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Bedrest and sarcopenia

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Abstract

Purpose of review—The primary focus of this review is to characterize the physiological elements of sarcopenia. In addition, we will also describe the impact of bedrest on sarcopenia and how various countermeasures may be able to offset the deleterious clinical consequences of unanticipated bedrest or hospitalization. It is well known that the aging process presents many challenges to the maintenance of overall health. With the increasing rate of obesity and the potentially simultaneous development of sarcopenia, bedrest presents a difficult clinical challenge to the elderly individual.

Recent findings—The etiology of accelerated sarcopenia has been described as a syndrome. The characteristics of this syndrome include combined alterations in neuromuscular control and muscle protein synthesis that increase the risk of morbidity and mortality in the elderly population. Moreover, the acute onset of bedrest-induced insulin resistance may further complicate the nutritionally derived maintenance of muscle mass and physical function.

Summary—Even though many questions remain unresolved concerning the optimal clinical management of elderly individuals who undergo unanticipated bedrest, the supplementation of essential amino acids has shown promise as a therapeutic strategy to minimize the detrimental influence of hospitalization in the elderly. In turn, this nutritional adjunctive therapy may reduce the length of stay and the likelihood of repeated hospitalization.

Keywords

aging; elderly; inactivity; insulin resistance; muscle loss; physical function; protein synthesis

INTRODUCTION

The term ‘sarcopenia’ was first suggested in the late 1980s [1]. Since that time, there has been tremendous increase in scientific investigation into the basic and clinical understanding of this syndrome [2]. Realizing that sarcopenia itself is a complex syndrome composed of nutritional deficiency, chronic inflammation, insulin resistance and a precipitous decline in

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Conflicts of interest

There are no conflicts of interest.

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anabolic hormones, it is not surprising that the acute influence of bedrest may exacerbate the cause of sarcopenia [3].

CLASSIFICATION OF SARCOPENIA

Sarcopenia is directly related to reductions in mobility and functional status that lead to an increased risk of mortality [4]. Due to the nature of the syndrome, European Working Group for Sarcopenia in Older Persons recently established a clinical definition and diagnostic criteria for the age-related development of sarcopenia [5]. These criteria were based on the consensus between several international societies, including the European Geriatric Medicine Society, the European Society for Clinical Nutrition and Metabolism, the International Association of Gerontology and Geriatrics European Region, and the International Association of Nutrition and Aging. Moreover, the syndrome was described in phases such as presarcopenia, sarcopenia and severe sarcopenia, depending on the loss of strength and power that is closely associated with the loss of muscle mass [5]. In addition, absolute strength and/or power have been proposed as a better predictor of decreased functional status that the change in strength itself [6■]. Along with the assessment of physical function and muscle mass [7], this information should be utilized in the clinical setting to classify muscle function and characterize the risk of subsequent disability.

The consensus of this working group was that the syndrome of sarcopenia should be established from an algorithm [5]. This algorithm would employ three primary components, and include low physical performance (i.e., gait speed), low muscle strength, and low muscle mass. In this way, the complex interplay between different physiological systems could be indirectly assessed and lead to the establishment of cut-off points for the classification of sarcopenia in its progressive stages, according to age and sex [6■].

SEX DIFFERENCES

It has been demonstrated that leg power in men less that 105 W results in a nine-fold increase in the risk of permanent disability. In women, leg power that falls below 64 W only increases the risk of disability by three-fold. These cut points in muscle strength provide strong evidence of the association between the sarcopenia-induced decrements in muscular strength and how they may ultimately predict permanent disability [7]. They also contribute to the notion that sex differences may exist with respect to the predictive influence of muscular strength on future disability, morbidity and mortality. In fact, studies have shown that age is the strongest predictor of decreased mobility in women, whereas strength remained the primary predictor of decreased mobility in men [7]. This is somewhat counterintuitive realizing that women have lower muscle mass/total mass throughout their adult years. However, studies have also demonstrated a steeper rate of age-related muscular mass and strength in men. This supports this contention that adverse changes in functional status may be more closely related to changes in muscle in men, and functional status may be more affected by osteoarthritis, osteoporosis and depression in women [8].

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COMPLEX CAUSE OF SARCOPENIA

The rationale behind the establishment of a multifaceted working definition for sarcopenia is based upon the fact that several physiological mechanisms are involved in the cause of the syndrome. These factors include changes in muscle mass, neuromuscular control, and muscle lipid infiltration [5]. In studies comparing the exercise-induced activation of satellite cells that are known to contribute to muscle growth and repair, older mice demonstrated a perturbed sensitivity to the stimulus of exercise that was linked to decreased satellite cell activation and elevations in myostatin [9]. This corroborates with a recent report in humans in whom older individuals were less responsive to the anabolic stimulation of resistance exercise, and this was demonstrated by the reduced activation of mammalian target of rapamycin complex (mTORC)1 signaling and muscle protein synthesis [10].

