a "muscle-full" plateau beyond the threshold, after which additional protein is largely oxidized; however, some studies suggest that the absolute peak MPS may remain modestly lower in older adults even at higher doses. Mechanistically, impaired mTORC1 signaling is the principal factor, but additional age-related changes, such as increased splanchnic amino-acid sequestration, reduced post-prandial muscle perfusion, and diminished insulin-mediated capillary recruitment, may further limit substrate delivery to skeletal muscle. These complementary mechanisms compound anabolic resistance and should be considered when designing nutrition-exercise interventions for the elderly.

The Leucine Threshold and Per-Meal Protein Requirements

Leucine has emerged as a key amino acid regulating the initiation of translation and muscle protein synthesis (MPS) through activation of the mTORC1 signaling complex. Mechanistic work shows that the availability of leucine in the post-prandial period is a major determinant of S6K1

phosphorylation and downstream translation-initiation events, particularly in older muscle (Hodson et al., 2019). The *leucine-threshold* or *leucine-trigger* hypothesis proposes that a sufficient leucine dose and resulting peak plasma leucine concentration are required to fully activate mTORC1 and maximize post-prandial MPS; below this threshold, MPS rises with increasing leucine, whereas above it, additional leucine is largely oxidized and confers diminishing returns for MPS (Zaromskyte et al., 2021; Layman, 2024).

In young, healthy adults, several dose–response studies indicate that approximately 20 g of high-quality protein (e.g., whey or egg), containing about 10 g essential amino acids and ~2 g leucine, maximally stimulates myofibrillar MPS at rest and after resistance exercise (Moore et al., 2009; Witard et al., 2014). Witard et al. (2014) reported that in resistance-trained young men, 20 g of whey protein maximized MPS, and increasing the dose to 40 g did not further augment synthesis but did increase amino-acid oxidation and urea production, consistent with the *muscle-full* phenomenon. These findings suggest that in a healthy 23-year-old, per-meal intakes of ~20–25 g of high-quality protein are sufficient to saturate the acute MPS response; additional free leucine provides little further benefit once this threshold is met.

In contrast, older adults exhibit a higher leucine and protein threshold. Yang et al. (2012) showed that in older men, ~20 g of whey protein (containing ~2 g leucine) was sufficient to stimulate MPS above rest, but after resistance exercise, MPS continued to rise when the dose was doubled to 40 g, indicating a higher post-exercise ceiling in older muscle. Complementary work in older adults demonstrated that increasing the proportion of leucine in an essential-amino-acid mixture from ~26% (~1.7 g leucine) to 41% (~2.8 g leucine) partially restored the MPS response that was otherwise blunted with the lower-leucine mixture, despite identical total EAA content, highlighting leucine's distinct but not exclusive signaling role in overcoming anabolic resistance (Katsanos et al., 2006; Deutz et al., 2014; PROT-AGE Study Group, 2013).

A common misinterpretation of the leucine threshold and the *muscle-full effect* is that protein intake beyond the acute post-prandial MPS response is simply oxidized and therefore wasted. This view conflates two distinct physiological concepts: (1) the short-term MPS response to a single feeding, and (2) the continuous, whole-body requirement for amino acids across multiple organ systems. The per-meal plateau in MPS is well documented: when a young adult consumes ~40 g of whey protein after resistance exercise (compared with the ~20 g leucine-threshold dose), myofibrillar MPS does not increase further; the surplus amino acids are transiently oxidized to urea and carbon dioxide, although this oxidation occurs through normal metabolic pathways that also generate nitrogen for ureagenesis and energy for cellular work (Moore et al., 2009; Witard et al., 2014). Similarly, in older adults, MPS plateaus at ~30–40 g protein per meal (≈ 2.8–3.0 g leucine) with no additional anabolic benefit beyond this range (Layman, 2024; Moore et al., 2015). However, amino acids exceeding a single meal's MPS capacity are not biologically wasted; they are continuously recycled and redeployed to sustain vital processes throughout the body. Because humans lack an inert storage pool for amino acids—unlike glycogen for glucose or triglycerides for fat—dietary protein must constantly replenish a dynamic metabolic reservoir in flux, where amino acids are continually synthesized into new proteins and broken down through turnover (Paulussen et al., 2021).

