Defining anabolic resistance: Implications for delivery of clinical care nutrition

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Defining anabolic resistance: implications for delivery of clinical care nutrition

Robert W. Morton[a], *Daniel A. Traylor*[a], *Peter J.M. Weijs*[b,c,d], *and Stuart M. Phillips*[a]

Purpose of review
Skeletal muscle mass with aging, during critical care, and following critical care is a determinant of quality of life and survival. In this review, we discuss the mechanisms that underpin skeletal muscle atrophy and recommendations to offset skeletal muscle atrophy with aging and during, as well as following, critical care.

Recent findings
Anabolic resistance is responsible, in part, for skeletal muscle atrophy with aging, muscle disuse, and during disease states. Anabolic resistance describes the reduced stimulation of muscle protein synthesis to a given dose of protein/amino acids and contributes to declines in skeletal muscle mass. Physical inactivity induces: anabolic resistance (that is likely exacerbated with aging), insulin resistance, systemic inflammation, decreased satellite cell content, and decreased capillary density. Critical illness results in rapid skeletal muscle atrophy that is a result of both anabolic resistance and enhanced skeletal muscle breakdown.

Summary
Insofar as atrophic loss of skeletal muscle mass is concerned, anabolic resistance is a principal determinant of age-induced losses and appears to be a contributor to critical illness-induced skeletal muscle atrophy. Older individuals should perform exercise using both heavy and light loads three times per week, ingest at least 1.2 g of protein/kg/day, evenly distribute their meals into protein boluses of 0.40 g/kg, and consume protein within 2 h of retiring for sleep. During critical care, early, frequent, and multimodal physical therapies in combination with early, enteral, hypocaloric energy (~10–15 kcal/kg/day), and high-protein (>1.2 g/kg/day) provision is recommended.

Keywords
amino acids, muscle, protein turnover

INTRODUCTION

Aging results in progressive and slow loss of skeletal muscle (sarcopenia) [1]. In contrast, critical illness results in rapid skeletal muscle atrophy [2,3]. Skeletal muscle atrophy is a risk factor for all-cause morbidity and mortality both as we age [4,5] and during critical illness [6,7]. Skeletal muscle mass is determined by the balance in muscle protein turnover [e.g. the algebraic difference between muscle protein synthesis (MPS) and muscle protein breakdown (MPB)]. Anabolic resistance is the inability of an anabolic stimulus (e.g. protein provision, hormonal stimulation, and/or muscle contraction) to stimulate MPS and occurs with increasing age [8▪,9,10▪,11▪,12], periods of inactivity [13,14], and during critical illness [15,16,17▪▪,18,19]. This review aims to provide evidence that anabolic resistance is a principal contributor of age-induced, a major contributor of disuse-induced, and a secondary contributor to critical illness-induced skeletal muscle atrophy. We discuss how whole-body and muscle protein turnover are altered with age, inactivity, and critical illness before elaborating on how insulin resistance, systemic inflammation, satellite cells, and alterations in the microvasculature contribute to anabolic resistance. The latter portion of the review prescribes strategies

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KEY POINTS

- Anabolic resistance is a chief regulator of age-induced skeletal muscle atrophy.
- Physical inactivity and muscle disuse accelerate skeletal muscle atrophy in health and critical illness primarily via anabolic resistance.
- Critical illness, unlike aging and inactivity, results in rapid skeletal muscle breakdown as well as anabolic resistance, and thus results in rapid reductions in skeletal muscle mass.
- Early, frequent, and multimodal physical therapies in combination with early, enteral (if possible), hypocaloric, and high-protein provision are effective strategies to maintain skeletal muscle mass during critical care.

that maintain muscle mass in older and critically ill persons.

ANABOLIC RESISTANCE

When fasted (postabsorptive) and at rest there is no difference in the net muscle protein turnover between young and older persons [8▪,9,10▪,11▪]; however, we spend approximately 16 h of the day under some degree of feeding-induced stimulation of MPS. With aging we become anabolically resistant to both feeding (e.g. amino acids) and muscle contraction [e.g. resistance exercise training (RET)] [8▪,9,10▪,11▪,12], both of which underpin an inability to increase or maintain skeletal muscle mass in older adults [20▪]. Anabolic resistance is chiefly responsible for skeletal muscle atrophy as we age.

Short periods of physical inactivity result in skeletal muscle atrophy in young [21], middle-aged [22], and old [13,14] healthy persons. Mild forms of inactivity (e.g. step reduction) do not result in any change in postabsorptive MPS [13], but substantial inactivity/disuse (e.g. bed rest) decreases MPS with no change in MPB [23]. Regardless, all inactivity-induced skeletal muscle atrophy is underpinned by anabolic resistance [13,14], which ultimately results in decreased integrated MPS over the period of inactivity [24▪] and skeletal muscle atrophy [13,14,21,22]. Anabolic resistance is primarily responsible for inactivity-induced skeletal muscle atrophy, though severe forms of disuse may deter postabsorptive muscle protein balance as well.

