Muscle Loss: Nutritional Countermeasures

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Abstract

Inactivity-mediated protein catabolism occurs in many circumstances ranging from catastrophic events such as severe illness or injury, to unique environments such as spaceflight/microgravity, to more insidious causes such as physical frailty and the progression of aging. Nevertheless, regardless of the etiology, the consequences of inactivity are readily observable and debilitating. Mechanistically, the loss of lean body mass during inactivity is the result of a chronic imbalance between muscle protein synthesis and breakdown. When inactivity is accompanied by the stress of trauma or disease, the rate of muscle protein catabolism can increase several fold. Bed rest studies in healthy volunteers provide a unique opportunity to examine the mechanisms contributing to muscle loss and evaluate strategies for intervention that may slow muscle catabolism and promote anabolism. The prerequisite for muscle protein synthesis and the most readily adaptable stimulus is dietary-derived amino acids. This review focuses on the role of amino acid supplementation in the maintenance of skeletal muscle mass during age-related and clinically mandated inactivity.

Introduction

The loss of skeletal muscle mass and functional capacity are undesirable yet inherent consequences of physical inactivity. Inactivity-mediated protein catabolism occurs in many circumstances ranging from catastrophic events such as severe illness or injury, to unique environments such as spaceflight/microgravity, to less overt causes such as physical frailty and the progression of aging. Regardless of the etiology, the consequences of inactivity are readily observable and debilitating. Nevertheless, the question remains: is this catabolic progression avoidable?

Mechanistically, the loss of lean body mass during inactivity is the result of a chronic imbalance between muscle protein synthesis and breakdown. This imbalance can be exacerbated during periods of stress. The stress response most commonly associated with illness or trauma entails the inherent loss of homeostatic balance including increases in circulating concentrations of cortisol, epinephrine, and glucagon (1–6), which can increase the rate of muscle protein catabolism several fold (3,7).

Although clinical studies can provide detailed information on morphological and functional changes associated with pathological conditions such as burn injury or orthopedic trauma (4,8–13), bed rest studies in healthy volunteers provide a unique means of isolating and examining many of the specific mechanisms contributing to muscle loss. Further, the bed rest model provides a unique opportunity to evaluate interventional strategies that may slow muscle catabolism and promote anabolism.

Muscle deposition occurs in response to a complex interplay of stimuli such as physical activity and hormonal signaling (e.g., testosterone, insulin, growth hormone, insulin-like growth factors). However, in all circumstances, the prerequisite for muscle protein synthesis and the most readily adaptable stimulus is dietary-derived amino acids. Therefore, this review will focus on the role of amino acid supplementation in the maintenance of skeletal muscle mass during age-related and clinically mandated inactivity.

Amino acid supplementation during inactivity. Physical interventions such as exercise clearly provide a potent anabolic stimulus (14,15). However, exercise may not be feasible in situations in which inactivity is the result of injury or illness. Consequently, there is a need to identify alternate or complementary interventions, such as nutrition, that may slow the catabolic process.

We demonstrated recently that ingestion or infusion of essential amino acids (EAA) provides a potent acute anabolic stimulus in healthy young and elderly subjects (16–18). Furthermore, EAA stimulate muscle protein anabolism to a greater degree than a common liquid meal replacement (19), (Fig. 1), or an isocaloric serving of whey protein (20).

Given these positive acute metabolic study results, we hypothesized that dietary amino acid supplementation would also provide an effective means of ameliorating muscle loss associated with prolonged inactivity. Our hypothesis was based on the fact that EAA administration stimulates muscle protein synthesis, the primary defect in muscle protein metabolism, during inactivity. The decision to use EAAs was further supported by the fact that dietary EAA supplements are easy to administer, the cost is relatively low, they can be used in almost all populations and in conjunction with other therapies, and they are intuitively and theoretically appropriate.

