Experimental Gerontology 99 (2017) 98–109

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Randomized, four-arm, dose-response clinical trial to optimize resistance exercise training for older adults with age-related muscle atrophy

Michael J. Stec[a,b], Anna Thalacker-Mercer[a,b], David L. Mayhew[a,b], Neil A. Kelly[a,b], Craig S. Tuggle[a,b], Edward K. Merritt[a,b], Cynthia J. Brown[a,c,f], Samuel T. Windham[a,d], Louis J. Dell'Italia[a,e,g], Scott C. Bickel[a,h], Brandon M. Roberts[a,b], Kristina M. Vaughn[a,b], Irina Isakova-Donahue[a,b], Gina M. Many[a,b], Marcas M. Bamman[a,b,f,*]

[a] UAB Center for Exercise Medicine, University of Alabama at Birmingham, Birmingham, AL 35294, United States
[b] Department of Cell, Developmental, and Integrative Biology, University of Alabama at Birmingham, Birmingham, AL 35294, United States
[c] Division of Gerontology, Geriatrics, and Palliative Care, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294, United States
[d] Department of Surgery, University of Alabama at Birmingham, Birmingham, AL 35294, United States
[e] Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294, United States
[f] Geriatric Research, Education, and Clinical Center, Veterans' Affairs Medical Center, Birmingham, AL 35233, United States
[g] Research Service, Veterans' Affairs Medical Center, Birmingham, AL 35233, United States
[h] Department of Physical Therapy, University of Alabama at Birmingham, Birmingham, AL 35294, United States

ARTICLE INFO

Keywords:
Aging
Exercise
Muscle mass
Muscle strength
Muscle inflammation
Exercise dose

ABSTRACT

Purpose: The myriad consequences of age-related muscle atrophy include reduced muscular strength, power, and mobility; increased risk of falls, disability, and metabolic disease; and compromised immune function. At its root, aging muscle atrophy results from a loss of myofibers and atrophy of the remaining type II myofibers. The purpose of this trial (NCT02442479) was to titrate the dose of resistance training (RT) in older adults in an effort to maximize muscle regrowth and gains in muscle function.

Methods: A randomized, four-arm efficacy trial in which four, distinct exercise prescriptions varying in intensity, frequency, and contraction mode/rate were evaluated: (Janssen et al., 2004) high-resistance concentric-eccentric training (H) 3 d/week (HHH); (Szulc et al., 2010) H training 2 d/week (HH); (Lexell et al., 1988) 3 d/week mixed model consisting of H training 2 d/week separated by 1 bout of low-resistance, high-velocity, concentric only (L) training (HLH); and (Doherty, 2003) 2 d/week mixed model consisting of H training 1 d/week and L training 1 d/week (HL). Sixty-four randomized subjects (65.5 ± 3.6 y) completed the trial. All participants completed the same 4 weeks of pre-training consisting of 3 d/week followed by 30 weeks of randomized RT.

Results: The HLH prescription maximized gains in thigh muscle mass (TMM, primary outcome) and total body lean mass. HLH also showed the greatest gains in knee extension maximum isometric strength, and reduced cardiorespiratory demand during steady-state walking. HHH was the only prescription that led to increased muscle expression of pro-inflammatory cytokine receptors and this was associated with a lesser gain in TMM and total body lean mass compared to HLH. The HL prescription induced minimal muscle regrowth and generally lesser gains in muscle performance vs. the other prescriptions.

Major conclusions: The HLH prescription offers distinct advantages over the other doses, while the HL program is subpar. Although limited by a relatively small sample size, we conclude from this randomized dose-response trial that older adults benefit greatly from 2 d/week high-intensity RT, and may further benefit from inserting an additional weekly bout of low-load, explosive RT.