Admission to critical care (e.g. the ICU) often results in nosocomial morbidities [25], an inability to fully recover [26,27], and significant economic burden [28]. The severe and rapid skeletal muscle atrophy that occurs during critical illness [2,3] is a well known risk factor for a variety of clinical care outcomes (e.g. length of stay, in-hospital mortality, and 6-month mortality) [6,7]. The anabolic resistance to amino acid provision during critical illness [15,16,17▪▪,18,19] is presumably a product of the bedrest necessitated during critical care and the increased age of critical ill populations [6,7]; however, unlike aging and inactivity, critical illness results in rapid changes in postabsorptive protein turnover. Critically ill patients are in a negative net whole-body [15,16,17▪▪,18,19,29,30] and muscle [2,3] protein balance with dramatic increases in the rate of whole-body [15,16,31] and muscle [3,29] protein turnover. The elevated whole-body protein turnover is accompanied by similar [3,29] or lower [2] rates of MPS and considerably elevated MPB [29]. In combination with anabolic resistance, the reduced synthesis and elevated breakdown of skeletal muscle proteins at rest results in accelerated skeletal muscle atrophy. It is likely that the rapid postabsorptive breakdown of skeletal muscle during critical care is necessary to support glycaemia (through gluconeogenesis) and the elevated protein turnover of other organs (e.g. the gut; Fig. 1).

CONTRIBUTORS TO ANABOLIC RESISTANCE: INSULIN RESISTANCE

Aging [8▪,10▪] and critical illness [2,15,16,32] are associated with an increase in insulin resistance, although it is hard to separate out the influence of inactivity [13,24▪,33]. Inactivity provokes insulin resistance in as little as 7–14 days compared with baseline values (circulating insulin: ~11 vs. 5–7 μIU/ml; [13,21,24▪]). Though critical illness is an independent risk factor for the development of type II diabetes [27], insulin resistance in this patient group is more probably a product of inactivity and disuse. In addition, low physical activity can precipitate obesity [34], which often leads to type II diabetes [10▪,35,36]. Individuals who are insulin-resistant do not have altered postabsorptive MPS [13,35,37] but may be anabolically resistant to hyperaminoacidemia [10▪,13,35]. As insulin resistance does not necessitate anabolic resistance (e.g. anabolic resistance in older adults [10▪]), insulin-mediated anabolic resistance is secondary to the development of anabolic resistance.

CONTRIBUTORS TO ANABOLIC RESISTANCE: INFLAMMATION

In contrast to insulin resistance, chronic low-grade systemic inflammation is a hallmark of aging and is an independent risk factor for both morbidity and mortality [38]. The most commonly measured markers of inflammation are tumor necrosis factor alpha (TNFα), C-reactive protein (CRP), and interleukin-6 (IL-6).

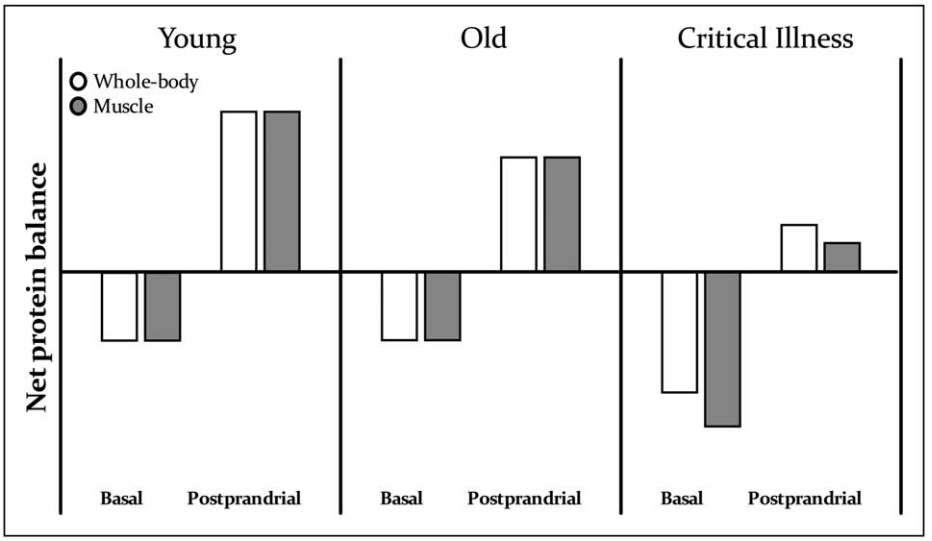

FIGURE 1. Net whole-body and muscle protein balance in young, old, and critically ill persons. There is no change in basal protein turnover between young and older individuals but there is a dramatic reduction in net whole-body protein balance with critical illness, primarily driven by skeletal muscle. Older individuals are anabolically resistant to hyperaminoacidemia, which is exaggerated during critical illness because of substantial disuse.

There are elevations in inflammation with aging (e.g. TNFα: ~3 vs. 1.5 pg/ml and IL-6: ~3 vs. 1 pg/ml [10▪,13,24▪]), disuse (IL-6: ~4 vs. 1 pg/ml [13,24▪,33]), and marked increases with critical illness (e.g. CRP: ~5 vs. 1 mg/l; [15,16,32]), compared with healthy controls. Although the severity depends on the condition (e.g. sepsis), critical illness results in the most severe systemic inflammation.