Protein supports far more than muscle growth: synthesis of antibodies and immune-cell proteins (critical against immunosenescence); enterocyte turnover and tight-junction proteins maintaining gut-barrier integrity; plasma proteins such as albumin and clotting factors; structural proteins including collagen, elastin, and extracellular-matrix components; hepatic acute-phase reactants and metabolic enzymes; and the obligatory daily replacement of nitrogen losses via ureagenesis (Paulussen et al., 2021; Hodson et al., 2019). Importantly, albumin synthesis itself increases post-prandially in response to amino acid availability, directly competing with skeletal muscle for circulating amino acids and underscoring the need for adequate daily intake. Accordingly, daily protein targets of 1.0–1.2

$g \cdot kg^{-1} \cdot day^{-1}$ for healthy older adults and 1.2–1.6 $g \cdot kg^{-1} \cdot day^{-1}$ in chronic disease or frailty (Bauer et al., 2013; Deutz et al., 2014; Layman, 2024) reflect these broader systemic demands, not merely the acute MPS response. Distributing protein across 3–4 meals, each meeting or exceeding the leucine threshold (~30 g per meal in older adults), optimizes both muscle anabolism and total-body amino-acid availability for immune, connective-tissue, hepatic, and epithelial maintenance (Aragon et al., 2020; Paulussen et al., 2021). In sum, while "more protein per meal" beyond the MPS plateau does not further stimulate muscle growth, the notion that excess protein is metabolically wasted is a harmful oversimplification. Instead, these amino acids fulfill essential, ongoing physiological functions across the entire organism—a distinction fundamental to understanding human protein metabolism.

A systematic review by Zaromskyte et al. (2021) evaluated studies that concurrently measured post-prandial plasma leucine and MPS following ingestion of different protein sources in young and older adults. Support for the leucine-trigger hypothesis was most consistent in older cohorts, particularly under standardized feeding conditions, when meal-like doses of isolated proteins (~20 g) were tested; in this context, formulations that produced a higher peak leucinaemia elicited greater MPS in older, but not necessarily younger, individuals. Collectively, these data underpin the practical recommendation that older adults, especially those ≥ 65 years, should consume approximately 25–40 g of high-quality protein per meal, providing at least ~2.5–3.0 g leucine, to help overcome the shifted leucine threshold and optimize post-prandial MPS in most, though not all, older adults (Katsanos et al., 2006; PROT-AGE Study Group, 2013; Layman, 2024).

By contrast, there is currently little direct evidence that healthy middle-aged adults (40–55 years) necessarily require a full "geriatric" leucine dose of ~3 g per meal. Most tracer and leucine-dose–response studies dichotomize participants into young (~18–35 years) and older (~65–80 years) groups, with very few including a distinct middle-aged cohort or systematically testing graded leucine doses in that age range (Zaromskyte et al., 2021; Deutz et al., 2014). The literature therefore does not define a

precise chronological cut-off (e.g., age 40) at which clinicians should shift from a "young-adult" leucine target (~2 g) to an "older-adult" strategy (~3 g). Instead, the evidence supports a continuum: structural and functional muscle decline begins in midlife (roughly ≥ 40–50 years), while clearly demonstrable anabolic resistance to standard protein doses is most consistently observed in relatively sedentary or clinically compromised adults aged ≥ 60–65 years (Wall et al., 2015; Hodson et al., 2019; Aragon et al., 2022).

Daily Protein Requirements and Temporal Dynamics of Muscle Protein Synthesis

The adult Recommended Dietary Allowance (RDA) for protein, set at 0.8 $g \cdot kg^{-1} \cdot day^{-1}$, was originally derived from short-term nitrogen-balance studies in healthy young men and represents the minimum intake needed to prevent deficiency, not the intake required to optimize muscle maintenance, metabolic function, or recovery across the lifespan (Bauer et al., 2013). Nitrogen-balance methodology systematically underestimates physiological needs because it fails to capture adaptive down-regulation of amino-acid oxidation and does not measure muscle-specific protein turnover. Consequently, while 0.8 $g \cdot kg^{-1} \cdot day^{-1}$ may prevent overt negative balance, it is insufficient to counteract anabolic resistance and sarcopenic trajectories that begin in midlife.

