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Maintenance of skeletal muscle function following reduced daily physical activity in healthy older adults: a pilot trial

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Abstract

Introduction—Older adults can experience periods of inactivity related to disease or illness, which can hasten the development of physical disability, in part, through reductions in skeletal muscle strength and power. To date no study has characterized adaptations in skeletal muscle physical function in response to reduced daily physical activity.

Methods—Participants (15 men, 69±2 years, 15 women, 68±4 years) restricted their daily steps (<750steps/d, SR) while being energy restricted (ER, −500kcal/d) for 2wks before returning to normal activity levels during recovery (RC, 1wk). Before and after each phase, measures of knee extensor isometric maximum voluntary contraction (MVC), time-to-peak torque (TTPT), and physical function were performed and muscle biopsies were taken from a subset of participants.

Results—Following the energy restriction and step-reduction phase (ER+SR), MVC was reduced by 9.1 and 6.1 Nm in men and women respectively ($p = 0.02$), which returned to baseline after RC in men, but not women ($p = 0.046$). Tmax (maximum isometric tension) in MHC IIA fibres ($p < 0.01$) and Pmax (maximum power production) in MHC I and IIA ($p = 0.05$) were increased by 14%, 25%, and 10% respectively following ER+SR. Reductions in muscle strength could not be explained by changes in single muscle fibre function in a sub-sample ($n=9$ men) of volunteers.

Discussion—These data highlight the resilience of physical function in healthy older men in the face of an acute period of ER+SR and demonstrate sex-based differences in the ability to recover muscle strength upon resumption of physical activity.

Keywords

skeletal muscle; muscle function; muscle strength; single fibre; older adults; physical inactivity

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Conflicts of interest

The authors have no conflicts of interest to report.

Introduction

Periods of absolute disuse (i.e., bed rest) (Kortebein et al. 2007; Coker et al. 2015), limb immobilization (Suetta et al. 2009; Dirks et al. 2014)) or a period of inactivity resulting in a relative muscle unloading (i.e., reduced daily steps) (Breen et al. 2013; McGlory et al. 2017; Oikawa et al. 2018) reduce muscle size and strength in older adults, which may accelerate habitual sarcopenic declines (Breen et al. 2013). Bed rest and limb immobilization are potent models of the most severe of disuse states and both promote rapid, profound loss of skeletal muscle mass and function (D'Antona et al. 2003; Kortebein et al. 2007; Glover et al. 2008; Suetta et al. 2009; Arentson-Lantz et al. 2016), which can be explained by atrophy and reduced contractility at the cellular level (Alkner et al. 2004); (Trappe et al. 2004) (D'Antona et al. 2003)

Although there is growing literature on the impact of complete muscle disuse on muscle mass and strength in older adults (D'Antona et al. 2003; Kortebein et al. 2007; Suetta et al. 2009), there is comparably less work examining the influence of seemingly benign periods of physical inactivity on changes in strength and functional capacity (Breen et al. 2013; Devries et al. 2015; McGlory et al. 2017; Oikawa et al. 2018; Reidy et al. 2018). Additionally, there are, so far as we are aware, no studies examining how inactivity impacts single muscle fibre function (isometric strength, tension, velocity). Previously, we have shown that reducing daily steps by 75–80% for two weeks induced a substantial negative impact on rates of muscle protein synthesis, a loss of muscle mass and a significant impairment in glucoregulation (Breen et al. 2013) (Devries et al. 2015). Further, during periods of illness or marked reduced activity, older adults tend to consume insufficient calories and specifically, insufficient protein (Drevet et al. 2014).

To make this investigation as applied to relevant clinical settings as possible, we designed the study to include both a reduction in physical activity via daily steps and a diet in energy deficit. We investigated the effects of two-weeks of reduced daily steps (<750/d) and hypocaloric diet on whole muscle and body function in healthy older men and women, and in a select group of older men, single fibre function. We hypothesized that combined step reduction (SR) and energy restriction (ER) would result in a reduction in whole muscle strength and whole body physical function. Furthermore, decrements in whole muscle strength would be associated with reductions in single muscle fibre contractile function.