Older individuals [10▪], obese individuals [10▪,35], and patients undergoing periods of disuse [13], all of which increase inflammation to varying magnitudes, do not necessitate alterations in postabsorptive protein turnover but instead result in anabolic resistance to hyperaminoacidemia. Though critically ill patients present altered postabsorptive protein turnover with systemic inflammation, other chronic conditions with severe muscle atrophy and inflammation do not perturb postabsorptive MPS (e.g. rheumatoid arthritis) [39]. Like insulin resistance, systemic inflammation does not necessitate perturbed postabsorptive MPS; however, unlike insulin resistance, inflammation is consistently present with anabolic resistance to hyperaminoacidemia. Systemic inflammation is a more probable instigator of anabolic resistance than insulin resistance, but a cause-and-effect relationship remains largely unstudied *in vivo*.

CONTRIBUTORS TO ANABOLIC RESISTANCE: SATELLITE CELLS AND MICROVASCULATURE

Satellite cells are stem cells on the periphery of skeletal muscle fibres that support the regeneration of skeletal muscle following damage (e.g. critical illness) [40]. The number of satellite cells, specifically around type II fibres, decreases with age [41,42], disuse [22], and critical illness [43], making them a potential candidate for contribution towards anabolic resistance. In addition, microvasculature (e.g. capillary density) decreases, specifically those that surround type II fibres, with age [11▪,41,42] and during periods of disuse [22], which was recently found to predict insulin resistance [44]. Though capillary density at baseline may influence RET-induced skeletal muscle hypertrophy [45▪], capillary perfusion has no influence on anabolic resistance to hyperaminoacidemia [11▪]. Aging and inactivity, despite a decrease in satellite cell and capillary density, have no effect on postabsorptive muscle protein turnover [8▪,9,10▪,11▪]. To date, beyond characterizing age-induced and/or RET-induced disparities in content, there is little human in vivo evidence to suggest satellite cell or capillary density modulate anabolic resistance.

CONTRIBUTORS TO ANABOLIC RESISTANCE: SUMMARY

Postabsorptive muscle protein turnover is largely unaffected by age, moderate inactivity, insulin resistance, systemic inflammation, satellite cell content, or capillary density. Any change in resting muscle protein turnover, particularly MPB, is driven by a demand for amino acids from other organs as seen in critical illness alone. Insulin resistance may contribute to existing anabolic resistance; however, systemic inflammation and decreased satellite cell

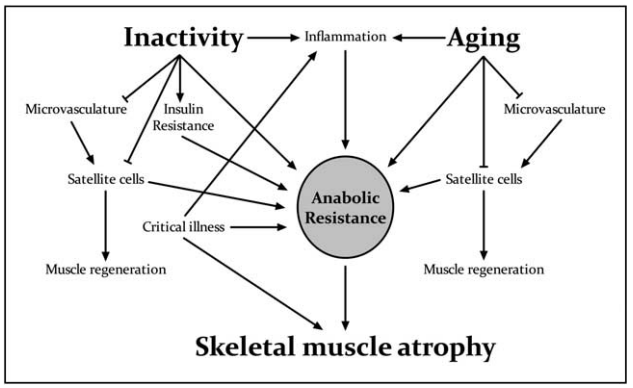

FIGURE 2. Moderators of anabolic resistance. Anabolic resistance occurs as we age and during periods of physical inactivity. Inactivity largely, and age to a lesser extent, contributes to anabolic resistance during critical care. Systemic inflammation occurs with increased age, inactivity, and during critical illness and may influence anabolic resistance. Inactivity, unlike aging and critical illness, results in insulin resistance, which may also contribute to anabolic resistance. Both physical inactivity and age result in a decrease in microvasculature, which may influence satellite cell function. The reduced satellite cell content in older adults and following periods of disuse may affect anabolic resistance but certainly impair muscle regeneration, which is particularly important following the disuse following critical care.

content are consistently present in populations with anabolic resistance. Anabolic resistance, insulin resistance, and systemic inflammation are augmented in obese older adults compared with healthy-weight older adults suggesting that, even if not the source, insulin resistance and systemic inflammation are secondary confounders of anabolic resistance [10▪]. Aging presents systemic inflammation, a reduction in satellite cells, a reduction in capillary density, and anabolic resistance but meek in relation to physical inactivity, which also yields insulin resistance. We propose physical inactivity is the chief contributor to anabolic resistance and its origin in older adults and critically ill patients (Fig. 2).

IMPLICATIONS FOR CRITICAL CARE: NUTRITION

Healthy older adults consume ~1.0 to 1.1 g protein/kg bodyweight/day in a skewed pattern that equates to approximately 10 g at breakfast, 25 g at lunch, and 35 g at dinner [1]. Healthy older individuals are anabolically resistant compared with their younger counterparts and require ~0.4 g protein/kg doses (or ~30 g in a 70 kg older adult) to maximally stimulate MPS [12]. Whey protein and leucine have been identified as the most anabolic protein source and amino acid, respectively [46], and it is well documented that supplementing suboptimal protein doses with additional leucine can offset anabolic resistance in both healthy [47▪,48] and unhealthy [32,48] older adults.

