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Protecting muscle mass and function in older adults during bed rest

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Abstract

Purpose of review—To highlight the losses in muscle mass, strength, power and functional capacity incurred in older adults during bed rest-mediated inactivity and to provide practical recommendations for both the prevention and rehabilitation of these losses.

Recent findings—In addition to sarcopenic muscle loss, older adults lose lean tissue more rapidly than the young during prolonged periods of physical inactivity. Amino acid or protein supplementation has the potential to maintain muscle protein synthesis and may reduce inactivity-induced muscle loss, but should ideally be part of an integrated countermeasure regimen consisting of nutrition, exercise and where appropriate, pharmacologic interventions.

Summary—In accord with recent mechanistic advances we recommend an applied, broad-based 2-phase approach to limit inactivity-mediated losses of muscle mass and function in older adults:

1. Lifestyle: a) consume a moderate amount (25-30 g) of high quality protein with each meal; b) incorporate habitual exercise in close temporal proximity to protein-containing meals.

2. Crises: react aggressively to combat the accelerated loss of muscle mass and function during acute catabolic crises and periods of reduced physical activity. As a base strategy, this should include nutritional support such as targeted protein or amino acid supplementation and integrated physical therapy.

Keywords

sarcopenia; aging; inactivity; muscle protein synthesis; nutrition

Introduction

Sarcopenia is an age-related, multi-factorial process that is phenotypically characterized by the loss of lean tissue mass. The onset of sarcopenia is insidious, but its progression may be greatly accelerated by physical inactivity and poor nutrition. The basic descriptors of sarcopenia are well known. After the age of 30, adults lose 3-8% of their muscle mass per decade. Over time, the loss of lean tissue contributes to a decrease in muscle strength and power; important predictors of balance, the occurrence of falls [1] and mortality [2]. Sarcopenia is highly prevalent in America as approximately 20% of community-dwelling

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adults < 70 years old and more than 50% of those over 80 years of age can be characterized as sarcopenic (> 2 SD below the appendicular skeletal muscle mass (kg)/height (m^2) of a young reference population) [3].

Models of muscle loss: sarcopenia and catabolic crises

Bed rest, or acute inactivity associated with hospitalization or disease state, poses a potent threat to muscle tissue and functional capacity. In older adults, physical inactivity during hospitalization is almost an accepted part of the inpatient experience, yet clearly contributes to a host of negative outcomes, including a reduction in the ability to perform activities of daily living, increased incidence of readmission and institutionalization [4]. While reduced or limited physical inactivity may be indicated in many patient populations, the practice of subjecting patients to continuous bed rest without a clear medical indication is a regrettable default position [5].

Aging *per* se also appears to facilitate inactivity-mediated muscle loss (*see below*). The consequences of accelerated muscle loss in bed-ridden elders may be further complicated by the fact that approximately 71% of male and 42% of female older Americans (≥ 65 y) can already be characterized as moderately sarcopenic based on skeletal muscle index [SMI = muscle mass (kg)/height (m^2); males: 8.51-10.75; females: 5.76-6.75] [6]. Further, 17% and 11% of older men and women, respectively, are severely sarcopenic (males: SMI < 8.51; females SMI < 5.76). Severe sarcopenia is also associated with a 79% greater likelihood of disability [6]. Thus, with advancing age, it becomes increasingly likely that even a brief, clinically mandated period of bed rest could initiate a serious decline in muscle strength and functional capacity, i.e., a "tipping point" from which some may not fully recover [4,7,8].

We propose that there should be a clear conceptual distinction between the traditional, insidious sarcopenic process and the accelerated episodic loss of muscle and functional capacity during a "catabolic crisis". This distinction is highlighted in **Figure 1** and as detailed in the following sections, provides a tactical framework for targeted intervention strategies.

Muscle loss is accelerated in older adults during bed rest

In the absence of a robust countermeasure (nutritional, exercise, or pharmacologic), lean tissue loss is largely inevitable during prolonged bed rest. Inactivity-induced loss of muscle mass predominantly affects the lower body musculature and is most rapid during the initials days/weeks of inactivity [9-11]. In young, healthy adults subjected to bed rest, the loss of lower body lean mass appears to be on the order of 100-200 $g \cdot wk^{-1}$. LeBlanc et al. reported a total body lean mass loss of 2.6 kg following 119 days of bed rest in healthy young males; of this, 2.4 kg was from the legs (0.14 $kg \cdot wk^{-1}$) [10]. In a similar cohort, Paddon-Jones et al. reported a loss of 0.4 kg of lean leg mass following 28 days of bed rest (0.10 $kg \cdot wk^{-1}$) [11]. More recently, Trappe et al. reported a 21% (quadriceps) and 29% (triceps surae) decrease in muscle volume after 60 days of bed rest in young females [12].