Methods

Ethical Approval

The study was approved by the Hamilton Integrated Research Ethics Board and conformed to the standards for the ethical use of human subjects in research as outlined by the Canadian Tri-Council Policy (http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf). Informed consent was obtained before enrollment. Participants reported on in this paper were a part of another cohort (Oikawa et al. 2018) investigating the effects of protein supplementation on muscle protein synthesis and lean mass retention in older adults (registered as [NCT03285737](https://clinicaltrials.gov/ct2/show/study/NCT03285737) on clinicaltrials.gov).

Participants

Thirty older adults were recruited from the greater Hamilton area to participate in this study. Potential participants were screened to ensure they were non-smokers, non-diabetic, and between the ages of 65–80 years. Detailed exclusion criteria can be found elsewhere (Oikawa et al. 2018). Participant characteristics are presented in Table 1.

Protocol

The protocol for this trial has been described previously (Oikawa et al. 2018). Participants underwent 5-weeks of controlled dietary intake (Supplementary Figure S1). During week 1, participants were in energy balance (EB) with protein intake at the recommended daily allowance (RDA – 0.8 g protein/kg/d) and were instructed to maintain their habitual levels of physical activity. During week 2, participants consumed an energy-restricted diet (ER, –500 kcal/d) to simulate a reduction in energy-intake congruent with dietary patterns observed in institutionalized adults (Konturek et al. 2015) while consuming a high protein diet (1.6 g protein/kg/d). During weeks 3 and 4, participants maintained the energy restricted and high protein diet from the previous week but reduced their daily step count to <750 steps/day (ER +SR) using a waist-mounted pedometer (PiezoX, Deep River, ON, Canada) with energy intake adjusted for the reduction in physical activity. During week 5, participants recovered (RC) and returned to habitual levels of activity and adequate caloric intake while maintaining their high protein intake (matching their daily step-count in EB and ER). In order to increase protein intake during weeks 2–5, participants were provided with a twice-daily supplement of either whey protein isolate, or collagen peptides (30 g/serve).

Physical function

Participants completed 4 assessments of physical function that were measured at baseline, and then at the end of each dietary phase (end of weeks 1, 2, 4, and 5). The 30s chair stand test (CST) required participants to rise from a chair without the use of their arms as many times as possible in 30 s (Jones et al. 1999). For the timed up- and-go (TUG), participants were instructed to rise from the same chair, walk to and from a clearly marked point a distance of 3 m away, and sit back down in the shortest amount of time possible (Bell et al. 2017). Participants were given a practice trial before both tests, and the best of 3 trials (with 2 min rest allowed between trials) (Bell et al. 2017) as recorded for each outcome. The 6 min walk test (6MWT) was performed on a 200 m indoor track as described previously (Bell et al. 2017). Participants were instructed to attempt to cover as much distance as possible within 6 min while walking at their usual walking speed. Gait power was calculated as (body mass (kg)·9.8 (m·s⁻¹)·average gait speed (m·s⁻¹)), where 9.8 represents the acceleration of gravity. Participants were familiarized with the protocol for the physical function tests and the MVC on 3 occasions prior to beginning the study to increase stability in the measurement (Wallerstein et al. 2010). Participants were seated in a Biodex dynamometer (Shirley, NY) with set up as described previously (Devries et al. 2015). Participants performed three 5-s maximal isometric unilateral knee extensions at 70° of knee flexion (0° being full knee extension) separated by a 60-s rest to determine MVC on their dominant leg. MVC was taken as the greatest peak torque from the three contractions. Time-to peak torque (TTPT) was analyzed manually with use of the curve analysis program of the Biodex

Dynamometer (Biodex Advantage Software 4.0). The peak torque was considered to be the highest point in each curve.

Muscle biopsy and single fibre function

In the fasted state, on the first day of week 1, 2, 3 and 5 and on the final day of the study, a muscle biopsy from the *vastus lateralis* was performed using a 5-mm Bergström needle under 1% xylocaine local anesthesia. Though sex based differences may exist, muscle biopsy samples for the measurement of single fibre function were taken only from a subset of male participants due to the cost of the analysis. Tissue was prepared for single fibre functional assessments, as described (Callahan et al. 2014b). Briefly, muscle fibre bundles were carefully dissected, tied to glass rods at slightly stretched lengths and ultimately stored at -20°C in storage solution (170 mM potassium propionate, 10 mM imidazole, 5 mM EGTA, 2.5 mM MgCl_2 , 2.5 mM ATP- Na_2H_2 , and 1 mM sodium azide) at pH 7.0 (Miller et al. 2009) and 50% glycerol (v/v). Samples were then shipped on dry ice to the University of Vermont. Contractile function was measured on chemically-skinned single fibre under maximal Ca^{2+} -activated (pCa 4.5) conditions. Shortening velocity and power output were assessed during isotonic load clamps performed at 15°C , as described (Callahan et al. 2014b). Single fibres were fibre typed by gel electrophoresis, as described (Toth et al. 2013). Biopsies were shipped within one week following collection and single fibre measurements were completed within 4 weeks following each biopsy.