In the ICU, feeding is either enteral or parenteral. Whenever possible, switching from parenteral to enteral methods of energy provision alone can reduce the time spent in critical care and risk of infection [49]. With enteral feeding, nutrition is either delivered continuously or intermittently but to date, there is no data to suggest one method is better than the other [50]. Regardless of the mode (enteral or parenteral) or pattern (continuous or intermittent) of delivery, providing protein improves whole-body protein balance in critically ill populations [15,16,17▪▪,18,19,30,32,48]. Current protein recommendations during critical illness are ~1.2 g/kg/day [51▪] but there is a positive correlation between the amount of amino acids provided and net protein balance [19,30,32,48] with little or no increase in oxidation or urea production with infusions upwards of 1.5–2.5 g/kg/day [17▪▪,19,30]. Independent of total energy intake [52,53▪], provision of greater protein may improve a variety of clinical outcomes including reduced length of hospitalization and mortality [52,54▪▪]. In addition, starting nutritional provision early can reduce risk of nosocomial infection and, along with increased protein provision, has been recommended by many expert groups [55▪▪,56].

IMPLICATIONS FOR CRITICAL CARE: RESISTANCE EXERCISE TRAINING AND PHYSICAL THERAPY

Protein supplementation alone does not improve muscle mass or strength in healthy older adults [57▪], which highlights the importance of muscle contraction as the more potent [20▪] and nutrient-sensitizing [47▪,58] stimulus. RET increases net muscle protein balance [9], increases skeletal muscle mass [8▪,45▪,59▪], improves insulin sensitivity [8▪], increases satellite cell number [45▪], improves vascular conductance [8▪], increases capillary density [42], and reduces risk for premature mortality [60▪▪] in older adults. Increasing muscle mass throughout our healthy lifespan is important considering pre-existing muscle mass and strength are predictors of morbidity and mortality in the ICU [6,7]. In critical care, physical therapy (e.g. bedside sitting, neuromuscular stimulation, stretching, cycle ergometers, walking) can increase strength, improve independence at discharge, and reduce 6-month posthospitalization mortality [61▪▪]. Physical therapies in combination with respiratory therapy (e.g. inspiring

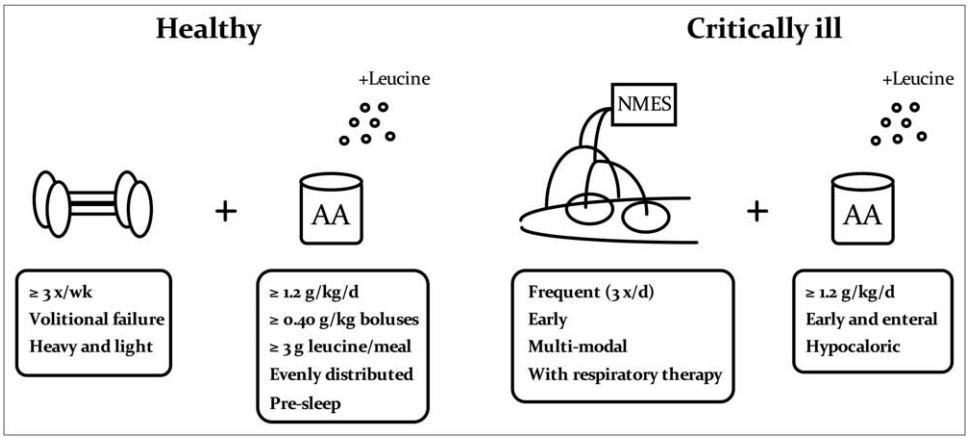

FIGURE 3. Recommendations for maintaining skeletal muscle mass in healthy and critically ill patients. AA, amino acids and NMES, neuromuscular electrical stimulation (as an example of a physical therapy to be combined with conventional therapies).

against resistance set by a mechanical ventilator, active coughing, deep breathing) are particularly effective, well tolerated [62,63▪–65▪], and cost-efficient [65▪,66] strategies during critical care.

Skeletal muscle weakness following ICU discharge is a common morbidity in critical illness survivors [26]. Patients discharged from the ICU have an attenuated rate and capacity to regain muscle mass [67], which highlights the benefit of pre-critical care RET to increase the regenerative capacity of skeletal muscle [45▪]. Following discharge from the ICU, home-based or hospital-based physical therapy improves a variety of clinical outcomes and should be a staple prescription following critical care [66,68].

IMPLICATIONS FOR CRITICAL CARE: SUMMARY

To maintain muscle mass as we age, older individuals should perform RET using heavier and lighter load resistance exercise at least three times per week [59▪], ingest at least 1.2 g of protein/kg/day [20▪] with evenly distributed protein boluses [1] of ~0.40 g/kg [12] with a recommendation to consume a protein-containing meal presleep [58]. Fortifying suboptimal protein meals with ~3 g of leucine is an emerging strategy in older individuals who cannot consume multiple high-protein meals [47▪]. During critical care, an integrative support team should include early and frequent physical therapies [62] and, though consideration for the individual's specific condition (e.g. renal failure, hyperglycemic shock, gastrointestinal surgery) is necessary, early [55▪▪], enteral [49], hypocaloric (~10–15 kcal/kg/day) [69], and high-protein (1.2–2.0 g/kg/day) [19,30,32,48] feeding. Similar to healthy adults, leucine fortification might be considered as an emerging strategy to offset anabolic resistance and maintain muscle mass during critical care, particularly if high energy or protein intakes are not well tolerated [32,48] (Fig. 3).