Trial registration: ClinicalTrials.gov NCT02442479

1. Introduction

The progressive loss of muscle mass during normal aging is a major contributor to functional disability (Janssen et al., 2004) and all-cause mortality (Szulc et al., 2010), and the rate of atrophy is greatly accelerated beyond the fifth decade (Lexell et al., 1988). This loss of muscle mass during normal aging is primarily due to atrophy of type II myofibers and death of motor neurons (resulting in a loss of up to

* Corresponding author at: UAB Center for Exercise Medicine, University of Alabama at Birmingham, Birmingham, AL 35294.
E-mail address: mbamman@uab.edu (M.M. Bamman).

http://dx.doi.org/10.1016/j.exger.2017.09.018
Received 24 April 2017; Received in revised form 25 July 2017; Accepted 25 September 2017
Available online 28 September 2017
0531-5565/ Published by Elsevier Inc.

~50% of total myofiber number by age 80) (reviewed in (Doherty (2003)). The functional consequences of age-related muscle atrophy include reduced muscle strength, power, mobility, and increased risk of falls (Landers et al., 2001; Petrella et al., 2005; Candow & Chilibeck, 2005; Landi et al., 2012). Thus, it is imperative to develop effective intervention strategies to promote muscle regrowth in older, atrophied adults to improve quality of life and reduce mortality.

Various interventions have been tested (e.g. nutritional, pharmacologic, exercise training) (reviewed in Waters et al. (2010)) and thus far resistance exercise training (RT) seems most effective; however, muscle regrowth results are generally suboptimal. For example, we (Kosek et al., 2006; Bickel et al., 2011; Petrella et al., 2007; Petrella et al., 2006) and others (Raymond et al., 2013; Latham et al., 2004; Peterson et al., 2010; Sherrington et al., 2011) have shown that RT induces meaningful increases in muscle strength, power, and functional mobility, but the hypertrophic response is, on average, blunted in old compared to young (Kosek et al., 2006; Bickel et al., 2011; Petrella et al., 2006), and more than one-third of older adults realize no myofiber hypertrophy in response to a 3 d/week high-intensity prescription (Bamman et al., 2007). The age-related attenuation of RT-induced hypertrophy may be partially driven by a reduced protein synthesis response (Mayhew et al., 2009), blunted ribosome biogenesis (Stec et al., 2015), attenuated myonuclear addition (Petrella et al., 2006; Petrella et al., 2008; Adams & Bamman, 2012), and other unknown mechanisms. We speculate inflammation/cell stress may negatively affect the anabolic sensitivity to RT in older muscle, which is supported by muscle inflammation susceptibility we have noted in both resting muscle and in myotubes derived from older adults (Merritt et al., 2013). Resistance exercise acutely elevates cell stress and inflammatory signaling in skeletal muscle (Buford et al., 2009; Morton et al., 2009), and if some of these pathways are already chronically elevated in resting muscles of older adults, they may negatively impact anabolic processes (Lang et al., 2002; Dreyer et al., 2006) and blunt hypertrophy.

The purpose of this trial (NCT02442479) was to titrate the dose of RT in older adults in an effort to maximize muscle hypertrophy, with particular emphasis on the weight-bearing muscle groups of the thigh (*primary outcome = thigh muscle mass gained*), which are central to mobility and postural stability. The goal was to identify a prescription that sufficiently loaded muscle to promote myogenic processes, while allowing adequate recovery between bouts to limit muscle inflammation signaling. A few studies have manipulated RT intensity and frequency among older adults in an attempt to optimize gains in muscle strength, power, and functional ability (Farinatti et al., 2013; de Vos et al., 2005; Galvao & Taaffe, 2005) but no dosing study to our knowledge has focused on treating muscle atrophy – i.e. "sarcopenia" as originally defined. Here we tested four, randomly assigned RT prescriptions with varying intensities, frequencies, and contraction modes. In brief, the four training prescriptions tested were: (1) high-resistance concentric-eccentric training (H) 3 d/week (HHH); (2) H training 2 d/week (HH); (3) 3 d/week mixed model consisting of H training 2 d/week separated by 1 bout of low-resistance, high-velocity, concentric only (L) training (HLH); and (4) 2 d/week mixed model consisting of H training 1 d/week and L training 1 d/week (HL). We hypothesized that 2 d/week of high-resistance loading (HH and HLH) would induce the greatest muscle regrowth – predicting this would optimize recovery time between high-resistance loading bouts, leading to enhanced muscle anabolism and minimal muscle inflammation – whereas HHH would not allow sufficient recovery between bouts, and HL would not provide a sufficiently frequent anabolic stimulus to induce hypertrophy. Secondarily, we hypothesized that HLH would experience the greatest gains in muscle function due to the incorporation of 1 d/week high-velocity L training as a supplement to 2 d/week H training for hypertrophy.