To test our hypothesis, we conducted a 28-d bed rest study using a cohort of 13 healthy young men (21). In additional to controlled mixed-nutrient meals, the subjects were randomly assigned to receive either a placebo (n = 6) or an EAA plus carbohydrate supplement (n = 7) 3 times/d during 28 d of bed rest. The results indicated that the initial stimulatory effect of
EAA supplementation was cumulative; specifically, EAA supplementation stimulated muscle protein synthesis on d 1 of bed rest and remained anabolic throughout 28 d of bed rest (21). In contrast, a standard mixed meal containing ~35 g of intact protein provided minimal anabolic stimulus in the absence of physical activity (21).

The repeated stimulation of net muscle protein synthesis afforded by EAA ingestion translated to a maintenance of lean body mass and the partial preservation of strength after 28 d of inactivity (Fig. 2). Further, it is likely that EAA supplementation conferred a direct anabolic effect, and the maintenance of muscle mass and strength was not due simply to additional energy intake. This is largely based on the fact that fat or carbohydrate ingestion alone does not promote protein anabolism. Further, the acute anabolic response to EAA ingestion was ~10-fold greater than the response to the standard mixed meal.

Although it is tempting to speculate that this simple EAA intervention may also ameliorate the loss of lean body mass in clinical populations, it is most likely not a singular solution. Nevertheless, in frail, aging populations or following trauma or illness, EAA supplementation used in conjunction with existing exercise/rehabilitation regimens offers great promise.

**Amino acid supplementation and aging.** Sarcopenia is an insidious process characterized in part by the progressive loss of muscle mass and functional capacity. Sarcopenia is all too common, with 16% of men and 12% of women aged 70–79 y likely to experience muscle loss and associated functional limitations (22). This is further exacerbated by the higher incidence of several pathologic conditions in aging populations.

For example, 75% of hip fracture patients will lose so much muscle mass that they never regain their previous level of function (23). Further, in patients hospitalized with chronic heart failure, 50–68% will experience cardiac cachexia due to disease progression and malnutrition (24,25).

In the absence of associated injury or illness, sarcopenia is likely facilitated by a combination of factors including the adoption of a more sedentary lifestyle and a less than optimal diet (26–28). A large percentage of homebound elderly consume <0.7 g mixed protein/(kg·d), well below the recommended daily intake of 0.8 g/(kg·d), which itself could be considered a minimal requirement (29). Understandably, the first instinct of many clinicians attempting to correct the protein-energy deficit is to simply add protein to the diet. Extensive trials with protein supplementation were conducted in attempts to ameliorate the debilitating progression of sarcopenia (30–32). Unfortunately, although nutritional supplementation is often necessary, a simple increase in total energy intake may not effectively reduce catabolism or promote muscle anabolism in the elderly. In some earlier studies, it was noted that when a nutritionally mixed supplement was given, total energy intake decreased by a reciprocal amount (30). In other words, the elderly consumed the supplement but, perhaps due to increased satiety, adjusted their total energy intake accordingly (33). Thus, to be effective, a supplement must at least be capable of stimulating net muscle protein synthesis to the same extent as conventional dietary protein, and should not interfere with subsequent meal intake. Fortunately, with EAA supplementation, this seems to be the case (19). In the elderly, we demonstrated that EAA supplementation is capable of stimulating net muscle protein synthesis to a greater degree than a traditional high-quality protein supplement (Fig. 3) and that this anabolic effect is independent of insulin response (20). Further, in a cohort of young volunteers, we demonstrated that the anabolic response to an EAA supplement does not diminish the subsequent anabolic response to a meal when separated by only 3 h (19). Thus, given the positive supporting evidence and practical viability, amino acids may provide an effective means of promoting muscle anabolism in aging populations.

**Inactivity and stress.** Skeletal muscle loss is one of the most phenotypically obvious consequences of chronic illness and disease. The physiological consequences can be devastating when prolonged inactivity is combined with an insult such as orthopedic trauma or burn injury (1,2). The loss of lean body mass of 0.7 g mixed protein/(kg·d) and for 2.5 h after ingestion of a mixed-nutrient meal or EAA supplement in healthy young men on d 1 and 28 of bed rest. Values are means ± SEM, n = 7. *Different from mixed-meal ingestion, P < 0.05; †different from fasting values, P < 0.05. Adapted from Paddon-Jones et al. (19).