The PROT-AGE Study Group (2013) concluded that older adults require higher intakes to maintain or regain lean mass and physical function. They recommended 1.0–1.2 $g \cdot kg^{-1} \cdot day^{-1}$ for healthy older individuals and 1.2–1.5 $g \cdot kg^{-1} \cdot day^{-1}$ (up to ≈ 2.0 $g \cdot kg^{-1} \cdot day^{-1}$ in illness or rehabilitation) for those with acute or chronic disease, with exceptions only for severe renal insufficiency without dialysis. These recommendations reflect recognition that aging muscle exhibits reduced sensitivity to dietary amino acids and to mechanical loading, requiring a greater substrate supply to achieve comparable MPS stimulation.

Similarly, the ESPEN Expert Group (Deutz et al., 2014) advised a baseline intake of 1.0–1.2 $g \cdot kg^{-1} \cdot day^{-1}$ for healthy older adults and 1.2–1.5 $g \cdot kg^{-1} \cdot day^{-1}$ for those at nutritional risk. ESPEN

emphasized that many older adults habitually consume ≤ 0.7 $g \cdot kg^{-1} \cdot day^{-1}$, well below the estimated average requirement, compounding sarcopenic decline. Mechanistically, this shortfall limits plasma essential-amino-acid availability and impairs mTORC1–S6K1 signaling, slowing post-prandial muscle repair and accelerating loss of functional capacity.

Building on these consensus statements, Layman (2024) synthesized mechanistic and clinical data showing that older adults (> 60 yr) benefit from 1.2–1.6 $g \cdot kg^{-1} \cdot day^{-1}$, provided intake is distributed across meals such that each feeding delivers ≈ 30 g high-quality protein (≈ 2.8 g leucine), the approximate threshold required to maximally stimulate or approach maximal MPS in most, though not all, older adults.

Acute tracer studies indicate that ingestion of a bolus of rapidly digested, high-quality protein elicits a transient increase in myofibrillar MPS that rises within ≈ 60 min, peaks at 90–120 min, and returns toward basal levels by ≈ 3 h despite sustained aminoacidemia (Atherton et al., 2010; Moore et al., 2009; Witard et al., 2014). This *muscle-full* or *refractory* response reflects the finite duration of a single post-prandial MPS burst rather than a rigid daily window during which protein must be consumed to be effective (Atherton et al., 2010; Layman, 2024).

Resistance exercise extends the period during which muscle remains sensitized to amino acids. A single bout enhances amino-acid sensitivity of myofibrillar MPS for up to 24 h in young men, such that protein ingestion at any time within this window evokes a greater synthetic response than at rest (Burd et al., 2011; Areta et al., 2013). Similar but often attenuated responses occur in older adults, consistent with age-related anabolic resistance (Breen & Phillips, 2011; Wall et al., 2015). Thus, daily muscle-protein accretion represents the integration of multiple discrete post-prandial MPS bursts superimposed on a prolonged period of exercise-induced sensitization, not a single brief “anabolic window.”

Ageing does not substantially alter basal (post-absorptive) MPS in healthy adults, but the magnitude of the post-prandial rise is blunted, an effect termed *anabolic resistance* or reduced *anabolic*

flexibility (Breen & Phillips, 2011; Markofski et al., 2015; Wall et al., 2015). Stable-isotope studies demonstrate a right-shift in the MPS dose–response curve: younger adults reach near-maximal MPS with ≈ 20 g high-quality protein (≈ 0.24 g·kg^{-1}), whereas older adults require ≈ 0.4 g·kg^{-1} per meal (≈ 30–40 g) to achieve a comparable response (Moore et al., 2009; Moore et al., 2015; Layman, 2024). This shift reflects a higher leucine threshold in older muscle; enriching an essential-amino-acid mixture from ≈ 1.7 g to ≈ 2.8 g leucine restores the MPS response in older adults to youthful levels, while further leucine enrichment yields no additional benefit in younger subjects (Katsanos et al., 2006; Layman, 2024). This shift reflects a higher leucine threshold in older muscle; enriching an essential-amino-acid mixture with ~40 % leucine (≈ 2.8 g total) has been shown to restore or substantially improve MPS in older adults (Katsanos et al., 2006; Deutz et al., 2014).