CONCLUSION

Anabolic resistance is a principal moderator of age-induced skeletal muscle atrophy. Physical inactivity results in anabolic resistance and, whenever substantial (e.g. bed rest), results in a reduction in postabsorptive muscle protein balance. Aging is characterized by low-grade systemic inflammation, a reduction in satellite cell number and activity, and a reduction in capillary density; however, physical inactivity and muscle disuse are more severe physiological challenges that exacerbate age-related conditions and result in rapid insulin resistance. Critical illness results in rapid skeletal muscle atrophy via the enhanced net breakdown of skeletal muscle (increased MPB and suppressed MPS) to support the amino acid demand for protein turnover and gluconeogenesis set by other organs. Skeletal muscle disuse, and to a lesser extent aging, accelerates skeletal muscle atrophy during critical care by bringing about anabolic resistance. Muscle contraction and protein feeding are important lifestyle interventions that are effective, feasible, and cost-efficient in both healthy and critically ill persons.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Farsijani S, Morais JA, Payette H, *et al.* Relation between mealtime distribution of protein intake and lean mass loss in free-living older adults of the NuAge study. Am J Clin Nutr 2016; 104:694–703.
2. Puthucheary ZA, Rawal J, McPhail M, *et al.* Acute skeletal muscle wasting in critical illness. JAMA 2013; 310:1591–1600.
3. MacDonald AJ, Johns N, Stephens N, *et al.* Habitual myofibrillar protein synthesis is normal in patients with upper GI cancer cachexia. Clin Cancer Res 2015; 21:1734–1740.
4. Metter EJ, Talbot LA, Schrager M, Conwit R. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. J Gerontol A Biol Sci Med Sci 2002; 57:B359–B365.
5. Fantin F, Di Francesco V, Fontana G, *et al.* Longitudinal body composition changes in old men and women: interraltionships with worsening disability. J Gerontol A Biol Sci Med Sci 2007; 62:1375–1381.
6. Mueller N, Murthy S, Tainter CR, *et al.* Can sarcopenia quantified by ultrasound of the rectus femoris muscle predict adverse outcome of surgical intensive care unit patients as well as frailty? A prospective, observational cohort study. Ann Surg 2016; 264:1116–1124.
7. Looijaard WG, Dekker IM, Stapel SN, *et al.* Skeletal muscle quality as assessed by CT-derived skeletal muscle density is associated with 6-month mortality in mechanically ventilated critically ill patients. Crit Care 2016; 20:386.
8. ■ Phillips BE, Williams JP, Greenhaff PL, *et al.* Physiological adaptations to resistance exercise as a function of age. JCI Insight 2017; 2(17). pii: 95581. doi: 10.1172/jci.insight.95581. [Epub ahead of print]

This study found that resistance exercise training improves insulin sensitivity in older indivduals, despite no change in leg vascular conductance. Older individuals were anabolically resistant to an acute bout of resistance exercise and protein feeding and there was an accompanying negative correlation between age-induced and training-induced muscle hypertrophy after the 20 weeks of training.

9. Brook MS, Wilkinson DJ, Mitchell WK, *et al.* Synchronous deficits in cumulative muscle protein synthesis and ribosomal biogenesis underlie age-related anabolic resistance to exercise in humans. J Physiol 2016; 594:7399–7417.
10. ■ Smeuninx B, McKendry J, Wilson D, *et al.* Age-related anabolic resistance of myofibrillar protein synthesis is exacerbated in obese inactive individuals. J Clin Endocrinol Metab 2017; 102:3535–3545.

This study compared young, old, and obese older individuals and found that age does not necessitate insulin resistance and that obesity is a greater moderator of insulin resistance and systemic inflammation. Though anabolic resistance was present in older adults, it was more pronounced whenever the older adults were obese, suggesting a role for insulin sensitivity and systemic inflammation on anabolic resistance.

11. ■ Mitchell WK, Phillips BE, Wilkinson DJ, *et al.* Supplementing essential amino acids with the nitric oxide precursor, l-arginine, enhances skeletal muscle perfusion without impacting anabolism in older men. Clin Nutr 2017; 36:1573–1579.

This study found that increased perfusion of muscle capillaries does not improve anabolic sensitivity in older men. This study suggests microvascular does not acutely govern anabolic resistance to hyperaminoacidemia.

