Resistance exercise and appropriate nutrition to counteract muscle wasting and promote muscle hypertrophy

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Purpose of review

Loss of skeletal muscle mass is a common feature of a number of clinical scenarios including limb casting, bed rest, and various disorders such as HIV-AIDS, sepsis, cancer cachexia, heart failure, and uremia. Commonly, muscle disuse (hypodynamia) is the sole reason, or a large part, of why muscle mass is lost. The reduction in strength, or dynapenia, that accompanies these conditions is also a function of the degree of hypodynamia and is related to muscle loss.

Recent findings

The major and consistent finding in a number of human-based models of muscle wasting is a decline in the synthesis of new muscle proteins both in the postabsorptive and fed states. Thus, countermeasures are best suited to those that augment muscle protein synthesis and not those that attempt to counteract proteolysis. Our main thesis is that retention of muscle mass in wasting conditions will be achieved to the greatest extent by focussing on increased muscle use with moderate-to-high resistance loads as the primary countermeasure with a secondary countermeasure being to provide adequate nutritional support. Either intervention alone will alleviate some part of hypodynamia-induced muscle mass loss and dynapenia; however, together nutrition and muscular contraction will result in greater mitigation of muscle loss.

Summary

Advances in our understanding of hypodynamia-induced muscle loss, a condition common to almost all syndromes of muscle wasting, has led to a focus on reduced basal and feeding-induced elevations in protein synthesis. Countermeasures for wasting should focus on stimulating anabolism rather than alleviating catabolism.

Keywords

atrophy, dynapenia, hypodynamia, protein turnover

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Introduction

The main purpose of this review is to examine the strategies that are available to counteract atrophy resulting from general muscle disuse. Disuse of skeletal muscle arises due to a number of relevant clinical conditions such as bed rest, immobilization due to fracture (for review see [1]), and abrupt sedentarism [2] due, for example, to illness. There are also nonclinical conditions such as spaceflight in which the gravitational loading that normally preserves our muscle mass is lost [1]. In a number of pathological conditions muscle wasting occurs in which disuse is certainly playing a role; however, these pathological conditions such as AIDS [3–5], sepsis [6,7], cancer cachexia [6,7], uremia [8], and burns [3] are also associated with a marked inflammatory condition and large elevations in inflammatory cytokines and cortisol [3–5] which are not characteristics of uncomplicated muscle atrophy [9–11], in fact to generate hypercortisolemia during prolonged bed rest exogenous source of glucocorticoids have to be administered [12]. Another important consequence of studying uncomplicated (i.e., nonpathological) disuse-induced muscle atrophy is that the causal mechanisms for why muscle mass is lost are largely opposite, or so it would seem, to those thought to occur in disease-induced wasting [13••,14]. We view disuse-induced atrophy as being the consequence of a reduction in the basal [10,15,16,17••,18,19••] and feeding-induced stimulation of muscle protein synthesis (MPS) [17••]. We have reviewed the evidence that is both supportive and counter to this thesis [13••] and so will not discuss it further here. By contrast, a number of observations, mainly relying on data from small mammals in pathological conditions (sepsis, prolonged starvation, cancer cachexia, and uremia), have pointed to increased markers of proteolysis and muscle protein breakdown (MPB) as being the driving force underpinning atrophy during disuse and in pathological states [6,20–22]. It is important

to realize that although atrophy/wasting is the clinical observation of all of the aforementioned conditions that inflammation and hypercortisolemia, a profound stimulator of muscle-specific proteolytic systems [23], may play a much more important role in pathological wasting conditions the result of which is a profound increase in the potential role of proteolysis resulting in atrophy [13••,14,23]. The consequence of the increased contribution of inflammation and a catabolic hormonal milieu is that the rate of muscle loss is also much more rapid than simple disuse; for a more detailed review see [14].

This review focuses on simple hypodynamia-induced, as opposed to disease-induced, muscle atrophy with the knowledge that hypodynamia is common to many conditions, even pathological, in which muscle atrophy/wasting occurs. We have summarized findings from studies in which exercise and/or nutrition have been used as countermeasures to prevent this form of atrophy. A main rationale for examining increased loading as a countermeasure is that it has been shown to be markedly effective in alleviating disuse atrophy (see below) and is more consistently associated with reduced even ablated atrophy than a number of nutrition-only interventions. Increasingly appreciated, however, is the fact that resistance exercise can also alleviate, even reverse, atrophic muscle loss in conditions such as HIV-AIDS [24], patients on dialysis [25,26], hypogonadal states [27,28], and various cancers [29,30]; thus, even pathologically induced wasting with both hypodynamia-mediated and hormonal/cytokine-mediated wasting can be offset by fairly moderate resistance exercise.

