

Hypo-activity induced skeletal muscle atrophy and potential nutritional interventions: A review

Emma L Bostock, Christopher I Morse, Keith Winwood, Islay McEwan, Gladys L Onambélé-Pearson

Emma L Bostock, Christopher I Morse, Keith Winwood, Islay McEwan, Gladys L Onambélé-Pearson, Institute for Performance Research, Department of Exercise and Sport Science, Manchester Metropolitan University, Crewe CW1 5DU, United Kingdom

Author contributions: All the authors contributed to this work. Correspondence to: Gladys L Onambélé-Pearson, PhD, Institute for Performance Research, Department of Exercise and Sport Science, Manchester Metropolitan University, Crewe Green Road, Valentine Building, Room 2-7, Crewe CW1 5DU, United Kingdom. g.pearson@mmu.ac.uk

Telephone: +44-161-2475594 Fax: +44-161-2476386

Received: May 24, 2013 Revised: September 7, 2013

Accepted: November 1, 2013

Published online: December 12, 2013

Abstract

Periods of hypo-activity result in profound changes in skeletal muscle morphology and strength. This review primarily addresses the differential impact of de-training, bed-rest, limb immobilisation and unilateral lower limb suspension on muscle morphology, strength and fatigability. The degree of muscle atrophy differs depending on the hypo-activity model and the muscles in question, with the leg and postural muscles being the most susceptible to atrophy. Hypo-activity also results in the dramatic loss of strength that often surpasses the loss of muscle mass, and consequently, the nervous system and contractile properties adapt to adjust for this excessive loss of strength. In addition, the degree of muscle strength loss is different depending on the hypo-activity model, with immobilisation appearing to have a greater impact on strength than unloaded models. There is a step-wise difference in the magnitude of muscle loss so that, even after accounting for differential durations of interventions immobilisation \geq unilateral lower limb suspension \geq bed-rest \geq de-training. Muscle fatigability varies between hypo-activity models but the results are equivocal and this

may be due to task-specific adaptations. This review also addresses potential nutritional interventions for attenuating hypo-activity induced muscle atrophy and strength declines, in the absence of exercise. Essential amino acid supplementation stands as a strong candidate but other supplements are good contenders for attenuating hypo-activity induced atrophy and strength losses. Several potential nutritional supplements are highlighted that could be used to combat muscle atrophy but extensive research is needed to determine the most effective.

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Key words: Immobilisation; Disuse; Muscle size; Muscle strength; Nutrition supplementation; Muscle fatigability

Core tip: This review summarises and compares the morphological, strength and fatigability changes in response to different models of hypo-activity. The hypo-activity models include de-training, bed-rest, immobilisation and unilateral lower limb suspension. There is a step-wise difference in the magnitude of muscle and somewhat strength losses so that, even after accounting for differential durations of interventions immobilisation \geq unilateral lower limb suspension \geq bed-rest \geq de-training. Muscle fatigability varies between hypo-activity models but the results are equivocal and this may be due to task-specific adaptations. This review also highlights several potential nutritional interventions for attenuating hypo-activity induced changes.

Bostock EL, Morse CI, Winwood K, McEwan I, Onambélé-Pearson GL. Hypo-activity induced skeletal muscle atrophy and potential nutritional interventions: A review. *World J Transl Med* 2013; 2(3): 36-48 Available from: URL: <http://www.wjgnet.com/2220-6132/full/v2/i3/36.htm> DOI: <http://dx.doi.org/10.5528/wjtm.v2.i3.36>

INTRODUCTION

Skeletal muscle is one of the most adaptable tissues in the body, and as such, it is capable of altering its structure in response to different levels of physical activity. Prolonged reductions in muscle activity and mechanical loading result in many physiological adaptations in skeletal muscle form and function^[1-4]. Muscle atrophy (decrease in muscle mass) is seen during reduced activity (*e.g.*, sedentary behaviour, de-training)^[5-8] or disuse models (*e.g.*, immobilisation, head-down tilt bed-rest)^[1,3,9,10]. It is evident that the degree of muscle atrophy is not constant across muscle groups or hypo-activity models^[2,3,11,12].

Simply reducing normal levels of activity can be classed as the first stage of disuse. Decrements in muscle mass and strength have been documented in trained humans undergoing de-training^[5-8,13-15]. Bed-rest conditions result in the removal of normal weight-bearing forces acting on the bones of the lower limbs in the vertical position and a decrease in number and/or magnitude of muscle contractions, particularly in the postural musculature. During bed-rest, muscular contraction is still possible although it is limited and the muscular force required for producing movement is very much diminished once ground reaction forces are removed. A more rigid immobilisation can be achieved by casting a limb, resulting in more rapid decrements in muscle mass than does bed-rest alone. The final method of hypo-activity commonly reported in the literature is that of unilateral lower limb suspension (ULLS), a method of reducing habitual activity whilst causing lesser degree of inconvenience to the participants.

The purpose of this review is to assess the varying impact of different hypo-activity models on the skeletal muscle system. This is broken down into the effects of hypo-activity on muscle morphology, muscle strength and muscle fatigability. In order to provide some homogeneity in the results based on the variable duration of the hypo-activity, values are presented per week and where relevant the duration of the hypo-activity is provided in parenthesis. Exercise prescription is not always a practical prescription, even when it would be recommendable to individuals under-going immobilisation or bed-rest after trauma or illness, due to the presence of counter indications for exercise such as pain, immobilisation in a cast, *etc.* Thus, other interventions are required to attenuate losses in muscle mass and function. Therefore, this review will also discuss potential nutritional interventions for preventing the loss of muscle mass/function seen with hypo-activity, where increased physical activity is not combined with the nutritional treatment. Studies were found using search terms “bed-rest and atrophy” and “immobilisation and atrophy” in PubMed. However, this returned over 1400 hits. To focus our search criteria, only data on healthy humans were selected through the inclusion of the “human” and “clinical trial” filters in the PubMed search. This resulted in 86 studies, suitable for inclusion in the present review.

