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Markers of oxidative stress, skeletal muscle mass and function, and their responses to resistance exercise training in older adults☆

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ABSTRACT

Background: Oxidative stress (OS) negatively affects skeletal muscle homeostasis in experimental models of ageing. However, little is known about the associations between circulating OS markers and parameters of muscle mass and function, and their responses to exercise training, in humans.

Methods: Maximal voluntary contraction (MVC, primary outcome) and isokinetic torque of the knee extensors at 30° s^{-1} (MIT), muscle cross-sectional area (MCSA) and quality (MQ, secondary outcomes), and plasma concentrations of malondialdehyde (MDA, pro-OS), homocysteine (HCY, pro-OS), taurine (TAU, anti-OS), and protein sulphydryl groups (PSH, anti-OS) were measured in 27 healthy older males and 23 females at baseline and after an 18-week resistance exercise program, with or without a nutritional intervention (fish oil vs. placebo).

Results: After adjusting for age, glomerular filtration rate, and nutritional intervention, there were no significant correlations between baseline OS markers and muscle parameters, barring a positive association between TAU and MIT in females (r = 0.53, P = .035) and between MDA and MCSA in males (r = 0.69, P = .001). Training did not significantly change OS markers, except for a reduction in MDA in females (−0.27 μmol/L, 95% CI −0.51 to −0.02, P = .034). In females, there were significant correlations between baseline MDA and exercise-induced changes in MVC (P = .018), baseline TAU and changes in MCSA (P = .026), and baseline HCY and changes in MCSA (P = .046) and MQ (P = .022). In males, baseline MDA was significantly associated with exercise-induced changes in MVC (P = .040).

Conclusions: Plasma MDA, HCY, and TAU were significantly associated with baseline and/or exercise-induced changes in muscle mass and function in healthy older adults, primarily in females. Pending further confirmation in other populations, specific OS markers, particularly MDA, might predict muscle responses to resistance exercise programs in old age.

1. Introduction

Ageing is associated with intracellular and extracellular morphological and functional changes, resulting in the progressive impairment of organ function and the development of disease states. One typical example is the significant decline in neuromuscular function and performance associated with the reduction of skeletal muscle mass (sarcopenia), which results in impaired muscle strength and physical performance (Hunter et al., 2016; Cruz-Jentoft et al., 2010; Morley et al., 2011). The estimated prevalence of sarcopenia in old age ranges

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between 25 and 50% (Patel et al., 2013). The progressive increase in the number of frail older adults will inevitably lead to an increased prevalence of sarcopenia, and its associated health-care costs, worldwide (Muscaritoli et al., 2010; Visser and Schaap, 2011).

Many factors have been proposed to play a role in the pathogenesis of sarcopenia, including physical inactivity, alterations in protein metabolism and hormones, neurodegeneration, inflammation, and oxidative stress (OS) (Rolland et al., 2008). There is good evidence that the process of ageing is associated with increased concentrations of reactive oxygen and/or nitrogen species (RONS), and a reduction in endogenous antioxidants, in the skeletal muscle (Reid and Durham, 2002). This can lead to modifications of nucleic acids, proteins and lipids, resulting in molecular damage and/or dysfunction.

High concentrations of RONS have been shown to negatively affect muscle mass and function by altering the balance between protein synthesis and proteolysis (Fulle et al., 2004; Powers et al., 2011). However, the assessment of the effect of OS on skeletal muscle homeostasis has primarily been conducted in in-vitro studies and animal models, and the generalizability of these findings in humans is uncertain (Ji, 2015; Scicchitano et al., 2017). The investigation of circulating markers of OS in older adults might be particularly useful for the identification of those at risk of developing sarcopenia and/or responders to specific interventions, such as exercise training.

The aim of this study was to investigate the associations between predefined pro-OS and anti-OS markers and established parameters of skeletal muscle mass and function, and their responses to an exercise training and nutritional intervention program, in healthy older adults. Since the direct measurement of OS markers in tissue or body fluids is challenging, we measured plasma concentrations of oxidation target products such as malondialdehyde (MDA), low molecular thiol (HCY), and the antioxidants sulphydryl group of proteins (PSH) and taurine (TAU). We hypothesized that plasma concentrations of pro-OS and anti-OS markers were associated, respectively, with lower and higher skeletal muscle mass and function at baseline, and their adaptations to exercise.