In addition to the challenges related to anabolic responses to exercise in the elderly, the age-related, progressive loss of motor units may attenuate neuroumuscular transmission [11]. This has been attributed as a contributing factor in the loss of strength and power with age, even though there may only be a 10–15% reduction in the total number of motor units. It has also been suggested that these deleterious, neuromuscular changes may occur in conjunction with the infiltration of lipids into skeletal muscle [11]. Although the initial studies only suggested a relationship between fatty acid infiltration into muscle and a decline in muscle strength [12], recent data suggest strong association between total fat mass and a 7-year decline in muscle mass and strength [13].

It has been previously suggested that increased fat storage (intramuscular, visceral and subcutaneous) may occur in conjunction with changes in plasma adipocytokines such as interleukin-6, tumor necrosis factor-α, and leptin that have a detrimental influence of muscle mass and strength, but recent, long-term studies in older adults did not find any significant changes in plasma adipocytokines over the 7-year period [13]. This is not to say these factors may not be involved but more a detailed analysis of other factors that may also influence the accumulation of intramyocellular lipid (IMCL) may be important. For example, adipose tissue triglyceride lipase (ATGL) catalyzes the first step in muscle triglyceride lipolysis, and ATGL-deficient mice show significant accumulation of IMCL and decreased fatty acid oxidation. We have recently shown that exercise training that results in weight loss increases ATGL mRNA in skeletal muscle [14]. Moreover, other factors that promote the oxidation of fatty acids in skeletal muscle such as carnitine palmitoyl transferase I, adiponection receptor 1, and adiponectin receptor 2 were also increased [14]. These data corroborate with the previous assertion by Lanza and Nair [15], whereby, the age-related sedentary lifestyle tends to foster perturbations in mitochondrial function and insulin resistance. Therefore, metabolic disease, sarcopenia and obesity may work together in a deleterious manner that ultimately results in the development of insulin resistance, decreased functional status, and higher risk of mortality in older individuals [13]. As a result, bedrest or assignment to a nursing home can present an even more challenging clinical situation.

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BEDREST-INDUCED SARCOPENIA

There is overwhelming evidence that bedrest induces the loss of skeletal muscle [16–18]. These detrimental changes in muscle mass due to bedrest have been shown to occur in the vastus lateralis and soleus resulting in decreased maximal torque [18]. In addition, chronically bedridden elderly individuals also lose significant thickness of postural muscles such as rectus abdominis, external oblique, internal oblique, transversus abdominis, thoracic erector spinae, and lumbar mutifidus muscle, leading to an increased risk of falls and disability [17]. Although the prevalence of sarcopenia may vary from 5 to 13% among 60–70 year old individuals, the existence of sarcopenia increases to 68% in the nursing home population. This is most likely due to the combination of increasing age, and more frequent and/or chronic periods of bedrest [19■]. Ultimately, sarcopenia can result in the development of a debilitating condition termed ‘severe sarcopenia’ that prevents an individual from accomplishing the activities of daily living and initiates a downward spiral in their clinical prognosis [5]. The continuum of sarcopenia has an important significance when it comes to the determination of threshold of muscle mass necessary to maintain physical function, and this seems especially relevant to those who may be confined to a nursing home or who undergo unanticipated bedrest [6■].

NUTRITIONAL COUNTERMEASURES

It is also important to mention that essential amino acid (EAA) supplementation has no influence on satiety and, therefore, does not reduce subsequent dietary intake. This is significant because meal replacement may decrease caloric intake due to enhanced satiety [20], potentially leading to malnutrition in the elderly. Although BMI is commonly utilized as an indicator for obesity and a greater risk of mortality, this relationship does not persist in elderly individuals [21]. Without realizing the unique clinical challenges of an elderly individual, it might be confusing. However, this ‘obesity paradox’ is largely on the basis of the notion that increased BMI in the elderly represents an index of protein storage rather than adiposity [22■], that a BMI below 21 kg/m^2 or an acute change in the activity levels of an elderly individual should elicit a modification in nutritional support.