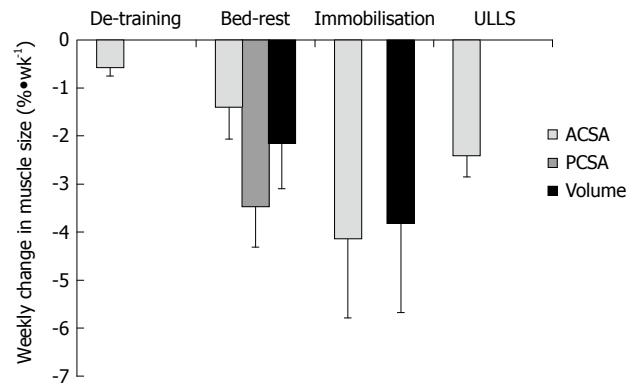


Figure 1 Relative change in muscle anatomical cross sectional area, physiological cross sectional area and volume. ULLS: Unilateral lower limb suspension; ACSA: Anatomical cross sectional area; PCSA: Physiological cross sectional area.

MUSCLE MORPHOLOGY

Muscle anatomical cross sectional area

Anatomical cross sectional area (ACSA) is the cross-sectional area of the muscle at right angles to its longitudinal axis. Muscle ACSA is a major determinant of maximum voluntary contraction (MVC) torque^[16,17] and hypo-activity models have been shown to result in the decrease in this parameter. [Figure 1 shows relative change in muscle anatomical cross sectional area (ACSA), physiological cross sectional area (PCSA) and volume in response to hypo-activity models. Values are taken from the references used in the text for de-training (ACSA-40 d and 24 wk)^[6,8], bed-rest (ACSA-30 d to 17 wk)^[2,11,18,19] (PCSA-20 d)^[11,20] (Volume-7 d and 32 d)^[11,21], immobilisation (ACSA-9 d to 4 wk)^[3,4,12,22-26] (Volume-2 wk and 4 wk)^[10,12,27] and ULLS (ACSA-23 d and 4 wk)^[28-31]. Where there are missing bars, this shows gaps in the literature (*i.e.*, values are not available for a parameter during a specific hypo-activity model). Values are presented as means; error bars denote SD]. Periods of detraining (24 wk) have resulted in a decrease in ACSA of the quadriceps^[6]. Likewise, Narici *et al.*^[8] reported decreases in leg ACSA (approximately 0.7%/wk) in response to 40 d de-training.

Stricter hypo-activity models result in greater decreases in muscle ACSA. Following 30 d bed-rest Convertino *et al.*^[11] reported decreases in ACSA of the calf (approximately 1.1%/wk) and thigh (approximately 1.9%/wk). Similarly, a 2.4%/wk decrease in plantar flexors was found following 5 wk horizontal bed-rest^[18]. Muscle group-specific adaptations have been demonstrated in skeletal muscle ACSA of the leg and lumbar musculature after 17 wk of bed-rest^[2]. The plantar-flexors were more susceptible to atrophy (approximately 1.8%/wk) than the dorsiflexors (approximately 0.9% to 1.2%/wk)^[2]. The intrinsic lumbar muscles atrophied approximately 0.5%/wk but there was no significant change in psoas muscle mass^[2]. Rittweger *et al.*^[19] reported a decrease in calf muscle ACSA (approximately 2.0%/wk), which was greater than the reported decrease in the forearm ACSA (0.5%/wk) in response to 90 d bed-rest.

Immobilisation of the leg through plaster cast has shown to decrease calf ACSA (approximately 3% to 5%/wk) after just 2 wk^[4,22]. Changes in quadriceps ACSA (approximately 8.3%/wk) have also been documented with as little as 10 d leg cast immobilisation^[25]. Similarly, Veldhuizen *et al*^[3] reported decreases in quadriceps ACSA (approximately 5.3%/wk) with 4 wk leg casting. Immobilisation of the knee using a brace has also resulted in decreases in muscle ACSA^[24,26]. Fourteen days of knee-brace immobilisation has resulted in ACSA decreases of the thigh (approximately 3.1%/wk), quadriceps (approximately 2.9% to 3.8%/wk), gastrocnemius (approximately 4.7%/wk) and soleus (approximately 3.3%/wk) muscles^[24,26]. Yasuda *et al*^[26] found no sex-based differences in the quadriceps ACSA response to knee-brace mediated immobilisation. There is considerably less data on immobilisation-induced atrophy of the upper limb muscles. Casting of the arm for as little as 9 d has shown to decrease ACSA of the forearm (approximately 3.2%/wk)^[23]. Yue *et al*^[12] investigated the effect of 4 wk elbow joint immobilisation with a fibre glass cast and reported a decrease in elbow flexor ACSA (approximately 2.8%/wk).

Tesch *et al*^[32] developed a model to study the effects of an unloaded limb in humans that allows for freely moveable joints but minimises load bearing. In this ULLS method, a sling suspends one lower leg and the contralateral shoe has an elevated sole to allow for a relaxed position of the unloaded limb. ULLS also results in decreases in muscle ACSA, though to a lesser degree than immobilisation. ULLS of 23 d has been reported to decrease knee extensor (approximately 3%/wk)^[30] and plantar flexor (approximately 2.7%/wk)^[31] ACSA. Correspondingly, Clark *et al*^[28,29] reported decreases in plantar flexor (approximately 2.0% to 2.3%/wk) and knee extensor (approximately 2.0%/wk)^[29] ACSA in response to 4 wk ULLS. It would therefore seem that in terms of ACSA at least, the most impactful model of hypo-activity is immobilisation.