2. Methods

2.1. Study population

We recruited 50 community-dwelling adults > 65 years old (27 males and 23 females) that were not participating in any resistance exercise training, had no history of cardiovascular disease, cancer, arthritis, respiratory disease, metabolic disease, recent fractures and loss of mobility, and did not take regular analgesics or nutritional supplements. However, one female was prescribed angiotensin converting enzyme inhibitors for mild hypertension, and one male was prescribed allopurinol for gout. The study was approved by the University of Aberdeen College of Life Sciences and Medicine Ethics Review Board (CERB/2011/6/644) and registered at clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT02843009). Written consent was obtained after explaining the aims, risks, and potential discomfort, in accordance with the declaration of Helsinki. Participants were part of a study investigating the effects of fish oil consumption on adaptations to 18 weeks of resistance exercise training, and were randomly assigned to either 3.0 g/day safflower oil or 3.0 g/day fish oil with data on other aspects of the project published elsewhere (Da Boit et al., 2017). All the measurements were taken at baseline and at the end of the 18 week intervention.

2.2. Resistance exercise training

Resistance exercise training was performed twice weekly for 18 weeks. Each session included four sets of nine repetitions for each exercise: leg press, leg extension, leg curl and calf press. The load for each exercise was set at 70% of the participant's one repetition maximum (1RM). This was assessed for each exercise at baseline and every six weeks, and the load adjusted accordingly.

2.3. Parameters of muscle mass and function

The following measurements were performed the morning after an overnight fast, as previously described (Da Boit et al., 2017). Measurements were made prior to and at least 48-h after the completion of the resistance exercise training intervention.

2.3.1. Knee extensor isometric and isokinetic torque

The maximal isometric torque of the knee extensor muscles of the right leg was determined during a maximal voluntary contraction (MVC) with the participant seated on a Biodex dynamometer with a knee angle of 73°. With the same seating position, maximal isokinetic torque (MIT) of the knee extensors was measured at $30^{\circ}\,s^{-1}$.

2.3.2. Magnetic resonance imaging (MRI)

Forty-five participants underwent MRI (3 others were claustrophobic and 2 had metal implants) on a Philips Achieva 3.0 Tesla whole body scanner using a 16-channel SENSE XL Torso coil. Muscle cross-section area (MCSA) was quantified mid-thigh. Muscle quality (MQ) was calculated as torque (knee extensor isometric strength) per unit MCSA.

2.4. Anthropometric and OS parameters

Body weight and height were measured, and body mass index (BMI) calculated, for each study participant at baseline. Blood samples were collected by venipuncture in K^+ EDTA vacutainers, placed on ice and processed within 30 min. After samples were centrifuged for 10 min at 4 °C at 800*g* plasma was aliquoted and stored at −80 °C until analysis. MDA was determined by spectrophotometry according to an established method (Esterbauer and Cheeseman, 1990). Briefly, plasma was mixed with 0.075% thiobarbituric acid and incubated at 95 °C for 30 min. MDA concentration was assayed by measuring the absorbance at 535 nm using a MDA standard curve. Protein–SH (PSH) was assessed by spectrophotometry at 405 nm using 5,5′, dithiobis-2-nitrobenzoic acid (Ellman, 1959). PSH concentration was determined using a glutathione standard curve and then normalized versus protein plasma quantity measured by the Lowry's method. The low molecular weight thiols HCY, and TAU were determined by capillary electrophoresis (CE) with Laser Induced Fluorescence detection (Carru et al., 2004; Zinellu et al., 2003; Zinellu et al., 2009). Following protein precipitation with trichloroacetic acid, samples were derivatized using 5-(Iodoacetamido) fluorescein as fluorophore for HCY, and with fluorescein isothiocyanate for TAU. Following dilution, samples were injected in CE. Plasma creatinine and creatine concentrations were measured using an Aquity UPLC coupled to a qToF Premier high-resolution mass spectrometer (Waters, Sydney, Australia). Estimated glomerular filtration rate (eGFR) was measured using the Modification of Diet in Renal Disease formula (Levey et al., 1999).

2.5. Statistical analysis

Results are expressed as means ± SD, medians and interquartile ranges, or frequencies as appropriate. After testing for normal distribution, using the Kolmogorov-Smirnov test, between-group differences were assessed either by one-way ANOVA or Mann-Whitney *U* test. Differences between baseline and post-exercise muscle mass and function were assessed either by paired Student's *t*-test or Wilcoxon test. In each sex, the effects of exercise and nutritional intervention on OS markers were assessed by ANCOVA. Partial correlations, adjusted for age, eGFR, and nutritional intervention, assessed the relationship between baseline OS markers and parameters of skeletal muscle mass and function, and their changes after the exercise training (MVC: primary