12. Moore DR, Churchward-Venne TA, Witard O, *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; 70:57–62.
13. Breen L, Stokes KA, Churchward-Venne TA, *et al.* Two weeks of reduced activity decreases leg lean mass and induces 'anabolic resistance' of myofibrillar protein synthesis in healthy elderly. J Clin Endocrinol Metab 2013; 98:2604–2612.
14. Tanner RE, Brunker LB, Agergaard J, *et al.* Age-related differences in lean mass, protein synthesis and skeletal muscle markers of proteolysis after bed rest and exercise rehabilitation. J Physiol 2015; 593:4259–4273.
15. Liebau F, Wernerman J, van Loon LJ, Rooyackers O. Effect of initiating enteral protein feeding on whole-body protein turnover in critically ill patients. Am J Clin Nutr 2015; 101:549–557.
16. van Dijk DP, van de Poll MC, Moses AG, *et al.* Effects of oral meal feeding on whole body protein breakdown and protein synthesis in cachectic pancreatic cancer patients. J Cachexia Sarcopenia Muscle 2015; 6:212–221.
17. ■■ Sundstrom Rehal M, Liebau F, Tjader I, *et al.* A supplemental intravenous amino acid infusion sustains a positive protein balance for 24 h in critically ill patients. Crit Care 2017; 21:298.

This is the newest study to measure protein metabolism in critically ill patients. Supplemental amino acid infusion on top of 1 g/kg/day for 24 h increased whole-body protein balance from negative to positive without an increase in amino acid oxidation or increase in plasma urea. This study supports the recommendation for high protein provision in critical care.

18. Berg A, Rooyackers O, Bellander BM, Wernerman J. Whole body protein kinetics during hypocaloric and normocaloric feeding in critically ill patients. Crit Care 2013; 17:R158.
19. Liebau F, Sundstrom M, van Loon LJ, *et al.* Short-term amino acid infusion improves protein balance in critically ill patients. Crit Care 2015; 19:106.
20. ■ Morton RW, Murphy KT, McKellar SR, *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 2017, doi: 10.1136/bjsports-2017-097608. [Epub ahead of print].

This large meta-analysis (>1800 participants) found that protein supplementation augments resistance exercise training-induced changes in muscle mass and strength, but that older adults are anabolically resistant to the benefit of protein supplementation. The meta-analysis also shows that resistance exercise training is more potent than protein supplementation on changes in strength and muscle mass.

21. Dirks ML, Wall BT, van de Valk B, *et al.* One week of bed rest leads to substantial muscle atrophy and induces whole-body insulin resistance in the absence of skeletal muscle lipid accumulation. Diabetes 2016; 65: 2862–2875.
22. Arentson-Lantz EJ, English KL, Paddon-Jones D, Fry CS. Fourteen days of bed rest induces a decline in satellite cell content and robust atrophy of skeletal muscle fibers in middle-aged adults. J Appl Physiol (1985) 19852016; 120:965–975.
23. Symons TB, Sheffield-Moore M, Chinkes DL, *et al.* Artificial gravity maintains skeletal muscle protein synthesis during 21 days of simulated microgravity. J Appl Physiol (1985) 2009; 107:34–38.
24. ■ McGlory C, von Allmen MT, Stokes T, *et al.* Failed recovery of glycemic control and myofibrillar protein synthesis with two weeks of physical inactivity in overweight, prediabetic older adults. J Gerontol A Biol Sci Med Sci 2017, doi: 10.1093/gerona/glx203. [Epub ahead of print].

This study found that step reduction reduced integrative muscle protein synthesis and glycaemic control and that they are not fully recovered when activity was returned back to baseline.

25. Rodriguez-Acelas AL, de Abreu Almeida M, Engelman B, Canon-Montanez W. Risk factors for healthcare-associated infection in hospitalized adults: systematic review and meta-analysis. Am J Infect Control 2017; 45:e149–e156.
26. Latronico N, Herridge M, Hopkins RO, *et al.* The ICM research agenda on intensive care unit-acquired weakness. Intensive Care Med 2017; 43: 1270–1281.
27. Ali Abdelhamid Y, Kar P, Finnis ME, *et al.* Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. Crit Care 2016; 20:301.
28. Unroe M, Kahn JM, Carson SS, *et al.* One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. Ann Intern Med 2010; 153:167–175.
29. Klaude M, Mori M, Tjader I, *et al.* Protein metabolism and gene expression in skeletal muscle of critically ill patients with sepsis. Clin Sci (Lond) 2012; 122:133–142.
30. Dickerson RN, Maish GO3rd, Croce MA, *et al.* Influence of aging on nitrogen accretion during critical illness. JPEN J Parenter Enteral Nutr 2015; 39:282–290.
31. Rooyackers O, Kouchek-Zadeh R, Tjader I, *et al.* Whole body protein turnover in critically ill patients with multiple organ failure. Clin Nutr 2015; 34:95–100.
32. Engelen MP, Safar AM, Bartter T, *et al.* High anabolic potential of essential amino acid mixtures in advanced nonsmall cell lung cancer. Ann Oncol 2015; 26:1960–1966.
33. Reidy PT, Lindsay CC, McKenzie AI, *et al.* Aging-related effects of bed rest followed by eccentric exercise rehabilitation on skeletal muscle macrophages and insulin sensitivity. Exp Gerontol 2017, doi: 10.1016/j.exger.2017.07.001. [Epub ahead of print].
34. Pietilainen KH, Kaprio J, Borg P, *et al.* Physical inactivity and obesity: a vicious circle. Obesity (Silver Spring) 2008; 16:409–414.
35. Beals JW, Sukiennik RA, Nallabelli J, *et al.* Anabolic sensitivity of postprandial muscle protein synthesis to the ingestion of a protein-dense food is reduced in overweight and obese young adults. Am J Clin Nutr 2016; 104:1014–1022.
36. Murton AJ, Marimuthu K, Mallinson JE, *et al.* Obesity appears to be associated with altered muscle protein synthetic and breakdown responses to increased nutrient delivery in older men, but not reduced muscle mass or contractile function. Diabetes 2015; 64:3160–3171.