No studies to date have directly compared young and older adults during bed rest. Nevertheless, data from the only study to examine older adults suggests that the loss of lean tissue in healthy older adults during bed rest far exceeds the losses experienced by their younger counterparts. Specifically, Kortebein et al. observed a 0.95 kg loss of lean leg mass (0.63 $kg \cdot wk^{-1}$) following just 10 days of bed rest in otherwise healthy older adults [13]. Assuming the rate of muscle loss is somewhat linear during the initial days/weeks of bed rest, this represents an approximate 3 to 6-fold greater rate of muscle loss in bed-ridden older adults. Notably, muscle loss in all age groups has been observed despite the provision

of diets meeting or exceeding the current recommended daily allowance (RDA) for protein (0.8 $g \cdot kg \cdot day^{-1}$) [11,13].

Muscle loss during bed rest appears to be driven primarily by a reduction in muscle protein synthesis [13-15]. However, while it appears that muscle protein breakdown is largely unaltered by bed rest in young adults [9,15], we are lacking corresponding data in older populations. While an increase in muscle protein breakdown would be consistent with the accelerated loss of muscle mass in older adults, we endorse the position of Phillips [16] and Rennie [17] and suggest that "anabolic resistance" or a blunted protein synthetic response to mixed nutrient meals is likely to play a much greater role. Although not studied during bed rest, Volpi et al. examined muscle protein synthesis, breakdown, and amino acid transport in young and older adults following administration of a simulated protein/carbohydrate mixed meal (40 g amino acids, 40 g glucose) [18]. Consistent with the *anabolic resistance* hypothesis, muscle protein breakdown did not change in either age-group, however, muscle protein synthesis increased only in the young. Supporting data have also been reported by researchers using a 14 day unilateral knee immobilization protocol [19]. In a cohort of young healthy subjects, post-absorptive muscle protein synthesis in the vastus lateralis of the immobilized leg fell by 27%. Further, after 14 days the non-immobilized leg had up to a 68% greater increase in muscle protein synthesis than the immobilized leg in response to increased amino acid availability. The authors conclude that the decrease in post-absorptive muscle protein synthesis coupled with an anabolic resistance to feeding causes much of the muscle loss that occurs during immobilization [19].

In more clinical contexts, an increased stress response (e.g., hypercortisolemia) secondary to injury or disease may also contribute to muscle loss during bed rest or periods of impaired physical activity. For example, recent work has demonstrated that the concomitant effects of pharmacologically induced hypercortisolemia (i.e., approx. 22 $\mu g \cdot dl^{-1}$) and 28 day of bed rest in young adults, resulted in a 3-fold greater loss of leg lean mass than eucortisolemic controls (-1.3 kg vs. -0.4 kg) [14]. Unfortunately, these data are all too consistent with the predicament facing older adults: i) many older adults are already in a sarcopenic state prior to a period of bed rest or illness/injury-induced inactivity, ii) hospitalization is commonly associated with hormonal dysregulation and an inflammatory response that contributes to an accelerated loss of lean tissue. The resultant muscle loss, particularly in the ambulatory and postural muscles of the lower extremities, can have devastating consequences on muscle strength and function [8,20].

Muscle strength, power, and functional capacity following bed rest

Functional disability due to a loss of muscular strength and power is arguably more important than changes in lean muscle mass alone [8,21]. In young adults, routine measures such as isokinetic torque and isotonic strength of the knee extensors have typically revealed decreases on the order of 5-6% per week for the first several weeks of bed rest (e.g., 23% after 28 days) [10,11]. In older adults, 10 days of bed rest resulted in a loss of knee extensor peak torque and 1-repetition maximum (1-RM) that corresponded to a decrement of approximately 11-12% per week [13,22]. This was consistent with a reduction in stair-climbing power (-14±4.1% in 10 days), a key measure of functional capacity [22].

In terms of predicting the likelihood of a poor outcome due to physical inactivity, it appears clear that older adults are at increased risk [4,7,23]. Not only do they start out with less lean muscle mass and strength than their younger counterparts, but they also experience an accelerated rate of loss once subjected to bed rest. Manini et al. established strength cut points to predict mobility maintenance in elderly adults [2]. They found that isokinetic knee extensor strength ($Nm \cdot kg^{-1}$) less than 1.13 (males) and 1.01 (females) was associated with a 7-fold increased risk of developing a severe mobility limitation; males and females with

strength less than 1.72 and 1.35 $Nm \cdot kg^{-1}$, respectively, saw their risk doubled [2]. To illustrate the potential of something as simple as bed rest (without concomitant pathology) to influence mobility, data from Kortebein et al. suggest that older adults bed rest subjects experience a relative strength decrease from 1.42 $Nm \cdot kg^{-1}$ to 1.20 $Nm \cdot kg^{-1}$ [13].