Consequently, older adults should aim for ≈ 2.8–3.0 g leucine per meal, typically provided by 30–40 g high-quality protein, to reliably overcome anabolic resistance and maximize the MPS response (Katsanos et al., 2006; Moore et al., 2015; Layman, 2024). The relationship is dose-responsive rather than binary: sub-threshold doses still stimulate MPS, but less efficiently, whereas larger doses predominantly increase amino-acid oxidation and urea production with minimal further anabolic gain (Witard et al., 2014; Layman, 2024). Over 24 h, optimal muscle maintenance therefore depends on (i) achieving this leucine/protein threshold in multiple meals and (ii) aligning one or more of these meals with the post-exercise period of enhanced amino-acid sensitivity (Areta et al., 2013; Breen & Phillips, 2011; Layman, 2024).

Meta-analytic data corroborate these mechanistic findings: Morton et al. (2018) identified a dose–response plateau at ≈ 1.6 g·kg^{-1}·day^{-1}, beyond which additional protein yields minimal gains in lean mass or strength. This breakpoint closely matches the upper end of the optimal range proposed by PROT-AGE, ESPEN, and Layman, demonstrating convergence between mechanistic physiology and clinical outcomes.

Taken together, the classic 0.8 g·kg^{-1}·day^{-1} RDA is a threshold for survival, not for thriving. For most adults over ~ 60 years, and for middle-aged individuals with metabolic or inflammatory burdens, daily intakes of 1.2–1.6 g·kg^{-1}·day^{-1} better preserve muscle mass, metabolic health, and independence. Higher intakes (up to ≈ 2.0 g·kg^{-1}·day^{-1}) may be warranted during illness or rehabilitation under medical supervision, provided renal function is adequate (Bauer et al., 2013; Deutz et al., 2014; Layman, 2024). Table 1 summarizes current evidence-based recommendations for daily protein intake and per-meal leucine targets across adulthood and clinical contexts.

Table 1. Age- and phenotype-specific dietary protein and leucine targets for optimizing muscle protein synthesis

Age / Physiological State	Typical Anabolic Sensitivity	Per-Meal Protein Target	Approx. Leucine Threshold per Meal	Daily Protein Goal	Key Rationale / References
Young adults (≤ 39 yr)	High; robust MPS response to ≈ 20 g high-quality protein	20–25 g high-quality protein	≈ 2.0 g Leu (≈ 20 g whey or egg protein)	1.0–1.2 g·kg^{-1}·day^{-1} for health; ≈ 1.6 g·kg^{-1}·day^{-1} for hypertrophy	MPS in young men is maximized at ≈ 20 g protein; 40 g does not further increase MPS but raises oxidation and urea (Moore 2009; Witard 2014; Morton 2018).
Midlife adults (40–59 yr)	Gradual onset of anabolic resistance ("early right-shift")	25–30 g protein	≈ 2.2–2.5 g Leu	1.2–1.4 g·kg^{-1}·day^{-1}	Pragmatic range; supports emerging decline in MPS efficiency; emphasis on meal distribution (Zaromskyte 2021; Deutz 2014). Evidence interpolated from young vs older comparisons.
Older adults (≥ 60 yr, active / regular physical activity)	Partially preserved anabolic sensitivity (maintained by exercise stimulus)	25–30 g protein	≈ 2.5–2.8 g Leu	1.2–1.6 g·kg^{-1}·day^{-1}	Regular resistance training or structured PA extends post-exercise anabolic window, maintaining muscle's amino-acid responsiveness. Requires less absolute protein per meal than sedentary counterparts while