Statistics

All variables were assessed for normality and statistical outliers. In our original paper (Oikawa et al. 2018), participants were randomized to a protein treatment, however that treatment did not have any main or interaction effects in any of our analysis and therefore groups were pooled for this study. Data were analyzed using a two-way mixed model ANOVA with between (sex) and within (time: EB, ER, ER+SR and RC) factors. Groups were also collapsed across sex with the exception of comparison of isometric MVC in which there was a significant time $\times$ sex interaction. All significant interaction terms for the ANOVA resulted in a follow-up post-hoc test to determine pairwise differences using Tukey's post hoc test. For single fibre function measures, a linear mixed model (SAS Version 9.3; SAS Institute, Cary, NC) was used, with time as a within-subject factor and fibre number as a random effect to account for the fact that individual fibres are clustered within volunteers. Relationships between variables were determined using Pearson correlation coefficients. Analyses, except those on single fibre, were conducted with SPSS software version 16 (SPSS Inc.; Chicago, IL, USA).

Results

Participants

Thirty participants completed the study (15 men, 15 women; 69 ± 3 yrs, 87 ± 17 kg) of which 11 men had muscle fibres collected for single fibre analysis at EB and post ER+SR. Two samples were unable to be analyzed due to technical problems, which left 9 participants available for analysis.

Isometric torque and function

MVC was reduced at ER+SR from EB by 9.2 ± 18.4 and 6.1 ± 7.7 Nm in men and women respectively ($p = 0.02$). MVC was recovered in men ($p > 0.05$) but not in women at RC ($p = 0.043$) (Figure 1). There were no significant differences in MVC reduction between men and women at ER+SR and no significant changes in time to peak torque (TTPT) between any phase ($p > 0.05$).

Gait power was reduced from baseline following ER+SR by 26.3 ± 38.9 and 22.3 ± 17.8 W in men and women respectively ($p < 0.05$), but no differences existed at any time point in any other functional task (30s CST, TUG, and 6MWT) ($p > 0.05$) (Table 2). Reductions in MVC were not correlated to changes in any whole body functional measure (Supplementary table S2)

Single fibre function (Table 3)

An average of 19 ± 1 fibres were measured per participant at EB with 19 ± 2 fibers measured per participant at ER+SR. There was a trend for reduction in CSA in MHCI fibres following ER+SR ($p = 0.07$) with no change in CSA in MHCII fibres. There was an increase in maximum power production (Pmax) in MHCI ($p = 0.02$) and MHCIIA fibres ($p = 0.05$) and an increase in maximum isometric tension (Tmax) in MHC IIA fibres ($p < 0.01$). Maximum shortening velocity (Vmax) was inversely correlated with MVC ($p = 0.024$).

Discussion

The novel finding of the present investigation was that 2 weeks of combined SR+ER resulted in reduced muscle isometric strength in older men and women. However, no alterations in physical performance measures were observed and single muscle fibre function was unchanged or paradoxically increased when measured in men. Finally, women, as opposed to men, did not recover strength as measured by MVC that was lost during the SR+ER period during RC.