Muscle physiological cross sectional area

PCSA is the area of the muscle at right angles to the longitudinal axis of the fibres. Muscle PCSA has been associated with the maximal force generating capacity of a muscle^[33] and has been shown to decrease with bed-rest^[1,9,20]. Twenty days bed-rest has been shown to decrease PCSA of the thigh (between approximately 2.7% to 3.6%/wk)^[1,20]. Akima *et al*^[9] described muscle group-specific adaptations, demonstrating a decrease in PCSA of knee extensor (approximately 2.5%/wk), knee flexor (approximately 4.0%/wk) and plantarflexor (approximately 4.5%/wk) muscles in response to 20 d of 6 degrees head-down-tilt bed rest. It is generally accepted that muscle losses are greater in the knee extensors than the knee flexors after unloading in humans^[34]. Akima *et al*^[9] demonstrated the opposite to this, which could be due to the methodology used to determine PCSA. In addition, since a muscle placed in a shortened position experiences a greater degree of atro-

phy than one placed in a lengthened position^[35], the pattern/magnitude of disuse would therefore be expected to be modulated by both the mode of hypo-activity and the joint angle adopted in the immobilisation. Bed-rest, however, had no effect on the PCSA of the tibialis anterior^[9]. The tibialis anterior experiences lower activation during habitual physical activities than other muscles such as the plantar flexor, and as such may explain the lack of decrease in tibialis anterior muscle PCSA with bed-rest. Comparisons of bed-rest to other hypo-activity models in terms of PCSA changes is not yet possible, as research is lacking with this parameter being measured.

Muscle volume

Muscle volume is a major determinant of joint torque^[36] and has been shown to decrease in response to bed-rest and immobilisation models^[10-12,21,27]. Muscle volume of the thigh decreases (approximately 3%/wk) with as little as 7 d bed rest^[21]. Following 30 d bed rest, Convertino *et al*^[11] reported decreases in calculated leg volumes of the calf (approximately 2.3%/wk) and thigh (approximately 1.1%/wk). Yue *et al*^[12] investigated the effect of 4 wk elbow joint immobilisation with a fibre glass cast and reported a decrease in elbow flexor volume (approximately 2.9%/wk). A case study of a orthopaedic patient who fractured the fifth metatarsal of the right foot displayed substantial and rapid losses in muscle volume, both proximally and distally to the immobilisation site after 4 wk subsequent immobilisation^[10]. The degree of muscle volume decrease varied between the different muscle sites of the triceps surae (approximately 5.5%/wk), quadriceps (approximately 6.0%/wk) and hamstrings (approximately 1.6%/wk)^[10]. This is in agreement with the general acceptance that muscle volume is lost to a greater extent in the knee extensors compared to the knee flexors^[34]. An age-related susceptibility to immobilization is also evident whereby, Urso *et al*^[27] demonstrated different responses to 2 wk adductor pollicis (AP) immobilisation between younger and older males. AP volume decreased approximately 2.1%/wk (not significant) in young males and significantly decreased by approximately 4.8%/wk in older males^[27].

Upper vs lower limb

Immobilisation through casting appears to have a greater effect on the lower limb musculature than the upper body. This is not surprising since the habitual loading of the lower extremities, because of body weight in normal ambulation and even in the absence of intended physical exertion, is far more substantial than that in the upper extremities. Understandably, this thereby affects the required threshold of decrease in muscle activity necessary to negatively impact on muscle metabolism. [Relative change in muscle ACSA, PCSA and volume in response to hypo-activity models. Values are separated into the effect of each hypo-activity model on the upper limb (UL) *vs* the lower limb (LL). The values are taken from the refer-

Table 1 Relative change in upper and lower limb muscle anatomical cross sectional area, physiological cross sectional area and volume

	ACSA_UL (%)	ACSA_LL (%)	PCSA_UL (%)	PCSA_LL (%)	Volume_UL (%)	Volume_LL (%)
De-training	-	-0.6	-	-	-	-
Bed-rest	-0.5	-1.5	-	-3.5	-	-2.1
Immobilisation	-3	-4.4	-	-	-3.3	-4.4
ULLS	-	-2.4	-	-	-	-
Mean (SD) of 4 models	-1.8 (1.8)	-2.2 (1.6)		-3.5 (0.01)	-3.3 (0.01)	-3.3 (1.6)

ACSA: Anatomical cross sectional area; PCSA: Physiological cross sectional area; ULLS: Unilateral lower limb suspension; UL: Upper limb; LL: Lower limb.

ences used in the text for de-training (ACSA_LL)^[6,8], bed-rest (ACSA_UL)^[19] (ACSA_LL)^[2,11,18,19] (PCSA_LL)^[1,9,20] (Volume_LL)^[11,21], immobilisation (ACSA_UL)^[12,23] (ACSA_LL)^[3,4,22,24-26] (Volume_UL)^[12,27] (Volume_LL)^[32] and ULLS (ACSA_LL)^[28-31]. Where there are missing values, this shows gaps in the literature (*i.e.*, values are not available for a parameter during a specific hypo-activity model) (Table 1)]. Forearm muscle ACSA decreased 4.1% with 9 d arm casting^[23], whereas, a similar period of immobilisation of the lower limb with 10 d casting resulted in an 11.8% decrease in quadriceps ACSA^[25]. Similarly, with longer periods of immobilisation the effect seems to be greater in the lower limbs. In response to 4 wk elbow joint casting, Yue *et al.*^[12] reported an 11.2% decrease in elbow flexor ACSA, whereas, Veldhuizen *et al.*^[3] reported a 21% decrease in quadriceps ACSA in response to 4 wk leg casting.

Intramuscular adipose tissue

Using signal intensity analysis of lower limb magnetic resonance images (MRI). Manini *et al.*^[37] discriminated between the relative changes in adipose and skeletal muscle tissue resulting from a 4 wk period of ULLS. In addition to the characteristic reduction in muscle ACSA, there was a concomitant 15% increase in intermuscular adipose content after 4 wk of lower limb suspension^[37]. Thus, these findings suggest, that hypo-activity induced alterations in skeletal muscle morphology goes beyond muscle atrophy alone.