37. Beals JW, Mackenzie RWA, van Vliet S, *et al.* Protein-rich food ingestion stimulates mitochondrial protein synthesis in sedentary young adults of different BMIs. J Clin Endocrinol Metab 2017; 102:3415–3424.

38. Fougere B, Boulanger E, Nourhashemi F, *et al.* Chronic inflammation: accelerator of biological aging. J Gerontol A Biol Sci Med Sci 2017; 72: 1218–1225.

39. Mikkelsen UR, Dideriksen K, Andersen MB, *et al.* Preserved skeletal muscle protein anabolic response to acute exercise and protein intake in well treated rheumatoid arthritis patients. Arthritis Res Ther 2015; 17:271.

40. Dos Santos C, Hussain SN, Mathur S, *et al.,* MEND ICU Group; RECOVER Program Investigators; Canadian Critical Care Translational Biology Group. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. a pilot study. Am J Respir Crit Care Med 2016; 194:821–830.

41. Nederveen JP, Joanisse S, Snijders T, *et al.* Skeletal muscle satellite cells are located at a closer proximity to capillaries in healthy young compared with older men. J Cachexia Sarcopenia Muscle 2016; 7:547–554.

42. Verdijk LB, Snijders T, Holloway TM, *et al.* Resistance training increases skeletal muscle capillarization in healthy older men. Med Sci Sports Exerc 2016; 48:2157–2164.

43. Fry CS, Porter C, Sidossis LS, *et al.* Satellite cell activation and apoptosis in skeletal muscle from severely burned children. J Physiol 2016; 594: 5223–5236.

44. Snijders T, Nederveen JP, Verdijk LB, *et al.* Muscle fiber capillarization as determining factor on indices of insulin sensitivity in humans. Physiol Rep 2017; 5:; pii: e13278.

45. ■ Snijders T, Nederveen JP, Joanisse S, *et al.* Muscle fibre capillarization is a critical factor in muscle fibre hypertrophy during resistance exercise training in older men. J Cachexia Sarcopenia Muscle 2017; 8:267–276.

This study found that capillary density is associated with resistance exercise training-induced skeletal muscle hypertrophy, suggesting that capillaries at least partially modulate contraction-induced muscle anabolism.

46. Gorissen SH, Horstman AM, Franssen R, *et al.* Ingestion of wheat protein increases in vivo muscle protein synthesis rates in healthy older men in a randomized trial. J Nutr 2016; 146:1651–1659.

47. ■ Wilkinson DJ, Bukhari SSI, Phillips BE, *et al.* Effects of leucine-enriched essential amino acid and whey protein bolus dosing upon skeletal muscle protein synthesis at rest and after exercise in older women. Clin Nutr 2017, doi: 10.1016/j.clnu.2017.09.008. [Epub ahead of print].

This study found that small essential amino acid supplements fortified with even small amounts of leucine (1.5 g) can similarly stimulate myofibrillar protein synthesis compared with that of higher protein intakes (40 g of whey protein) in older women. This study provides support for additional leucine 'top ups' in older populations to maintain muscle mass.

48. Jonker R, Deutz NE, Erbland ML, *et al.* Effectiveness of essential amino acid supplementation in stimulating whole body net protein anabolism is comparable between COPD patients and healthy older adults. Metabolism 2017; 69:120–129.

49. Elke G, van Zanten AR, Lemieux M, *et al.* Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care 2016; 20:117.

50. Di Girolamo FG, Situlin R, Fiotti N, Biolo G. Intermittent vs. continuous enteral feeding to prevent catabolism in acutely ill adult and pediatric patients. Curr Opin Clin Nutr Metab Care 2017; 20:390–395.

51. ■ Arends J, Bachmann P, Baracos V, *et al.* ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017; 36:11–48.

These are the latest critical care nutrition guidelines, which advocate for ~1.2 g of protein/kg/day.

52. Nicolo M, Heyland DK, Chittams J, *et al.* Clinical outcomes related to protein delivery in a critically ill population: a multicenter, multinational observation study. JPEN J Parenter Enteral Nutr 2016; 40:45–51.

53. ■ Rugeles SJ, Ochoa Gautier JB, Dickerson RN, *et al.* How many nonprotein calories does a critically ill patient require? A case for hypocaloric nutrition in the critically ill patient. Nutr Clin Pract 2017; 32(1 Suppl):S72–S76.

This recent review recommends reduced caloric provision (~15 kcal/kg/day) with higher protein intakes (1.5 g/kg/day).

