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Original Research

Impacts of sarcopenia and resistance exercise training on mitochondrial quality control proteins

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ABSTRACT

Background: The progression of sarcopenia with aging may be related to mitochondrial dysfunction due in part to altered mitochondrial dynamics (fusion, fission, mitophagy, and biogenesis). Previous work has identified altered expression of proteins associated with these processes in with aging, but whether further changes occur in sarcopenia remains unclear.
Objectives: The purpose of this study was to assess protein expression of markers of mitochondrial fusion (Mfn2, Opa1), fission (Drp1, Fis1), mitophagy (Parkin), biogenesis (PGC-1α), and content (Complex IV: CIV) in sarcopenic and non-sarcopenic older adults. We also determined whether resistance training affected skeletal muscle mitochondrial content and expression of mitochondrial quality control proteins in sarcopenic older adults.
Design: Longitudinal exercise training study, with cross-sectional baseline comparison.
Setting and participants: Ten older adults with mild-moderate sarcopenia, plus ten non-sarcopenic, matched older adults from Maryland, USA.
Intervention: Twelve-week resistance training.
Measurements: Strength, sarcopenic index (ALM/BMI: appendicular lean mass divided by body mass index), body composition, and mitochondrial morphology and protein expression in vastus lateralis muscle.
Results: No differences in protein expression were observed between sarcopenic and non-sarcopenic participants at baseline; however, ALM/BMI was inversely related to CIV expression ($r = -0.55$, $P = 0.013$) across all subjects. Similarly, lean body mass and ALM correlated inversely with expression of the fusion protein Opa1-S ($r = -0.55$ - -0.51, $P \leq 0.022$). Resistance training increased strength in sarcopenic older adults by 13 % ($P = 0.02$), but this group's expression of mitochondrial quality control proteins was mostly unaltered.
Conclusions: The presence of sarcopenia identified by ALM/BMI was not associated with changes in protein expression that are consistent with impaired mitochondrial dynamics beyond those changes that might occur with aging alone. While short-term resistance training increased strength in older adults with sarcopenia, this was not accompanied by changes in protein expression, with the possible exception of fusion protein Mfn2.

1. Introduction

Aging is accompanied by a progressive decline in skeletal muscle mass known as sarcopenia, which contributes to declines in strength and function [1,2]. While there are currently no proven pharmaceutical treatments for sarcopenia, mitochondria are a potential target to mitigate the negative effects of sarcopenia due to their role in adenosine triphosphate (ATP) production, calcium handling, reactive oxygen species (ROS) production, and programmed cell death. A number of studies have shown that mitochondrial dysfunction increases with age and may contribute to reduced skeletal muscle mass and function through these pathways [3–8]; however, the exact mechanisms underlying these effects remains unclear.

The mitochondrial reticulum is maintained through multiple cellular

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processes collectively referred to as mitochondrial dynamics or quality control. In skeletal muscle the reticulum is dynamic, and its structure is regulated by fusion, fission, mitophagy, and biogenesis [9]. This regulation involves several proteins to ensure mitochondria function effectively [10]. Fusion joins adjacent mitochondria together through outer mitochondrial membrane proteins mitofusin-1 and −2 (Mfn1 and Mfn2) and inner mitochondrial membrane protein optic atrophy type 1 (Opa1) [11,12]. Separation of the mitochondrial reticulum via fission involves, dynamin-related protein 1 (Drp1), fission protein 1 (Fis1), among other proteins [13–15]. Subsequent mitophagy of dysfunctional portions of mitochondria is largely regulated by mitophagy proteins PTEN-induced kinase1 (Pink1) and Parkin [16–18]. The accumulation of Pink1 on the outer surface of the mitochondria then recruits Parkin, which subsequently undergoes ubiquitination, signaling the mitochondrion for degradation. Balancing mitophagy is mitochondrial biogenesis, which is largely regulated by transcription coactivator peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) [19].

Few studies have evaluated mitochondrial dynamics in the context of sarcopenia. Marzetti et al. [20] found lower Mfn2 protein expression in physically frail and hospitalized sarcopenic adults compared to non-sarcopenic, age-matched controls; however, no differences were observed in Fis1, Mfn1, or Opa1 protein content. One other transcriptomics study found nearly the opposite, with lower Opa1 and Fis1 gene expression in sarcopenic men compared with non-sarcopenic, older men suggesting possible alterations in fusion and fission, but Mfn2 gene expression was similar between groups [21]. Given the paucity of data and discordant findings in this area, our goal was to assess the protein expression of proteins regulating mitochondrial dynamics in community-dwelling individuals with sarcopenia compared with their non-sarcopenic counterparts. Moreover, we sought to investigate the effects of resistance training on these proteins in the sarcopenic older adults.

Resistance exercise training is recommended to increase muscle size and strength in older adults with or without sarcopenia [22], and increased mitochondrial volume and respiration (function) have been observed in older adults after resistance exercise training [23,24]. Despite this, to our knowledge, there are currently no investigations into the effects of resistance training on mitochondrial content and quality control in individuals with sarcopenia. Mesquita et al. [25] recently reported that older adults who underwent 12 weeks of whole-body resistance exercise training exhibited increased skeletal muscle protein expression of Mfn1, Mfn2, Opa1, and Drp1 suggesting increases in both fusion and fission, but this study did not address sarcopenia. The present investigation extends this previous work to further our understanding of the pathophysiology of sarcopenia and potential effects of resistance training on mitochondrial targets to mitigate sarcopenia.