Summary

Together, these findings show that the extent of muscle atrophy differs depending on the hypo-activity model. Certain factors may modulate the differential responses to hypo-activity models (*e.g.*, age, nutritional status). Indeed, both Kortebein *et al.*^[38] and Urso *et al.*^[27] suggested that older individuals experience greater losses in muscle mass when compared to younger individuals. A change in nutritional status, whether it is due to physiological changes directly caused by hypo-activity or to altered behaviour that is caused by hypo-activity and leads to changes in diet, could affect the physiological systems in question. The above also suggest that the degree of muscle atrophy differs between muscle groups, with the leg and postural muscles being most susceptible to atrophy. This is likely to be due to the comparatively substan-

tial decrease in habitual weight-bearing forces applied to the lower limb during hypo-activity. Hypo-activity not only decreases muscle content, but also impacts on the intrinsic composition of the said skeletal muscle through increased adiposity^[37] and altered muscle architecture^[39].

The decrease in muscle mass seen with hypo-activity may be the result of an imbalance between protein synthesis and protein breakdown^[40-42]. In response to 14 d simulated microgravity, Ferrando *et al.*^[40] reported a loss of lean muscle mass, accompanied with a 14% decrease in protein synthesis and no change in protein breakdown. Similarly, Gibson *et al.*^[41] reported a marked fall in muscle protein synthesis in response to 7 wk leg immobilisation. A shorter period of immobilisation (21 d) provided little evidence of increases in mRNA for catabolic enzymes or increases in enzyme activity during this period^[43]. However, there is some evidence to suggest that increases in catabolic potential do occur, and that this event happens very quickly (48 h) after immobilisation^[42]. Nevertheless, collectively the evidence suggests that protein breakdown is unlikely to be a key modulator in the process of muscle atrophy occurring during immobilisation in humans^[44,45].

The molecular signalling responses to de-training are only just beginning to be investigated, and to date, only changes in metabolic proteins have been reported in human skeletal muscle^[46,47]. With bed-rest, Ogawa *et al.*^[48] reported increased mRNA expression of the E3 ligases, Cbl-b and Atrogin-1 in response to 20 d bed-rest. This was accompanied by a threefold increase in ubiquitinated proteins^[48]. Investigation into the effects of limb immobilisation on cell signalling in humans is limited. Modest changes in mRNA for many genes in the first 2 d after immobilisation have been reported but these changes do not affect protein levels of most transcripts^[42]. However, the Akt protein synthesis pathway and extracellular matrix components seem to be affected within 48 hours of immobilisation^[42]. Chen *et al.*^[49] and Jones *et al.*^[50] reported increases in the E3 ligases, Atrogin-1 and MuRF-1 in response to 11 to 14 d immobilisation in humans. These changes were not seen with 48 h immobilisation^[42] and are therefore thought to only occur after long duration (days rather than hours) immobilisation. Increased metallothionein expression in human skeletal muscle fibres has been associated with exposure to physiological stress, which results in elevated levels of reactive oxygen species

(ROS)^[51]. Urso *et al.*^[42] reported a more than two-fold increase in metallothioneins in human skeletal muscle with 48 h of immobilisation. However, neither Chen *et al.*^[49] nor Jones *et al.*^[50] identified changes with longer periods of immobilisation. This may suggest that metallothioneins are increased in the first few days of hypo-activity to prevent ROS-mediated DNA or cellular damage. de Boer *et al.*^[43] investigated the effects of ULLS on gene expression and cell signalling. They reported increased expression of mRNA for MuRF-1 by approximately 3 fold after 10 d without changes in MAFbx or tripeptidyl peptidase II mRNA, but all decreased between 10 and 21 d^[43]. These authors concluded that both myofibrillar and tendon protein synthetic rates show progressive decreases during 21 d of disuse; in muscle this is accompanied by decreased phosphorylation of FAK, with no marked increases in genes for proteolytic enzymes^[43]. Overall, whilst it is clear that cell signalling responses differ between hypo-activity models; further research is needed to provide a definitive description of the timing, magnitude and nature of these molecular adaptations.

MUSCLE STRENGTH

The associated decline in strength through hypo-activity can be best described based on the mode of assessment. Both isometric and dynamic strength have been reported to decline with hypo-activity, the relative magnitude of which appears to largely reflect the patterns of atrophy described above.

Isometric strength

Hypo-activity models alter muscular isometric torque. After 40 d de-training, Narici *et al.*^[8] reported a decrease in knee extension isometric MVC (approximately 2.1%/wk). Similarly, maximum isometric quadriceps strength has been reported to decrease with 90 d de-training (approximately 1.3%/wk)^[5]. More dramatic losses in isometric torque are seen with stricter hypo-activity models. Bed-rest models have been shown to decrease maximum voluntary force of plantar flexion (approximately 7.5%/wk)^[52] and knee extensor torque (approximately 4.1% to 5.0%/wk)^[53]. Correspondingly, Kawakami *et al.*^[1] showed a decrease in muscle force for knee extension (approximately 3.8%/wk) with 20 d bed-rest.

Studies using 2 wk of cast immobilisation have reported decreases in triceps surae isometric MVC torque (approximately 8.5 and 12%/wk)^[4,54]. A discrepancy between the two studies may be due to the degree of immobilisation. Gondin *et al.*^[54] simply immobilised the ankle joint, whilst, White *et al.*^[4] utilised a full leg cast. Knee-brace mediated immobilisation has resulted in a decrease in knee extensor and plantar flexion isometric strength (approximately 11.2 and 12.7%/wk, respectively)^[24]. Knee-cast mediated immobilisation resulted in a slightly larger decrease in isometric leg strength (approximately 15.7%/wk)^[55]. Christensen *et al.*^[22] utilised a knee-to-toe plaster cast and reported a decrease in isometric calf

muscle strength (approximately 4.5%/wk). Studies using casting to immobilise the elbow joint have found decreases in isometric MVC of the elbow flexors (approximately 5.3% to 8.8%/wk)^[12,56,57], and a decrease in the maximum load that could be lifted^[12]. A more dramatic decrease in isometric MVC torque has been reported in the flexors and extensors of the wrist (approximately 22.8% to 25.3%/wk) in response to immobilisation^[23,58].