Age / Physiological State	Typical Anabolic Sensitivity	Per-Meal Protein Target	Approx. Leucine Threshold per Meal	Daily Protein Goal	Key Rationale / References
					achieving same daily goal (Breen & Phillips 2011; Aragon et al. 2022; Deutz et al. 2014).
Older adults (≥ 60 yr, sedentary / minimally active and healthy)	Reduced amino-acid and exercise sensitivity (chronic anabolic resistance)	30–40 g protein	≈ 2.8–3.0 g Leu	1.4–2.0 $g \cdot kg^{-1} \cdot day^{-1}$	Chronic disuse and absence of exercise stimulus blunts MPS response; larger per-meal doses required. Protein distribution across ≥3 meals critical. Initiation of resistance training rapidly restores sensitivity (Katsanos 2006; Moore 2015; Layman 2024; PROT-AGE 2013).
Frail / Sarcopenic (Non-Catabolic)	Severe anabolic resistance; disuse atrophy (Compensatory needs)	30–40 g protein (with exercise if possible)	≈ 3.0 g Leu	1.4–1.8 $g \cdot kg^{-1} \cdot day^{-1}$	High protein dose required to compensate for disuse-related anabolic resistance in non-diseased frailty; protein distribution across ≥3 meals critical. If any resistance training is initiated, MPS response will improve (Breen 2011; Wall 2015; Aragon 2022; Kilroe 2025).
Disease / Rehabilitation / Severe Catabolism	Blunted MPS; significantly elevated breakdown (Catabolic stress)	35–45 g protein	≈ 3.0 g Leu	1.5–2.0 $g \cdot kg^{-1} \cdot day^{-1}$ †	ESPEN / PROT-AGE upper end for acute or chronic illness and severe malnutrition or injury; higher protein offsets catabolism and blunted signaling (Bauer 2013; Deutz 2014). Intake over 1.8 g·kg−1·day−1 requires medical supervision.

Note. Values reflect average requirements derived from stable-isotope tracer studies, consensus position papers (Bauer et al., 2013; Bauer et al., 2014), and dose-response analyses in healthy and clinical populations (Moore et al., 2009; Witard et al., 2014). Daily protein goals are expressed as

grams per kilogram body-weight per day ($g \cdot kg^{-1} \cdot day^{-1}$). Per-meal protein targets are the amounts that typically exceed the leucine "threshold" needed to maximally stimulate MPS (≈ 2 g Leu for young adults; ≈ 2.8–3 g Leu for older or frail adults) (Katsanos et al., 2006; Moore et al., 2015). Protein should be distributed across ≥ **3 meals/day** (Areta et al., 2013); when resistance exercise is performed, the per-meal dose can be at the lower end of the range (Wall et al., 2015; Aragon et al., 2022). † Intakes ≥ 1.8 $g \cdot kg^{-1} \cdot day^{-1}$ should only be used under medical supervision, e.g., in severe catabolic states (Bauer et al., 2013; Deutz et al., 2014). *Abbreviations:* MPS = muscle protein synthesis; Leu = leucine.

Age- and Phenotype-Specific Clinical Implications

For a healthy, resistance-trained 23-year-old, current evidence supports conventional sports-nutrition targets without the need for additional free leucine beyond that provided by dietary protein. A daily intake of approximately 1.6 $g \cdot kg^{-1} \cdot day^{-1}$, distributed across three to four meals containing 20–25 g of high-quality protein (~2 g leucine) per meal, appears sufficient to maximize training-induced hypertrophy and strength gains (Moore et al., 2009; Morton et al., 2018; Witard et al., 2014). In this population, the primary focus should be on meeting total protein and energy needs and maintaining consistent resistance training, rather than pharmacologic leucine supplementation.

For an individual around 40 years of age, the literature does not support an abrupt transition to a "3 g leucine per meal" regimen. However, because muscle mass and metabolic flexibility begin to decline during midlife, it is prudent to gradually move beyond RDA-level intake toward 1.0–1.3 $g \cdot kg^{-1} \cdot day^{-1}$, emphasizing even protein distribution such that each meal supplies at least ~25 g of high-quality protein and ~2–2.5 g leucine (Breen & Phillips, 2011; Deutz et al., 2014; Layman, 2024). Regular resistance exercise (≥ 2 sessions per week) and minimization of sedentary time remain critical, as nutrition and physical activity jointly regulate anabolic sensitivity (Deutz et al., 2014; Hodson et al., 2019).