From the standpoint of nutritional countermeasures to atrophy the results are a little less clear than those from exercise with a mixed set of results (see below). There are, however, some nutritional strategies that show promise in attenuating muscle loss in muscle wasting. Once again, we have avoided discussing pathological wasting due to the difference in mechanistic origins of the wasting that occurs.

Resistance exercise countermeasures to combat disuse atrophy

This section provides a review of countermeasure studies performed with healthy younger adults undergoing disuse atrophy. More than 20 years ago, electrical stimulation was shown to prevent immobilization [16] and bed rest-induced skeletal muscle atrophy [31] and the associated fall in MPS [16]. Although these findings were mechanistically informative and useful in clinical situations where voluntary exercise cannot be performed (e.g., immobilization due to fracture and spinal cord injury), the need for strategies that take into account patient tolerance, convenience of application, and relevance to other states of decreased loading and inactivity (bed rest, spaceflight, sedentarism) has driven workers to determine the type and volume of voluntary exercise sufficient to counteract disuse atrophy. A progressive program of resistance exercise will result in hypertrophy of exercised muscles [32]; dynamic endurance exercise generally results in oxidative adaptations but little fibre hypertrophy [33]. As a result, resistive exercise has been the exercise mode of choice in the majority of atrophy countermeasure studies performed to date. Accordingly, research efforts initially focussed on applying progressive resistance protocols to models of reduced loading (bed rest, unilateral lower limb suspension (ULLS), immobilization – reviewed in [1]. Decreases in leg lean mass or cross-sectional area are measureable 7–14 days after the onset of bed rest [15,34], ULLS [18,35] or immobilization [9,17••,36]. Dynamic or isometric leg press/squat training every 12–48 h [34,37–41] or flywheel-based knee extension [42] or leg press [43,44] exercise every 72 h have been reported to prevent decreases in vastus muscle protein synthesis, task-specific strength (1 repetition maximum), knee extensor fibre, and muscle size or mass in 14–90 days bed rest and unilateral lower limb studies. Strength in modes other than that used for training was not generally preserved in these studies, underscoring the need for a diversified exercise program to maintain strength and function [32,45]. When a combination of isometric and isokinetic or isotonic resistance exercises was used, strength was maintained in both testing modes after 20–28 days bed rest [46] and ULLS [47]. Interestingly, inclusion of a treadmill-based aerobic training component (horizontal treadmill 'running') in combination with a flywheel-based leg press regimen in a 60-day bed rest study of women did not interfere with the protective effect of the resistance training on thigh muscle and fibre atrophy [48], and may have helped maintain or increase both isometric and dynamic strength measures particularly in the soleus.

A concern during states of unloading is maintenance of the plantar flexors, which tend to atrophy to a greater extent than knee extensors [1]. In studies where the plantar flexors were not specifically targeted, neither strength nor mass was preserved [40]. When a calf press exercise was included, no [38,42], partial [42–44,49,50], or complete [47,51,52] attenuation of calf muscle or plantar flexor strength loss was achieved. These differences in findings may be ascribable to study differences in model, countermeasure protocols and measures taken. Interestingly, addition of an endurance training component to flywheel-based leg press training during bed rest enhanced the protective effect of resistance exercise on triceps surae muscle atrophy [48]. Whether this was simply due to a greater volume of exercise compared to that used in other studies is not clear and clearly this finding requires further study to ascertain why the

introduction of aerobic exercise would be so beneficial for the plantar flexors.

Although unloaded muscle generally does not hypertrophy in response to resistive loading, the minimal volume and intensity of contractions required to prevent atrophy are currently unknown. The aforementioned studies employed routines that, by comparison to known hypertrophy-inducing models [32], would normally induce hypertrophy in the loaded state [34,42,51]. High-volume exercise may not always be practical or safe in a clinical population. In our recent 14 days knee brace-mediated immobilization study [50], 20 high-intensity (80% of maximal strength) contractions targeting thigh and calf (10 repetitions each of leg press with plantar flexion, knee extension, and seated calf raise) every 48 h was sufficient to prevent atrophy of the quadriceps femoris and maintain isometric strength. This program was also effective at preserving soleus cross-sectional area (CSA) plantar flexion peak torque, and attenuated atrophy in the gastrocnemius. Further work is required to determine the optimal countermeasure for complete preservation of the triceps surae during unloading, but clearly quite minimal volumes of exercise can be effective.

On balance, resistance exercise is a remarkably potent disuse countermeasure in terms of preservation of strength and muscle mass/cross-sectional. Although we appreciate that high force contractions are not always possible in clinical settings we emphasize three points. First, as we describe above, the volume of exercise required to offset strength loss and atrophy is likely quite minimal in terms of the number of contractions [50]. Second, there are paradigms of resistance exercise that have shown very-low-intensity contractions, approximately 15–30% of maximal strength, can increase strength and also result in hypertrophy [53] and (Mitchell and Phillips, unpublished observations). Simple surface electrical stimulation is remarkably effective at preserving muscle mass in people with spinal cord injury [54,55] as well as other clinical populations [56,57] where voluntary high intensity force generation is not possible. These are important points because they point to the fact that lower than previously recognized volumes of exercise employing lower intensities of exercise are quite likely to have a measurable and positive impact in neutralizing muscle loss if practised diligently even in clinical populations.