54. ■■ Compher C, Chittams J, Sammarco T, *et al.* Greater protein and energy intake may be associated with improved mortality in higher risk critically ill patients: a multicenter, multinational observational study. Crit Care Med 2017; 45:156–163.

This large study (>202 intensive care units and > 2500 patients) showed that patients with a high-risk for malnutrition (quantified with the NUTRIC score) had reduced mortality and shorter time to discharge with greater protein and energy provision.

55. ■■ Reintam Blaser A, Starkopf J, Alhazzani W, *et al.* Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med 2017; 43:380–398.

This series of meta-analyses highlight the lack of quality data that compare timing (early vs. late) and mode of delivery (parenteral vs. enteral) in critical care nutrition but conclude that early eneteral nutritional support is the most advantageous.

56. Weijs PJM. Protein nutrition and exercise survival kit for critically ill. Curr Opin Crit Care 2017; 23:279–283.

57. ■ Tieland M, Franssen R, Dullemeijer C, *et al.* The impact of dietary protein or amino acid supplementation on muscle mass and strength in elderly people: individual participant data and meta-analysis of RCT's. J Nutr Health Aging 2017; 21:994–1001.

This meta-analysis illustrates the lack of efficacy protein supplementation has on older individuals without exercise interventions.

58. Holwerda AM, Kouw IW, Trommelen J, *et al.* Physical activity performed in the evening increases the overnight muscle protein synthetic response to presleep protein ingestion in older men. J Nutr 2016; 146:1307–1314.

59. ■ Stec MJ, Thalacker-Mercer A, Mayhew DL, *et al.* Randomized, four-arm, dose-response clinical trial to optimize resistance exercise training for older adults with age-related muscle atrophy. Exp Gerontol 2017; 99:98–109.

This resistance exercise training trial in older adults provides evidence that combining high- and low-load resistance exercise training may be optimal.

60. ■■ Stamatakis E, Lee IM, Bennie J, *et al.* Does strength promoting exercise confer unique health benefits? A pooled analysis of eleven population cohorts with all-cause, cancer, and cardiovascular mortality endpoints. Am J Epidemiol 2017, doi: 10.1093/aje/kwx345. [Epub ahead of print].

This large epidemiological study (>80 000 participants) found that performing resistance-type exercise at least two times per week decreased all-cause and cancer mortality.

61. ■■ Tipping CJ, Harrold M, Holland A, *et al.* The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. Intensive Care Med 2017; 43:171–183.

This systematic review and meta-analysis (>1700 patients) found that active mobilization and rehabilitation in the intensive care unit improves muscle function upon discharge and days free-living after 6 months of discharge.

62. Laurent H, Aubreton S, Richard R, *et al.* Systematic review of early exercise in intensive care: a qualitative approach. Anaesth Crit Care Pain Med 2016; 35:133–149.

63. ■ Dall' Acqua AM, Sachetti A, Santos LJ, *et al.* Use of neuromuscular electrical stimulation to preserve the thickness of abdominal and chest muscles of critically ill patients: a randomized clinical trial. J Rehabil Med 2017; 49:40–48.

This study found that combining neuromuscular stimulation with conventional physical therapies maintained muscle mass whereas conventional physical therapy did not. This study adds to the support for neuromuscular stimulation in critically ill populations.

64. ■ Machado ADS, Pires-Neto RC, Carvalho MTX, *et al.* Effects that passive cycling exercise have on muscle strength, duration of mechanical ventilation, and length of hospital stay in critically ill patients: a randomized clinical trial. J Bras Pneumol 2017; 43:134–139.

This study found that passive cycling in combination with conventional physical therapy resulted in greater increases in physical strength than conventional physical therapy alone. This study supports the use of passive cycling and multiple physical therapies in critically ill patients.

65. ■ Gruther W, Pieber K, Steiner I, *et al.* Can early rehabilitation on the general ward after an intensive care unit stay reduce hospital length of stay in survivors of critical illness?: a randomized controlled trial. Am J Phys Med Rehabil 2017; 96:607–615.

This study found that early phsyical therapy following discharge from the intensive care unit reduced hospital stay and decreased total hospital costs, supporting the importance for early mobilization in critically ill populations.

66. Vitacca M, Barbano L, Vanoglio F, *et al.* Does 6-month home caregiver-supervised physiotherapy improve postcritical care outcomes?: a randomized controlled trial. Am J Phys Med Rehabil 2016; 95:571–579.

67. Fischer A, Spiegl M, Altmann K, *et al.* Muscle mass, strength and functional outcomes in critically ill patients after cardiothoracic surgery: does neuromuscular electrical stimulation help? The Catastim 2 randomized controlled trial. Crit Care 2016; 20:30.

68. Patsaki I, Gerovasili V, Sidiras G, *et al.* Effect of neuromuscular stimulation and individualized rehabilitation on muscle strength in intensive care unit survivors: a randomized trial. J Crit Care 2017; 40:76–82.

69. Reignier J, Boisramé-Helms J, Brisard L, *et al.,* NUTRIREA-2 Trial Investigators; Clinical Research in Intensive Care and Sepsis (CRICS) group. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). The Lancet 2017; 391:133–143.