For a 57-year-old adult seeking to preserve or regain muscle mass and function, the case for adopting "older-adult" targets becomes stronger. Daily intake in the range of 1.2–1.6 $g \cdot kg^{-1} \cdot day^{-1}$ is reasonable, especially if the individual is active, has minor comorbidities, or shows early sarcopenic changes (Bauer et al., 2013; Deutz et al., 2014). Per-meal doses of 25–35 g protein providing ~2.5–3.0

g leucine are recommended to ensure the leucine threshold is reached and to offset reduced anabolic sensitivity (Katsanos et al., 2006; Yang et al., 2012; Layman, 2024). These strategies should be paired with structured resistance training tailored to ability and clinical status to maximize the MPS response (Breen & Phillips, 2011; Deutz et al., 2014).

For very old, frail, or clinically compromised adults (≥ 75 years with multiple comorbidities or established sarcopenia), protein requirements are typically higher—1.4–2.0 $g \cdot kg^{-1} \cdot day^{-1}$—to sustain anabolism despite severe anabolic resistance and catabolic stress (Bauer et al., 2013; Deutz et al., 2014). In these cases, leucine-enriched whey or essential-amino-acid formulations delivering ~25–30 g protein and ~3 g leucine per meal in smaller volumes are particularly useful for patients with low appetite or dysphagia (Katsanos et al., 2006; Rieu et al., 2006; PROT-AGE Study Group, 2013). Protein prescriptions must be individualized, with close monitoring of renal function and disease status, especially in advanced chronic kidney disease (Bauer et al., 2013; Deutz et al., 2014). See Table 2 below for clinical considerations

Table 2. Age-specific practical applications and clinical considerations

Age / Phenotype	Daily Protein Target ($g \cdot kg^{-1} \cdot day^{-1}$)	Per-Meal Protein & Leucine Target	Exercise Guidance	Clinical / Practical Considerations
Young adults (≤ 39 yr)	1.0–1.2 for health; ≈ 1.6 for hypertrophy *	20–25 g high-quality protein (~2 g Leu)	≥ 3 resistance sessions / wk emphasizing progressive overload	Focus on total energy and protein adequacy; additional leucine unnecessary when meals reach threshold (Moore et al., 2009; Witard et al., 2014; Morton et al., 2018).
Midlife adults (40–59 yr)	1.2–1.4	25–30 g protein (~2–2.5 g Leu)	≥ 2 resistance sessions / wk + daily activity (> 7,000 steps/day)	Gradual onset of anabolic resistance; ensure even protein distribution (≥ 3 meals/day). Pragmatic range interpolated from young vs older comparisons (Zaromskyte et al., 2021; Deutz et al., 2014).

Age / Phenotype	Daily Protein Target ($g \cdot kg^{-1} \cdot day^{-1}$)	Per-Meal Protein & Leucine Target	Exercise Guidance	Clinical / Practical Considerations
Older adults (≈ 60–70 yr)	1.2–1.6	30–40 g protein (~2.8–3 g Leu)	≥ 2–3 resistance sessions / wk + balance & mobility work	Use leucine-rich sources (whey, dairy, eggs); co-ingest with carbohydrates to enhance insulin-mediated perfusion (Breen et al., 2011; Katsanos et al., 2006; Layman, 2024).
Frail / sarcopenic or clinical adults (≥ 75 yr)	1.4–2.0 †	25–30 g protein (~3 g Leu) in small, frequent meals	Light resistance or neuromuscular electrical stimulation if immobile	Employ leucine-enriched whey or EAA blends; monitor renal function, hydration, and appetite (Bauer et al., 2013; Deutz et al., 2014; Rieu et al., 2006).
Rehabilitation / illness (catabolic states)	1.5–2.0 †	30–40 g protein (~3 g Leu) post-therapy	Protein-timed around physiotherapy sessions	Combine with adequate energy, omega-3 fatty acids, and vitamin D to enhance anabolic response; adjust for renal status (Breen et al., 2011; Burd et al., 2011; Areta et al., 2013).