With ULLS, isometric torque appears to be affected to a lesser degree than with immobilisation models. An explanation for the above observation may be that ULLS removes weight-bearing but allows for freely moveable joints (hence a degree of muscular activity) whereas immobilisation is a more rigid model that does not allow joint movement (hence a greater restriction of muscular activity). Studies have reported plantar flexor isometric MVC torque to decrease (approximately 5% to 7%/wk) with ULLS^[28,31]. With ULLS, increased fluctuations in plantar flexion (approximately 3%/wk) and knee extension (approximately 5.5%/wk) isometric force have been demonstrated^[29].

Isokinetic strength

In addition to the established decline in isometric strength (torque and force), hypo-activity models (de-training, bed-rest, immobilisation and ULLS) also result in reductions in dynamic torque outputs. Hypo-activity models also result in changes to dynamic torque outputs. After 14 d de-training isokinetic eccentric and concentric knee extension force has been shown to decrease by approximately 6% and 1.2%/wk, respectively^[7]. With as little as 14 d bed-rest decrements in knee extensor 1 repetition maximum (approximately 4.5%/wk) are seen along with a fall in MVC (approximately 7.5%/wk)^[59]. After 6 wk bed-rest maximum voluntary concentric knee extensor torque was shown to decrease uniformly across angular velocities (approximately 4.1% to 5.0%/wk)^[53]. Muscle-specific adaptations are evident with bed-rest, as shown by Dudley *et al.*^[60] who reported a decrease in concentric and eccentric isokinetic knee extensor peak torque (approximately 4.4%/wk), with no alterations in knee flexors in response to 30 d 6 degrees head-down bed-rest. Again muscle-specific adaptations were demonstrated by LeBlanc *et al.*^[18] who reported a decrease in plantar flexor concentric isokinetic strength (approximately 2.6%/wk) and no change in the isokinetic strength of the dorsiflexors with 5 wk bed-rest. As with the knee extensors *vs* knee flexors difference in sensitivity to hypo-activity alluded to above, the plantar flexor muscles experience a greater level of recruitment during gait than the tibialis anterior. Thus, habitual muscle recruitment prior to hypo-activity would appear to be a large determinant of the relative magnitude of hypo-activity-induced changes.

Results from lower limb immobilisation models indicate that short-term immobilisation is associated not only with atrophy but with a diminished capacity of the muscle to perform both concentric and eccentric strength^[23,55]. Lower limb casting results in a dramatic

decrease in isokinetic quadriceps strength (approximately 29.1%/wk)^[25]. There is evidence that the effect of leg cast immobilisation on isokinetic strength of the knee extensors and flexors is greater in the knee extensors, demonstrated by a fall in peak torque of approximately 13.3%/wk for the knee extensors and approximately 3.3%/wk for knee flexors^[3]. Cast immobilisation of the arm also results in decreased concentric (approximately 6.9% to 16.9%/wk) and eccentric (approximately 9.7% to 14.4%/wk) strength for flexion, extension, pronation and supination of the wrist^[23].

Less dramatic decreases in isokinetic strength are seen with ULLS compared to immobilisation. de Boer *et al*^[30] found a decrease in isokinetic knee extensor torque in response to 23 d ULLS (approximately 6.4%/wk). Similarly, after 4 wk ULLS mean average peak isokinetic torque is decreased (approximately 4.3%/wk)^[61]. With as little as 14 d ULLS, a decrease in peak isokinetic torque (approximately 5% to 8.6%/wk) and total work performed (approximately 7.5% to 10.0%/wk) by knee extensors and flexors was reported^[62].

Strength vs size changes

There is evidence to suggest that decreases seen in strength in response to hypo-activity models are greater than the changes seen in muscle size. With de-training the loss in leg muscle ACSA (approximately 0.7%/wk) was not as great as the decrease seen in knee extension MVC (approximately 2.1%/wk)^[8]. Similarly, in bed-rest Kawakami *et al*^[11] suggested that the decrease in knee extension mean muscle force (approximately 3.8%/wk) seen after 20 d head down bed-rest was related more to changes in neural activation to those in PCSA (approximately 2.7%/wk). Correspondingly, Berg *et al*^[53] suggested that the decline seen in strength (approximately 4.1% to 5.0%/wk) could not be entirely accounted for by decreased ACSA (approximately 2.3%/wk), and that the strength loss could also be due to factors resulting in decreased neural input to muscle and/or reduced specific tension of muscle, as evidenced by a decreased torque to EMG ratio. Discrepancies between decreases in muscle size and muscle strength have also been reported in upper and lower immobilisation studies. White *et al*^[4] reported an approximately 5%/wk decrease in muscle ACSA whilst triceps surae MVC decreased approximately 12%/wk. Additionally, the upper limb decreases in forearm ACSA (approximately 3.2%/wk) were much smaller than those reported in forearm flexor and extensor strength (approximately 22.8% to 25.3 %/wk)^[23]. Again, in ULLS models muscle torque (approximately 5% to 7%/wk) appears to decrease to a greater degree than muscle ACSA (approximately 2.3% to 2.7%/wk)^[28,31].

Summary

Bed-rest appears to have varying degrees of impact on the upper and lower body. After 14 d of 6 degrees head down bed-rest maximum voluntary force for plantar flexion was decreased (approximately 7.5%/wk) whilst no effect was observed on maximal voluntary force of