It is quite clear that the most effective strategy to mitigate the impact of bedrest on the development of sarcopenia is adequate nutrition and/or the utilization of resistance exercise [23]. In a recent study in which EAAs were provided with and without the addition of resistance training during bedrest, myostatin levels increased in the group that received EAAs without resistance exercise [24]. From these data, the authors speculated that EAAs provide the least effective countermeasure against muscle loss. Although these results are interesting, it was unclear whether the changes in myostatin transcripts resulted in significant changes in muscle mass or function. In addition, it was not clear whether the formulation of EAAs contained the requisite amount of leucine necessary to provoke the optimal anabolic response in skeletal muscle [25]. It has been shown that the supplementation of EAAs promotes the accretion of lean tissue through increased muscle protein synthesis in older women [26]. Along these lines, recent studies have demonstrated a significant improvement in the insulin-mediated activation of protein kinase B (AKT)/mammalian target of rapamycin (mTOR) in the soleus muscle of aged rats [27], and may be

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partially responsible for the preservation of muscle function in the elderly when challenged by the deleterious influence of bedrest [28■■].

The rationale for the supplementation of EAA may stem from the notion that the recommended daily allowance for protein in the elderly is inadequate. Moreover, this requirement may increase even more when compromising by acute inactivity [28■■], and this notion is supported by our data in which elderly individuals without EAA supplementation were found in negative nitrogen balance despite the provision of a diet containing 0.8 g protein per kilogram of body weight [16]. In contrast, supplementation of EAA promoted the preservation of muscle protein synthesis and was closely associated with the preservation of muscle function in these studies, as indicated by maintenance of plantar flexion strength, stair ascent power, stair descent power, and floor transfer time [28■■]. The beneficial influence of EAAs may be derived from their simultaneous positive impact on muscle fiber size and motor coordination, and improvements in age-associated alterations in AKT/mTOR signaling have been linked to these positive changes. Other studies in rodents have suggested that amino acids may also protect against protein breakdown and protect against atrophy.

Recently, the positive benefits of EAA supplementation on improving quality of life and muscle strength has even been demonstrated in the institutionalized elderly individuals [29]. In these studies, elderly patients reported a decrease in depressive symptoms and suggested that EAAs may act through direct and indirect pathways. Realizing that improvement of depressive symptoms is of great clinical significance, EAAs may have increased tryptophan levels and this may have been indicative of increased serotonin synthesis. From an indirect standpoint, EAAs improved the Mini Nutritional Assessment Score of these patients, indicating an improvement in nutritional status that would have a beneficial influence on relieving depression. Therefore, supplementation of EAAs may be beneficial in the concomitant improvement of muscle anabolism and amelioration of depressive symptoms, ultimately improving the quality of life in institutionalized elderly patients.

LOW MAGNITUDE MECHANICAL SIGNAL AND VIBRATION COUNTERMEASURES

Even though bedrest may be necessary in some clinical scenarios, it has been demonstrated that ambulation and minimizing bedrest are preferred to prevent the deterioration of balance and physical function [30]. Unfortunately, mobilization is not always possible and nutritional supplementation may be logistically challenging in some individuals, other strategies such as low magnitude mechanical signals (LMMS) or vibration countermeasures have been proposed to provide an anabolic stimulus to bone [31] and muscle [32] during bedrest. In a recent study in which middle-aged volunteers were confined to bedrest for 90 days, the utilization of LMMS for 10 min/day promoted significant improvements in ankle, knee and back strength as well as knee endurance [33■]. These beneficial changes also seemed to attenuate the bedrest-induced deterioration of stability and postural control. Additional studies are necessary that it can be determined whether this type of therapy would be effective in the elderly, and whether the combination of LMMS and EAA

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supplementation might be even more beneficial in reducing the risk of morbidity and mortality associated with bedrest.

CONCLUSION

There are many factors responsible for the development of sarcopenia with aging. It seems that the anabolic potential of skeletal muscle may be reduced in the elderly. Insulin resistance, perturbations in muscle metabolism and decreased muscle proliferation may contribute to the difficult clinical condition of sarcopenia. Although bedrest is a common therapy in older adults who are critically ill, deleterious changes in the neuromuscular control and muscle atrophy may become exacerbated by bedrest. Future studies are needed to elucidate whether age-related insulin resistance is a primary factor in facilitating the loss of physical function due to bedrest. We must also further delineate the role or EAA supplementation in the treatment of depression in the elderly. It is clear that the supplementation of EAAs have a beneficial influence on maintaining skeletal muscle mass and muscle function, and may represent an important therapeutic tool in the clinical care of the elderly who undergo unanticipated hospitalization. In addition, LMMS has been shown to also improve muscular strength and preserve postural control. However, many questions still remain regarding how to attenuate the bedrest-induced development of insulin resistance, and other cofactors important to the maintenance of physical function like neuromuscular control and satellite cell proliferation. As these questions are addressed through studies utilizing nutritional supplementation, it may be possible to shed some light on the mitigation of physiological derangements that would otherwise decrease the quality and quantity of life.

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