Functional capacity, such as the ability to walk at a reasonable speed for a moderate duration, are vital components of independence. Although some performance measures (e.g., 5-min walk, 50-ft walk, 5-step test, functional reach, and floor transfer), may not be sensitive enough to detect change in a small cohort of study volunteers following short periods of bed rest [22], studies in bed-ridden hospitalized elders have demonstrated a clear negative relationship [4,23,24]. A similar pattern has been observed in community-dwelling elders. Gill et al. [21] studied the association between bed rest and functional decline over 18 months in a community setting. They found a relationship between the amount of time spent at home in bed rest and the magnitude of functional decline in instrumental activities of daily living, mobility, physical activity, and social activity.

Exercise countermeasures

Although not specifically evaluated in older adults during bed rest, there is clear evidence that resistance exercise is an effective means of combating the loss of muscle mass and function in a variety of populations [25-34]. An important caveat, however, is that resistance exercise should be accompanied by an adequate protein- and energy-rich diet to optimize the potential for a synergistic anabolic response. Exercise in the post-absorptive state increases muscle protein synthesis, but net balance (synthesis – breakdown) remains negative [35,36]. Correspondingly, a low-protein (≤15 g $protein \cdot meal^{-1}$) and/or a hypocaloric diet is likely to provide only a minor improvement to a catabolic environment and offer only limited potential for the maintenance of muscle mass or functional capacity [37].

While challenging to implement in some populations, resistance exercise remains an effective stimuli to combat inactivity-induced losses in muscle mass, strength, and functional capacity. A recent study highlighted the potency of resistance exercise to improve key physiologic outcomes in older, chronically ill individuals. Specifically, in a cohort of chronic heart failure patients, improvements in strength, $VO2_{peak}$, work capacity, and economy were identified following a resistance and endurance exercise program [25]. Another investigation examined the effects of 12 weeks of high intensity (80% 1-RM) resistance exercise in the extremely old (85-97 y). The authors reported significant increases in quadriceps cross-sectional area (10%), Type II muscle fiber hypertrophy (22%), percentage of Type IIa fiber area (6%), and isokinetic knee extensor strength (47%) [32].

Despite general acceptance of its efficacy, the volume or intensity threshold of resistance training needed to protect skeletal muscle mass and function during bed rest is still unclear. Many studies have successfully employed relatively high intensity resistance training programs [32,38]. However, in acutely ill patient populations, high intensity exercise interventions may be medically contraindicated or simply not feasible. While limited in direct applicability, there are recent data suggesting that even relatively low intensity, short duration bouts of physical activity such as weight bearing or walking many confer some benefit. Specifically, a recent NASA-supported bed rest study demonstrated that 1 $h \cdot d^{-1}$ on a specially designed human centrifuge (producing 2.5x gravity at the feet) maintained muscle protein synthesis [15] and attenuated muscle performance decrements in the knee extensors and plantar flexors [39].

In situations where resistance training or ambulation is impossible either due to illness severity or injury, neuromuscular electrical stimulation (NMES) may represent a viable alternative. Gibson et al. examined NMES as a skeletal muscle countermeasure in patients

with an immobilized (casted) lower leg fracture [40]. Experimental subjects received electrical stimulation to the affected leg for 1 $h \cdot d^{-1}$ for 6 weeks and experienced no decrements in muscle cross sectional area (CSA) or muscle protein synthesis. In contrast, the control group experienced significant decreases in both outcomes (CSA: -17%, protein synthesis: -23%). Similar data in a variety of patient groups have been presented, and efforts to refine the technique and reduce skin discomfort continue.

Nutritional support during bed rest

A variety of professional organization such as the Joint Commission for the Accreditation of Healthcare Organization (JCAHO), the American Dietetic Association (ADA), the American Society for Parenteral and Enteral Nutrition (ASPEN)) and the European Society for Clinical Nutrition and Metabolism (ESPEN) have published guidelines and position stands outlining nutritional standards of care for hospital patients [41]. Unfortunately, there is a lack of implementation of these standards [42-44].