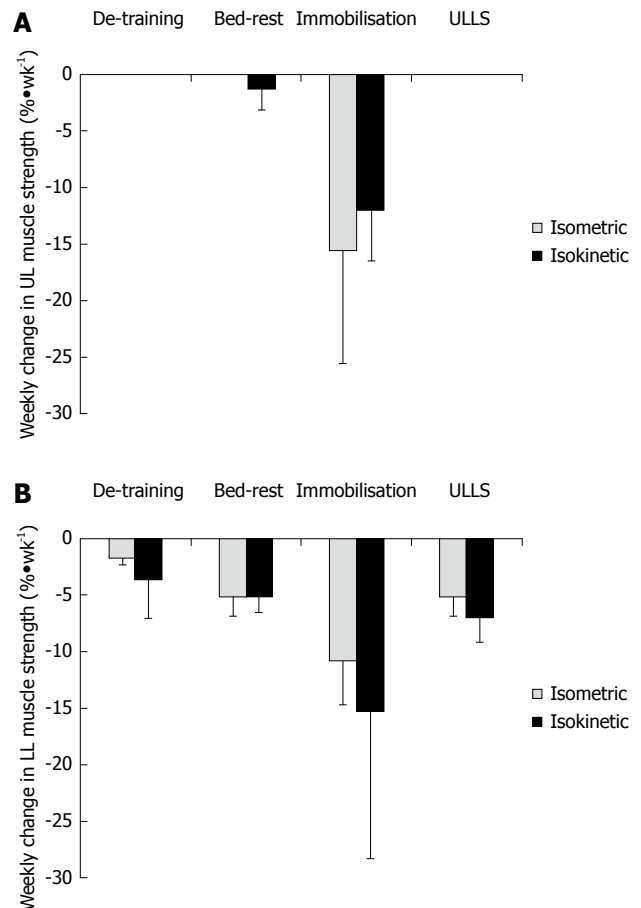


Figure 2 Relative change in isometric and isokinetic strength. A: Upper limb; B: Lower limb. ULLS: Unilateral lower limb suspension; UL: Upper limb; LL: Lower limb.

hand grip^[52]. Similar results were demonstrated by LeBlanc *et al*^[2] who showed after 17 wk of continuous bed-rest that isokinetic muscle strength decreased significantly in the thigh and calf with no loss in the arms. These results further support the idea that the lower limbs are primarily affected by bed-rest, more so than the upper limb. However, Gogia *et al*^[63] did observe a decrease in elbow flexor torque (approximately 3.8%/wk) and a non-significant decrease in elbow extension torque (approximately 1.4%/wk) after 5 wk of bed-rest. Thus, suggesting that strength in the upper limb is affected by bed-rest but only in specific muscles during specific tasks.

Together, these findings show that in addition to the reduction in muscle mass, hypo-activity also results in a dramatic loss of strength [Figure 2 relative change in isometric and isokinetic strength in response to hypo-activity models. Figure 2A Values taken from references in the text for upper body changes in strength in response to de-training, bed-rest (isokinetic)^[2,52,63], immobilisation (isometric)^[12,23,56-58] (isokinetic)^[25] and ULLS. Figure 2B values taken from references in the text for lower body changes in strength in response to de-training (isometric)^[5,8] (isokinetic)^[7], bed-rest (isometric)^[1,52,53] (isokinetic)^[18,53,59,60], immobilisation (isometric)^[4,22,24,54,55] (isokinetic)^[3,25] and ULLS (isometric)^[28,29,31] (isokinetic)^[30,61,62]. Where there are missing bars, this shows gaps in the

literature (*i.e.*, values are not available for that parameter during a specific hypo-activity models). Values are presented as means; error bars denote SD]. Models in which the joint is immobilised appear to have a greater impact on strength than unloaded models. These changes in muscular strength vary between hypo-activity models. The degree of loss in muscular strength surpasses the loss of muscle mass. Therefore, other alterations in the neuromuscular system, other than the reduction in contractile proteins must contribute to the excessive loss of strength. Voluntary force production is associated with neurological and skeletal muscle properties, thus suggesting these two factors as mechanisms accounting for the loss of strength with hypo-activity models.

Muscle fatigability

Studies have also examined the impact of hypo-activity models on the fatigability of skeletal muscle. Kamiya *et al.*^[64] showed no change in time to fatigue after 14 d bed-rest. After a longer period of bed-rest (8 wk), Mulder *et al.*^[65] demonstrated an increase in fatigability (7.2%-10.2%/min decrease in maximum voluntary isometric torque per minute exercise; or approximately 0.9%-1.3%/wk fatigability increment). The contrast between the two studies would tend to suggest a delay in the impact of hypo-activity on muscle fatigability.

The effect of immobilising a limb has various different effects on skeletal muscle fatigability. Two weeks of full leg cast immobilisation resulted in no effect on muscle fatigability^[4]. In contrast, Veldhuizen *et al.*^[3] found a decrease in isokinetic quadriceps endurance work from 9.1 kJ to 5.6 kJ after 4 wk leg cast immobilisation. These results suggest that short periods of lower limb immobilisation (≤ 2 wk) have little effect on muscle fatigability whilst longer periods of immobilisation (≥ 4 wk) increases muscle fatigability. Studies investigating the effects of immobilisation on skeletal muscle fatigability in the upper limbs have found different effects to those in the lower limbs. Similar to lower limbs shorter periods of immobilisation in the upper limbs appear to have minimal effects on muscle fatigability^[23]. Unlike the lower limb, longer periods of immobilisation of the upper limb show a trend towards increased resistance to fatigability. Following 3 wk of hand-forearm immobilisation time to task failure increased by 21% (approximately 7%/wk)^[66]. Semmler *et al.*^[56] investigated the effects of fiberglass cast immobilisation of the elbow joint, and reported 7 out of the 12 immobilised participants exhibited an unusual pattern of muscle activity during a fatiguing contraction after immobilisation. In those individuals with this unusual pattern of muscle activity there was an associated increase in the ability to maintain a contraction over an extended period of time in the elbow flexor muscles^[56]. The physiological basis for the sometimes observed immobilisation-induced decreased fatigability, is not clear but it is likely to be related to neural factors^[56]. In contrast to this, Miles *et al.*^[67] found an increase in fatigability in

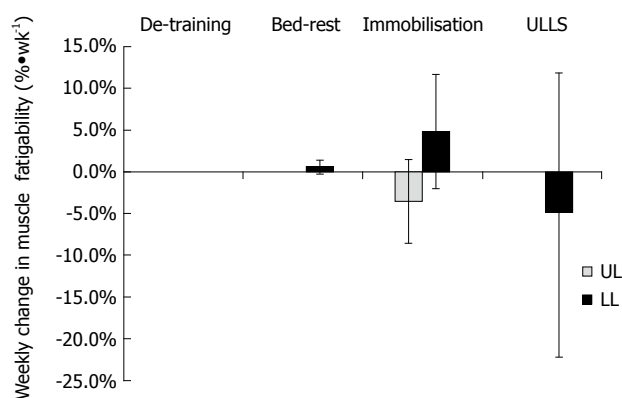


Figure 3 Relative change in muscle fatigability. ULLS: Unilateral lower limb suspension; UL: Upper limb; LL: Lower limb.

response to 3 wk arm suspension in untrained but not trained individuals. Previous research showed that ULLS led to increased fatigability after 4 wk of unloading^[61]. Results from Deschenes *et al.*^[62] found a contrasting decrease in fatigability after just 2 wk of unloading.