Following ER+SR, isometric knee extensor MVC was reduced by ~5%, confirming that 2 weeks of SR provides a sufficient stimulus to impair muscle function, albeit the magnitude is less than previous investigations in older adults who were on complete disuse of -15% (Kortebein et al. 2007; Hvid et al. 2010). Moreover, following one week of RC (recovery), muscle strength recovered to baseline. Though the decrements in strength in the present investigation are relatively small, periods of reduced physical activity occur at frequently in older populations (Milanovic et al. 2013), increasing the frequency of scenarios during which older adults have compromised strength. Interestingly, when men and women were analyzed separately, women failed to recover strength losses, suggesting impaired resiliency in older women that may portend greater functional impairment over time (Janssen et al. 2002). Similar findings have been shown comparing the recovery of forearm flexor strength following 3 weeks of cast immobilization demonstrating that women had slower voluntary strength recovery (Clark et al. 2009). Data from the aforementioned work draws attention to a similar reduction in central activation in comparing men and women following casting suggesting that decrements at the level of the muscle may be the cause for a slower recovery

in voluntary strength in women rather than differences in neural activation. How these contributions are altered with increasing age however, cannot be determined from the current investigation.

We found no alterations in functional performance outcomes following SR in our cohort of healthy older men and women, with the exception of a small reduction in gait power. Although muscle strength is a strong predictor of whole body functional measures (Bean et al. 2008), the decrement in strength observed in our volunteers may be insufficient to elicit reductions in physical function. Alternatively, there may be adequate reserve in other physiologic systems to maintain physical function. Reductions in physical performance may be expected in clinical populations with SR, where physiological reserve is compromised.

Interestingly, single fibre function, which we measured in only the male participants, remained unchanged or increased with SR+ER, in contrast with changes in whole muscle strength. Our results are not unprecedented, as a recent longitudinal study reported discordance in single fibre and whole muscle contractile performance in mobility limited individuals (Reid et al. 2014). Considering that we observed these cellular level adaptations in response to acute disuse related to SR, we posit that they may reflect compensatory adaptations to mitigate decrements in whole muscle contractility. Our results are congruent with previous literature comparing single fibre function with a disuse model (knee osteoarthritis) highlighting a potential mitigation of muscle force decrements by the increase of single fibre velocity (Callahan et al. 2014a). Enhanced single fibre function may occur in response to deficits in neuromuscular activation or muscle cellular components of excitation-contraction coupling that develop with disuse, although we acknowledge that a larger cohort of volunteers with single fibre analysis will be needed confirm that SR potentiates myofilament function.

Our ability to compare men and women following a stimulus akin to acute illness was a significant strength of the current investigation. However there are limitations of the present study that we acknowledge. Firstly, our sample size, specifically for the single fibre analyses were small and therefore observations in single fibre function, notably increases in Pmax and Tmax parameters, may be at risk for type II errors. Further investigations into the effects of energy restriction, step reduction, on single fibre function are warranted. Secondly, we did not include women in our analyses of single fibre function due to cost of the analyses. As mentioned previously, women may be at greater risk for the recovery of voluntary strength due to alterations at the peripheral level (rather than central activation) and therefore changes in single fibre in women would provide valuable insight into sex based differences in single fibre function with disuse. Previous literature has attributed slowing of myosin actin-cross-bridge kinetics, increases in myofilament lattice stiffness, and increases in isometric tension associated with aging to be primarily driven by women (Miller et al. 2013). Thus, including women in future analyses of single fibre function with disuse may provide valuable insight into the mechanisms underlying disparate responses between men and women.

Our data show the resiliency of physical function in healthy older men as a whole despite reduced whole muscle function. In women, the failure to remediate muscle function following resumption of activity levels may hasten disability however other measures of

physical function evaluated were unchanged. The investigation of SR on muscle function may provide a more relevant model of real-world disuse in comparison to bed rest or immobilization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

6MWT	six-minute walk test
30 CST	30 second chair stand test
CSA	muscle fibre cross sectional area
DXA	dual-energy x-ray absorptiometry
EAA	essential amino acid
EB	energy balance phase
EER	estimated energy requirement
ER	energy restricted phase
ER+SR	energy restricted and step reduction phase
LBM	lean body mass
LLM	leg lean mass
MVC	maximum voluntary contraction
RC	recovery phase
RDA	recommended daily intake
TTPT	time to peak torque
TUG	timed up-and-go test

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Figure 1.

Isometric maximum voluntary contraction of the knee extensors at 70° of flexion in men (A) and women (B). MVC, maximum voluntary contraction; EB, energy balance phase; ER, energy restriction phase; ER+SR, energy restriction and step reduction phase; RC, recovery phase. Means that do not share a letter are significantly different within the group, $p < 0.05$. Data were analyzed with 2-factor ANOVA with repeated measures.

Table 1.