![Figure 2](https://academic.oup.com/jn/article-abstract/136/8/2123/4664762)

**Figure 2** Change in lean leg mass (DEXA) and one repetition maximum leg extension strength after 28 d of bed rest in healthy young men. Values are means ± SEM, n = 7. *Significant reduction, P < 0.05. †different from placebo, P < 0.05. Adapted from Paddon-Jones et al. (21).

![Figure 3](https://academic.oup.com/jn/article-abstract/136/8/2123/4664762)

**Figure 3** Muscle protein synthesis (FSR) before and after ingestion of 15 g EAA (n = 7) or 15 g WY protein (n = 7) in healthy elderly volunteers. Values are means ± SEM. †EAA and Whey differ, P < 0.05. *Different from fasting values, P < 0.05. Adapted from Paddon-Jones et al. (20).
mass in these clinical populations is facilitated and amplified by increased circulating concentrations of the counterregulatory hormones epinephrine, norepinephrine, glucagon, and cortisol. The increase in the concentration of these hormones, in turn, generally proportional to the severity of the injury (2,4,34). Although each of the counterregulatory hormones plays a role in the initial phase of metabolic deregulation (35), it appears that a chronic elevation in plasma cortisol is a primary hormonal stimulus for muscle protein catabolism. In an early study examining whole-body nitrogen balance, Gelfand et al. (35) noted that while exogenously induced hypercortisolemia had a minimal effect on nitrogen loss during the first 3 d of administration, the catabolic effects increased markedly thereafter and were similar to the combined effects of exogenous catecholamine and glucagon administration.

Our laboratory also demonstrated a catabolic interaction between inactivity and hypercortisolemia (4). Young subjects were challenged with 12 h of hypercortisolemia before and after 14 d of bed rest (Fig. 4). Cortisol was infused over this period to mimic the blood concentrations observed after severe trauma (e.g., \( \sim 910 \) nmol/L). The hypercortisolemia challenge before inactivity did not produce any greater muscle catabolism than fasting alone. However, after 14 d of inactivity, the same cortisol challenge increased protein breakdown and negatively affected net muscle protein balance. Specifically, inactivity appears to facilitate the deleterious catabolic response to hypercortisolemia. Fortunately, recent evidence suggests that the acute anabolic response to amino acid ingestion is not impaired by concurrent hypercortisolemia (27). These data raise the possibility of successfully using amino acids as a countermeasure for muscle loss associated with longer-term periods of stress or inactivity including hospitalization and convalescence after injury or illness.

**Summary**

Periods of prolonged inactivity are inherent in many conditions associated with the loss of lean muscle mass. In aging populations, the progression of sarcopenia is intimately associated with the gradual loss of functional capacity and metabolic reserve. This progressive loss of lean tissue is exacerbated in individuals after inactivity associated with trauma or disease. In these instances, muscle protein catabolism is accelerated by the combined deleterious effects of muscular inactivity, a generalized stress response and associated increase in counterregulatory hormone concentrations. We demonstrated that EAA supplementation acutely stimulates muscle protein synthesis in elderly subjects and in young volunteers with and without accompanying hypercortisolemia. The increase in protein synthesis after EAA ingestion is greater than that achieved by a mixed meal or an isocaloric serving of intact protein. Consistent with the acute findings, EAA supplementation can also ameliorate the loss of muscle mass and function during prolonged periods of strict bed rest in healthy individuals. These data hold promise that EAA supplementation may also have a potentially beneficial role in clinical populations.

**Literature Cited**


**Figure 4** Change in lean muscle mass following bed rest with chronic hypercortisolemia (n = 6). (Paddon-Jones, unpublished observation). Values are means ± SEM. *Significant decrease, P < 0.05. For comparison, the loss of lean leg mass after 28 d of bed rest alone is also presented (n = 6). Adapted from Paddon-Jones et al. (21).