The adequacy of the recommended dietary allowance (RDA) for protein (0.8 g protein$\cdot kg \cdot d^{-1}$) continues to be questioned, with many suggesting that it should be increased [45-48]. We recently recommended an approach based more specifically on the quality and quantity of protein consumed with each meal [49]. In broad terms, we propose that individuals should consume a moderate amount of high quality protein with each meal. This recommendation was based on a series of recent studies [50-53] and focuses on the potential longer-term benefits of increased muscle protein synthesis at each meal period. By establishing a “recommended” protein intake in this manner, the argument over total daily protein intake is largely avoided and the focus shifted to an evidence-based approach that emphasizes repeated maximal stimulation of skeletal muscle anabolic pathways throughout the day. For a reference 75 kg individual, an intake of 25-30 g of protein for each of three daily meals represents a daily protein consumption of 1.0-1.2 $g \cdot kg \cdot d^{-1}$.

Essential amino acid (EAA) supplementation represents another nutritional option for some older adults - one that avoids some, but not all of the pitfalls associated with traditional protein-energy supplementation [29]. In the only study to date to examine the effects of EAA supplementation in healthy elderly during bed rest, subjects consumed 15 g EAA $3 \cdot d^{-1}$ between meals that provided the RDA for protein (0.8 $g \cdot kg \cdot d^{-1}$). After 10 days of bed rest, muscle protein synthesis was decreased 30% in controls but maintained in the supplementation group. EAA also protected functional abilities such as floor transfer time and exhibited a trend for the protection of stair ascent power and standing plantar flexion [54]. While these data are encouraging, the successful translation or application to a less controlled, real-world population is uncertain and should be treated with a measure of skepticism. Ideally, protein or amino acid supplementation should be implemented in concert with resistance exercise as together they are more effective at attenuating the loss of muscle mass and strength than supplementation alone [55]. When exercise during chronic unloading is performed without adequate nutritional support (i.e., a hypocaloric diet), losses in muscle mass and power are likely to persist [37].

Conclusion

In older adults, bed rest facilitates a reduction in protein synthesis and an accelerated loss of muscle mass, strength, power, and functional capacity. The negative metabolic and morphologic consequences of bed rest are compounded by pre-existing sarcopenia. We recommend a broad-based approach to limit losses of muscle mass and function in older adults: a) consume a moderate amount (25-30 g) of high quality protein with each meal; b) incorporate habitual exercise in close temporal proximity to protein-containing meals; c)

react aggressively to combat the accelerated loss of muscle mass and function during acute catabolic crises and periods of impaired physical activity.

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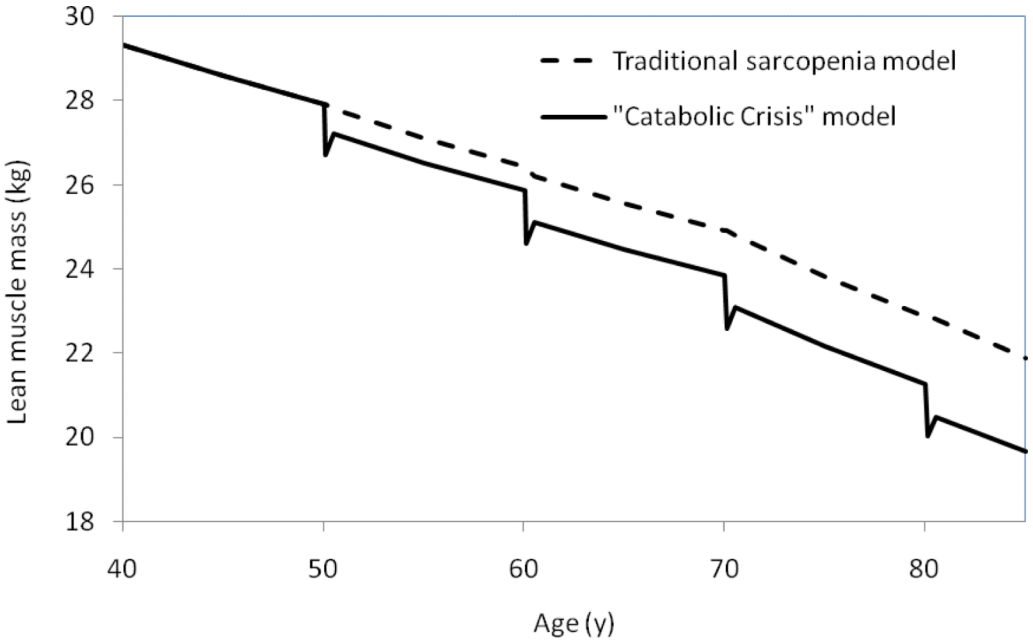

Figure 1.
Proposed model of age-related muscle loss punctuated by episodes of acute illness or injury and characterized by accelerated muscle loss and incomplete recovery.