2. Methods

Subject recruitment began in January 2008 and final follow-up outcome measures were collected in May 2012 (tissue assays and data analyses concluded in 2015). An overview diagram of recruitment, informed consent, screening, randomization, follow-up, retention, and analysis/completion is shown in Fig. 1.

2.1. Human subjects

Older men and women (age 60–75 y) were recruited from the greater Birmingham, Alabama catchment region via newspaper and e-news advertisements. Each subject passed a comprehensive physical examination performed by a geriatrician and diagnostic graded exercise stress test (GXT) with 12-lead electrocardiogram reviewed by a cardiologist prior to participation in the study. Exclusion criteria: neurological, musculoskeletal, or other disorder that would preclude one from completing resistance training and all performance tests; uncontrolled hypertension; unstable or exercise-induced angina pectoris or myocardial ischemia; diabetes mellitus; any other medical condition that would interfere with testing or increase one's risk of complications during exercise; inability to walk on a treadmill for 10 min; lidocaine allergy; prescription anti-coagulant (e.g., Coumadin) therapy; androgen (e.g., testosterone) or anabolic (e.g., GH, IGF-I) therapy; regular leg resistance exercise during the previous 3 years; food allergy to cow's milk; currently adherent to a weight reduction diet; obesity, or body mass index (BMI) ≥ 30. All female participants were at least 5 years post-menopausal. Estrogen replacement therapy (ERT) was not an inclusion or exclusion criterion as ERT does not affect gains in muscle strength or lean mass during resistance training and does not alter single myofiber function. In a previous trial (Bickel et al., 2011), we found no differences in rates of myofiber hypertrophy, muscle mass gain, or strength gain between older women on and off of ERT. The study was approved by the Institutional Review Board (IRB) of the University of Alabama at Birmingham, and all subjects provided written informed consent prior to participation.

2.2. Overall trial design

The design was a randomized, four-arm efficacy trial (NCT02442479) in which four, distinct RT prescriptions varying in intensity, frequency, and contraction mode/rate (see details below) were evaluated to determine which dose(s) yielded the greatest muscle regrowth and gains in muscle function. In an effort to differentiate the effects of the four prescription doses, randomized RT was protracted to 30 weeks, and was preceded by 4 weeks of familiarization and pre-training (described below). Because thigh muscle mass (TMM) was the primary outcome, the DXA lean mass assessments defined the total number of subjects in the final data set (n = 63; 29F, 34 M). For a variety of reasons leading to missing data, sample sizes for some secondary and tertiary outcomes were subsets of n = 63 as reported in results for each of these outcomes.

2.2.1. Adherence plan

Because this was an efficacy trial (i.e. not "intent-to-treat"), adherence to the exercise regimen was imperative in order for the outcome data to be interpreted. Consequently, we established an IRB-approved incentives plan to ensure a minimum adherence rate, which included rewards for participation/adherence as well as a stepwise warning system and a plan for administrative withdrawal from the study if a subject failed to adhere per the established guidelines. A minimum adherence rate of 83.3% was required (i.e. 5 of every 6 consecutive sessions completed). Written warnings were issued to any subject who missed > 1 of 6 consecutive sessions. We required that issuance of a warning be followed by 100% adherence during the subsequent 6 sessions in order for a subject to be considered in good