Nutritional countermeasures

There is much less evidence for the efficacy of nutritional supplements, particularly amino acids and protein, to offset disuse atrophy. Although amino acids are well known to stimulate muscle protein synthesis in people in the ambulatory state (see [58–60] for further review), unloading blunts the amino acid-induced rise in whole body [61,62] and muscle protein synthesis [17••]. In light of this, it is perhaps not surprising that provision of branched-chain amino acids (BCAA) during a 14-day bed rest did not produce differential effects compared to nonessential amino acids (NEAA) provision on whole body and muscle protein synthesis [63]. Findings from studies of long-term hypodynamic models are mixed. Inclusion of additional protein and branched chain amino acids in the diet of a group of women undergoing 60 days of strict 6° head down bed rest actually exacerbated loss of thigh muscle [48] relative to a control group who received an isocaloric diet. The reason for this is not clear but may be associated with potential upregulation of amino acid catabolic enzymes [64]. Such an adaptation with a higher protein diet in persons subject to bed rest would be deleterious if an enzyme such as branched chain oxoacid dehydrogenase (BCOAD) were upregulated, which is possible [65]. This, in turn, may promote increased basal and fed-state oxidation of the BCAA and thus deplete muscle of precursors for muscle protein synthesis and/or leucine which, beyond being a substrate for protein synthesis, is an important amino acid in actually stimulating muscle protein synthesis [66,67]. In contrast, preservation of leg lean mass was reported to occur in men who received essential amino acids (EAAs) and carbohydrate supplementation during a 28-day bed rest study [12,68]. However, a reduction in calf CSA occurred in both supplemented and nonsupplemented groups suggesting that measurement of changes in thigh mass by DXA scans may mask losses in mass of the lower leg. It should be noted that in this study participants were allowed out of the bed to use a bedside commode for a period of 5 min. Thus, in conjunction with minimal regular activation of the knee extensors, daily supplementation with 49.5 g essential amino acids protected against bed rest induced thigh muscle protein loss in this study. Brooks *et al.* [69] reported no attenuation of wasting with amino acid supplementation in a bed rest group in mild energy deficit, but it could be argued that catabolism is accelerated during negative energy balance. Biolo *et al.* [61] recently reported a greater loss of lean mass in the study group during a hypocaloric bed rest phase relative to a eucaloric phase, attributed to an increase in leucine oxidation during hypocaloric bed rest. In this study, postabsorptive and amino acid-induced values of whole body protein synthesis and breakdown were not different between phases. Biolo *et al.* [70] have also reported that receiving a hyperenergetic diet will also promote lean tissue catabolism and muscle loss. Participants with greater gains in body fat during a 28-day bed rest study had greater losses in fat free mass and vastus lateralis thickness than those below the median for fat gain [70]. In this study, fat gain was taken as a proxy for positive energy balance, but fat mass can increase or remain largely unchanged during

negative energy balance during bed rest [69]. Paddon-Jones *et al.* [68] reported a net gain in body fat mass for both his amino acid supplemented and nonsupplemented study groups, whereas exercise reduced fat mass, maintained muscle and thus improved body composition during bed rest, even in the face of mild negative energy balance in both studies. Therefore, the strategy of supplementation alone in conjunction with a eucaloric diet during states of inactivity like bed rest may not be conducive to maintenance of body composition that supports a healthy metabolic profile. In fact, Paddon-Jones *et al.* [68] reported changes in insulin response to feeding that may reflect development of mild insulin resistance.

To date, a well controlled study to determine the potential additive effects of amino acid feeding and exercise training during unloading has not been performed. Brooks *et al.* [69] reported no difference in timing of an amino acid supplement in conjunction with resistance exercise in offsetting muscle loss during 28 days of bed rest, but the potential contribution of supplementation to the exercise cannot be evaluated in the absence of an exercise-only group.

Conclusion

In summary, resistance exercise is effective at preventing loss of muscle mass and dynapenia in various models of hypodynamia-mediated atrophy. The volumes and intensities typically employed appear to be more than what is required for prevention of atrophy, however, as many of the programs are merely adopted from programs known to result in hypertrophy. Currently, the evidence for the capacity of amino acid or protein supplementation alone to prevent disuse atrophy is not consistent. Future work is required to determine the potential roles of exercise regimens of varying intensities and volumes and protein supplementation in minimizing the impact of atrophy due to hypodynamia, be it of simple or disease origin.

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There are no conflicts of interest.

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

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 750–753).

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