Notes.

- Meta-analysis indicates resistance-training-induced fat-free-mass gains plateau around ~1.6 $g \cdot kg^{-1} \cdot day^{-1}$ (Morton et al., 2018).
  † Upper-end intakes (≥ 1.8–2.0 $g \cdot kg^{-1} \cdot day^{-1}$) should be used only under medical supervision and with adequate renal function.
- See supporting Supplementary Table S1. Expanded evidence summary for age-specific protein and leucine recommendations

Conclusion

Anabolic resistance is a gradual yet modifiable phenomenon, defined by a blunted muscle-protein-synthesis (MPS) response to both protein ingestion and resistance exercise with advancing age (Breen & Phillips, 2011; Wall et al., 2015; Hodson et al., 2019). It reflects not a substantial decline in basal MPS in otherwise healthy aging, but rather a reduced dynamic responsiveness of muscle to anabolic stimuli—particularly in the post-prandial state (Wall et al., 2015; Markofski et al., 2015). The transition from anabolic sensitivity to resistance unfolds along a continuum beginning in midlife and is

strongly influenced by inactivity, adiposity, and comorbidities (Aragon et al., 2020; Breen & Phillips, 2011; Deutz et al., 2014).

A substantial body of evidence demonstrates that the classic adult RDA of 0.8 $g \cdot kg^{-1} \cdot day^{-1}$ is insufficient to sustain muscle health or function in older age (Bauer et al., 2013; Deutz et al., 2014; Morton et al., 2018). Consensus statements and recent reviews recommend that most older adults—particularly those ≥ 65 years—consume at least 1.0–1.2 $g \cdot kg^{-1} \cdot day^{-1}$, with 1.2–1.6 $g \cdot kg^{-1} \cdot day^{-1}$ emerging as a practical target range for optimal muscle health. Intakes approaching apprximately 2.0 $g \cdot kg^{-1} \cdot day^{-1}$ may be appropriate during periods of severe illness or rehabilitation, provided renal function is adequate; this represents an upper pragmatic target rather than a universal prescription (Bauer et al., 2013; Deutz et al., 2014; Traylor et al., 2018; Aragon et al., 2020).

Per-meal protein doses should meet the leucine threshold—approximately 20–25 g of high-quality protein (≈ 2 g leucine) in young adults, and 25–40 g (≥ 2.5–3.0 g leucine) in older adults—particularly when combined with resistance exercise (Moore et al., 2009; Witard et al., 2014; Breen & Phillips, 2011; Layman, 2024; Zaromskyte et al., 2021).

For clinicians, the practical implications are clear. In young, resistance-trained adults, standard sports-nutrition practices—around 1.6 $g \cdot kg^{-1} \cdot day^{-1}$ distributed across 3–4 protein-rich meals—are sufficient to maximize training-induced gains without additional leucine supplementation once per-meal protein reaches ≈ 20 g (Morton et al., 2018; Aragon et al., 2020; Layman, 2024; Zaromskyte et al., 2021). In middle-aged adults, especially those with early metabolic risk, a gradual shift toward higher-than-RDA protein intakes, balanced meal distribution, and consistent resistance training provides an evidence-based preventive approach against emerging anabolic resistance (Breen & Phillips, 2011; Hodson et al., 2019; Aragon et al., 2020). In adults in their late 50s and beyond—particularly those ≥ 65 years—protein prescriptions should generally fall within 1.2–1.6 $g \cdot kg^{-1} \cdot day^{-1}$, with per-meal leucine targets of ≈ 2.5–3.0 g and a strong emphasis on regular resistance exercise to

counteract anabolic resistance and sarcopenia (Bauer et al., 2013; Deutz et al., 2014; Layman, 2024; Aragon et al., 2020; Breen & Phillips, 2011). Tailoring these recommendations to individual health status, renal function, appetite, and functional capacity remains essential to optimize outcomes in clinical practice (Bauer et al., 2013; Deutz et al., 2014).

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