Participants' characteristics.

	EB	ER	ER+SR	RC
Body mass (kg)	86.4 ± 16.4 ^a	85.9 ± 16.5 ^b	84.7 ± 16.4 ^c	85.2 ± 16.3 ^b
LBM (kg)	50.2 ± 10.3 ^a	50.0 ± 10.4 ^a	49.5 ± 10.3 ^b	50.4 ± 10.2 ^a
Body fat (%)	39.2 ± 8.7 ^a	39.2 ± 8.9 ^a	38.9 ± 9.2 ^b	38.2 ± 9.2 ^c
Steps (day ⁻¹)	7315 ± 3757 ^a	7883 ± 3814 ^a	920 ± 370 ^b	7919 ± 3371 ^a

Values are means ± SD. LBM, lean body mass; EB, energy balance phase; ER, energy restriction phase; ER+SR, energy restriction and step reduction phase; RC, recovery phase. Means that do not share a letter are significantly different, $p < 0.05$.

Table 2.

Functional measures

	EB		ER		ER+SR		RC	
	Men	Women	Men	Women	Men	Women	Men	Women
<i>Whole body</i>								
30 CST		15.7 ± 3.4 ^a		15.7 ± 3.3 ^a		15.5 ± 3.1 ^a		15.8 ± 3.5 ^a
TUG (sec)		7.3 ± 1.7 ^a		7.2 ± 1.6 ^a		7.3 ± 1.7 ^a		7.2 ± 1.6 ^a
6MWT (m)		560.9 ± 93.2 ^a		554.2 ± 91.0 ^a		561.8 ± 94.8 ^a		561.7 ± 89.8 ^a
Gait speed (m/s)		1.6 ± 0.3 ^a		1.5 ± 0.3 ^a		1.6 ± 0.3 ^a		1.5 ± 0.4 ^a
Gait power (W)		1290.6 ± 424.7 ^a		1267.0 ± 418.2 ^b		1265.2 ± 415.0 ^b		1258.9 ± 491.5 ^b
<i>Whole muscle</i>								
MVC (Nm)	180.0 ± 49.7 ^a	107.7 ± 24.2 ^a	180.1 ± 42.4 ^a	108.8 ± 26.2 ^a	170.9 ± 41.0 ^b	102.7 ± 23.1 ^b	174.9 ± 44.8 ^a	100.8 ± 22.9 ^b
TTPT (sec)	2.9 ± 0.9 ^a	2.5 ± 1.1 ^a	3.0 ± 1.1 ^a	2.6 ± 1.1 ^a	3.2 ± 1.1 ^a	2.5 ± 1.2 ^a	3.2 ± 0.9 ^a	2.6 ± 1.1 ^a

Values are means ± SD. EB, baseline phase; ER+SR, step reduction phase; MVC, Maximum voluntary contraction; 30 CST, 30 second chair stand test; TUG, timed up and go test velocity; 6MWT, six minute walk test distance; TTPT, time to peak torque; EB, energy balance phase; ER, energy restriction phase; ER+SR, energy restriction and step reduction phase; RC, recovery phase. Data were analyzed a 2-way ANOVA (sex and time). Means that do not share a letter are significantly different, $p < 0.05$.

Table 3.

Single fiber contractile function in older men (n = 9)

	Fiber Type	EB	ER+SR	p value
Tmax (mN/mm ²)	MHC I	102.0 ± 8.5	107.8 ± 8.4	0.16
	MHC IIA	138.9 ± 14.1	167.3 ± 13.8	< 0.01
Vmax (ML/s)	MHC I	0.68 ± 0.12	0.72 ± 0.12	0.29
	MHC IIA	1.29 ± 0.11	1.34 ± 0.11	0.41
Pmax (W/L)	MHC I	0.03 ± 0.01	0.04 ± 0.01	0.02
	MHC IIA	0.09 ± 0.02	0.10 ± 0.02	0.05
CSA (μm ²)	MHC I	6089 ± 622	5602 ± 616	0.07
	MHC IIA	5596 ± 483	5382 ± 472	0.47

Values are least squared means ± SE derived from the mixed model analysis. EB, baseline phase; ER+SR, step reduction phase; Tmax, maximum isometric tension; Vmax, maximum shortening velocity; Pmax, maximum power production.