Collectively these results suggest that muscle fatigability varies between different hypo-activity models [Figure 3 relative change in muscle fatigability in response to hypo-activity models (mean \pm SD). Positive percentage change depicts an increase in fatigability whilst negative percentage change shows a decrease in fatigability. Values are separated into the effect of each hypo-activity model on the upper limb (UL) *vs* the lower limb (LL). The values are taken from the references used in the text for bed-rest (LL)^[64,65], immobilisation (UL)^[23,66] (LL)^[3,4] and ULLS (LL)^[61,62]. Where there are missing bars, this shows gaps in the literature (*i.e.*, values are not available for a parameter during a specific hypo-activity model)]. Shorter periods of hypo-activity (≤ 2 wk) generally appear to have little impact on fatigability. Muscle fatigability appears to increase in weight-bearing muscles but immobilisation in the upper body suggests an increase in resistance to fatigue. Differences between studies could be due to the duration of unloading or in the method used to test fatigue resistance. The mechanisms that cause fatigue are specific to the task being performed^[68,69]. Therefore, variability between fatigue resistance responses to hypo-activity models may be due to task specificity. Studies investigating a comparison of different fatigue tasks before and after hypo-activity are sparse. Yue *et al.*^[12] demonstrated a task-dependent effect on muscle fatigue with substantially increased endurance time (reduced fatigability) at a low force (20% MVC) and no statistical effect at a moderate force (65% MVC) in the elbow flexors. The selective improvement of fatigue resistance for the low-force contraction was accompanied by the absence of a change in the time course of the twitch, suggesting that the immobilisation-induced adaptation included and improved efficacy of some excitation-contraction processes and underscored the major role of these mechanisms in determining the endurance time for low-force, long-duration contractions. It appears that the hypo-

activity induced adaptations in muscle fatigability vary with the specifics of the task being performed. More research is needed to investigate these task-specific responses to different models of hypo-activity.

Numerous adaptations in fatigue mechanisms have been hypothesised to explain the observed preservation and decrease in fatigability in response to hypo-activity. As stated previously, hypo-activity results in muscle atrophy and a decrease in muscle strength, have been reported to be accompanied by myofiber transitions from slow to fast^[70] and a shift in fuel metabolism away from lipid fuels toward glycolysis^[71]. Typically these changes are associated with increased fatigability. Cardiovascular adaptations with hypo-activity^[72] reduces oxygen delivery and oxygen utilization which may impair prolonged exercise capacity. Additionally, exercise tolerance may be influenced by impaired muscle activation after hypo-activity^[1,54]. In light of this, the reports of decreased fatigability with hypo-activity are puzzling, and the underlying mechanisms remain unclear. It is possible that an atrophy-induced decrease in absolute force production will result in decreased intramuscular pressure. This in turn, will increase blood flow to the muscle and increase supply to match the metabolic demand^[56,73]. Other potential mechanisms include adaptations in the neural activation strategy utilised^[56], adaptations in the basal inorganic phosphate concentration^[74], and changes in excitation-contraction coupling^[12].

NUTRITIONAL SUPPLEMENTATION

As mentioned above, there is strong evidence that protein synthesis is decreased in response to periods of bed-rest and immobilisation^[40,41,43]. That resistance exercise provides an anabolic stimulus during hypo-activity is undisputed^[9,59,75]. When supplemented with nutritional interventions, the benefits of exercise during bed-rest appear additive^[76], thereby suggesting different synergistic pathways for counteracting atrophy. It may not always be practical to prescribe exercise to counteract the atrophy brought about by inactivity. In these cases, such as trauma, pharmaceuticals may be used and have been tried with varying degrees of success^[77]. However, effective long-term medication is not a palatable option (*e.g.*, costs, side effects, repeated injections). Where exercise is not a practical prescription, supplementing the diet with potential/recognised hypertrophic nutrients may be an effective and easily adhered to intervention programme for preventing the loss of muscle mass/function seen with hypo-activity. In this latter therapeutic group, potential candidates include proteins (essential amino acids (EAAs) and Leucine in particular), creatine, omega-3 fatty acids, vitamin-D (Vit-D) and antioxidants, to name but a few^[78,79].

Protein

Stuart *et al*^[80] sought to determine whether the catabolic effects of bed-rest in humans was due to a decrease in

protein synthesis, and if so, to assess whether increasing the amount of dietary protein might be beneficial *i.e.* The calculated non-oxidative Leucine disappearance was used as a measure of whole-body-protein synthesis, which was shown to decrease when dietary protein was low. Bed-rest resulted in a 24% decrease in nonoxidative Leucine disappearance in participants assigned to a lower-protein diet (0.6 g protein·kg body wt⁻¹·d⁻¹), whereas Leucine kinetics were unchanged by the same bed-rest protocol in participants who received a higher-protein diet (1.0 g protein·kg body wt⁻¹·d⁻¹)^[80]. In other words, whereas protein synthesis is suggested here to decrease with bed-rest, dietary supplementation of protein appears to protect against this deleterious response.

Essential amino acids

Bolus oral ingestion of EAAs produces a several-fold increase in plasma amino acid levels^[81] and has been shown to stimulate net protein synthesis to a greater extent than a mixed meal or a solution containing nonessential amino acids^[82]. Studies have shown that providing a nutritional supplement enriched with EAAs could improve lean body mass, strength and physical function even without exercise^[83]. Previous studies by Stein *et al*^[84,85] have shown improved nitrogen balance during both 6 and 14 d of bed-rest when provided with a daily supplementation of 11 g of branch-chain amino acids (BCAA), compared with the same dose of nonessential amino acids. It appears that a greater dose of EAAs (49.5 g/d) during 28 d bed-rest prevented any noticeable changes in muscle mass^[86]. Paddon-Jones *et al*^[86] however, reported that during this 28 d period that although no changes in muscle mass were observed they did find a decline in muscle strength. Nonetheless, the decrease in muscle strength with EAAs (11%) was still noticeably less than the decrease in strength seen in the control group (23%)^[86]. These results collectively demonstrate a positive effect of EAAs supplementation during periods of bed-rest ranging from 6 to 28 d on both muscle mass and function^[84-86].

Creatine

Creatine supplementation is another potential supplement that may attenuate hypo-activity induced decreases in muscle size and strength. Johnston *et al*^[87] reported that short-term (29 d) creatine supplementation (20 g/d) attenuates the loss in muscle mass and strength during upper arm immobilisation. It is well known that muscle total creatine content can be rapidly raised by a high-dose oral creatine intake^[88] and that long-term creatine intake can enhance the effects of weight training on muscle size and strength^[89,90]. Creatine supplementation during 10 wk of resistance training has been shown to accelerate the rate of muscle hypertrophy in young adults who previously had their knee flexors immobilised for 2 wk^[91]. Furthermore, 14 d creatine supplementation during hind-limb immobilisation lessened the rate of loss in the plantarflexors in a rodent model^[92]. Additionally, Op't Eijnde *et al*^[93] showed that creatine supplement-

tation prevented the loss of glucose transporter type 4 (GLUT4) during muscle disuse and increased muscle GLUT4 content above normal levels during subsequent rehabilitation. Collectively these studies suggest that creatine supplementation during resistance training and rest may be effective at reversing or maintaining lower-body muscle mass during and after an immobilised state.

Antioxidants

Intricate antioxidant defence systems in the body work to continually manage oxidative stress. To counteract ROS, enzymatic and nonenzymatic antioxidants work together^[94]. Enzymes work to improve or maintain an antioxidant balance and to avert oxidative damage by scavenging or preventing transformation of ROS to intracellular molecules and inhibiting their conversion to more deleterious forms. Endogenous nonenzymatic antioxidants such as vitamins-C and -E, carotenoids and flavonoids play important roles by contributing to the antioxidant system as cofactors for antioxidant enzymes. Results from Zwart *et al.*^[95] provide evidence that increased oxidative stress occurs during bed-rest. These data are also supported by results of several other studies that show evidence for elevated oxidative stress and increased ROS^[96-98]. It would be interesting to see whether antioxidant supplementation during hypo-activity models will have beneficial effects on these outcome measures and furthermore, see whether this would then result in the attenuation of muscle loss in these models.

Vitamin-D

Ceglia proposed Vit-D supplementation as an effective nutritional intervention to attenuate age related sarcopenia^[99]. Vit-D supplementation (800 IU per day) for periods of 8 to 12 wk has been reported to reduce postural sway and improve the risk of falling in elderly individuals^[100,101]. Longer periods (12 mo) of Vit-D supplementation (800 IU per day) in the elderly has been shown to increase strength, decrease body sway and increase physical performance^[102]. However, in a healthy elderly population with no Vit-D deficiency Vit-D supplementation does not appear to improve muscle strength or function^[103,104]. It remains to be seen whether Vit-D supplementation in healthy persons with no Vit-D deficiency, any enhancement in muscle structural or contractile properties can be attained in the presence of hypo-activity.

Omega-3 (EPA)

Recent studies by Smith *et al.*^[105,106] supplemented healthy young and elderly individuals with omega-3 fatty fish-oils for 8 wk and found a significant increase in the muscle protein synthetic response to amino acid administration. They concluded in the elderly model that omega-3 fatty acids might be useful for the prevention and treatment of sarcopenia^[105]. Dietary fish oil has also been shown to alleviate soleus muscle atrophy during immobilisation in association with Akt signalling in rats^[107]. It would there-

fore seem reasonable to suggest that more investigation is needed into the potential of omega-3 fatty acids as a nutritional supplement for attenuating muscle atrophy with hypo-activity. In parallel, it is believed that omega-3 fatty acids may impact on lean body mass though decreasing the effectiveness of catabolic cytokines, reduced protein degradation and improving insulin sensitivity^[108]. There is evidence to suggest that eicosapentaenoic acid (EPA) an omega-3 fatty acid may reduce the pro-inflammatory cytokines associated with inflammation^[109]. Magee *et al.*^[109] demonstrated *in vitro* that EPA inhibits the effects of TNF- α by reducing its apoptotic effects and enabling myogenesis. It is however debatable whether this supplement would be useful in combating muscle atrophy where, as seen in human hypo-activity models, there is scant evidence for increased protein breakdown^[40].

CONCLUSION

Hypo-activity models result in profound changes in skeletal muscle morphology and strength. Muscle mass and strength losses vary between different hypo-activity models, with immobilisation causing the most profound decreases, greater than bed-rest and limb suspension. Decrements in muscle size and strength are seen in response to hypo-activity models with the greatest decrements seen in antigravity muscles. The decreases in strength seen with hypo-activity models surpass the losses in muscle mass and as such, the nervous system and contractile properties adapt to adjust for this excessive loss of strength. Nutritional supplementation may stand as a viable intervention to combat muscle atrophy with hypo-activity when exercise is not a practical prescription. There are several potential nutritional supplements that could be used to combat muscle atrophy but extensive research is needed to determine the most effective.

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P- Reviewer: Gorgey AS **S- Editor:** Song XX
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