2. Methods

2.1. Participants & study design

Ten sarcopenic, community-dwelling, older adults between the ages of 65–88 were recruited from Baltimore and College Park, Maryland areas for the prospective resistance exercise training intervention in this study, with participant testing and muscle biopsies before and after the intervention. Baseline data and muscle specimens from ten non-sarcopenic, age-, sex-, and BMI-matched participants in a previous study with no resistance training were used as a baseline comparison group. At baseline, data from sarcopenic participants were compared with non-sarcopenic participants. Sarcopenic participants then completed 12 weeks of supervised lower-body resistance training. Expression of mitochondrial quality control proteins was measured in all muscle samples, while transmission electron microscopy (TEM) was used to assess mitochondrial content in only the prospective samples from sarcopenic subjects before and after the intervention. Additional measurements of body composition, aerobic capacity, and muscular strength testing were obtained to characterize participants and responses to resistance training.

Inclusion criteria for all participants were as follows: BMI = 18–35 kg/m^2, no regular vigorous physical activity (<20 min exercise, 2x/week), and for women, > 1-year past menopause and not on hormone replacement therapy. All participants were free of metabolic, pulmonary, and renal diseases, and did not have a history of smoking within the last two years, cancer, or stroke. For initial inclusion in the sarcopenic group, bioelectrical impedance analysis (Quantum X Body Composition Analyzer, RJL Systems, Clinton Township, MI) was conducted with participant lying supine to calculate skeletal muscle mass index (SMI: skeletal muscle mass/height squared) [26]. To be eligible for the study subjects needed to be least moderately sarcopenic (men SMI < 10.75 kg/m^2; women SMI < 6.75 kg/m^2) as defined by Janssen et al. [27]. All procedures were approved by the University of Maryland Institutional Review Board and conformed with the Declaration of Helsinki. All participants provided written informed consent. This research was part of a study registered with ClinicalTrials.gov: NCT03984994.

2.2. Body composition

Height and weight were measured to calculate BMI. Body fat, total lean mass, and appendicular lean mass (ALM) were assessed using dual-energy X-ray absorptiometry (DXA: GE Lunar Prodigy, GE Healthcare, Madison, WI, USA). Participants were fasted for the DXA and were instructed to consume only water before the scan, while wearing comfortable clothes with no metal or jewelry. ALM was subsequently divided by BMI to serve as the primary index of sarcopenia in this study (ALM/BMI).

2.3. Maximal graded exercise test

Maximal aerobic capacity (VO_{2max}) was measured by indirect calorimetry during a graded exercise test on a treadmill as previously described in our lab [28]. Briefly, treadmill speed was kept constant while the incline was increased 2 % every 2 min until the subject was unable to continue. A true VO_{2max} was confirmed by the achievement of at least two of the following criteria: respiratory exchange ratio ≥ 1.10, maximum heart rate > 90 % of age-predicted maximum (220-age), or a plateau in VO_2 (<200 mL/min change).

2.4. Strength testing

Maximal force production of the knee extensors was measured before and after exercise training on a Biodex System 4 Pro dynamometer (Shirley, New York). Participants performed three maximal single-leg isometric contractions at 60° of knee flexion with at least 90 s of rest between trials. The averages of three values for the right leg were used as the maximal isometric force production.

2.5. Exercise training intervention

Following baseline testing, sarcopenic participants underwent 12 weeks of supervised resistance training, 3 days per week. All exercise training sessions were conducted at the University of Maryland College Park or the Baltimore Veterans Affairs Medicine Center under the supervision of exercise physiologists. Exercises focused on the lower-extremity muscles and were performed on Keiser K-300 pneumatic resistance machines (Keiser Corporation, Fresno, CA). To target muscles associated with mobility, the leg press, knee extension, and leg curl were used. Resistance started at 60 % of 1-repetition maximum (1-RM; determined before the first day of training) and progressed to 70–75 % of 1-RM within the first 2 weeks of training. Each session began with a five-minute warm-up on a treadmill at a self-selected pace. The

resistance exercise consisted of two sets of 12 repetitions of each exercise and participants were given two minutes of rest between each set. The session concluded with a five-minute cool-down on a treadmill. Resistance was progressively increased throughout the study as strength increased. Criteria for progression was as follows: successful completion of two sets of 12-repetitions at a rate of perceived exertion less than 8 out of 10. Each time this criterion was met, resistance was increased by 5 %.

2.6. Muscle sampling

Percutaneous needle biopsies of the vastus lateralis muscle were obtained using a Bergstrom needle (Stille, Solna, Sweden) as previously described [28]. All biopsies were taken from the right leg, except for one sarcopenic participant who requested the left side. Muscle specimens were flash frozen and stored at −80ºC until analysis. For the sarcopenic participants, a separate 1mm [3] sample of muscle was immediately fixed for electron microscopy as described below. One sarcopenic participant was excluded from electron microscopy analysis due to technical issues with muscle processing during their baseline muscle biopsy. All biopsies at the post-training time point were taken 24–48 h following the last exercise bout.

2.7. Muscle protein expression

Muscle samples were homogenized with equal amount (weight/volume) of 1 % Triton buffer with protease and phosphatase inhibitors (Thermo Fisher Scientific, Waltham, MA, USA) as previously described [29]. Following centrifugation at 16,000 x g for 5 min at 4ºC, supernatant protein content was quantified by Pierce BCA Assay (Thermo Fisher Scientific, Waltham, MA, USA). Protein samples containing Laemmli buffer (Bio-Rad, Hercules, CA) and beta-mercaptoethanol were warmed for 5 min at 70º C. Equal amounts (30ug/well) of protein were loaded into 4–15 % Bio-Rad TGX stain free gels (Hercules, CA, USA) and were separated by SDS-PAGE. Gels were activated before transferring onto polyvinylidene difluoride membranes (Trans-Blot Turbo Mini 0.2µ m PVDF Transfer Packs, Bio-Rad, Hercules, CA) and total protein fluorescence was imaged following transfer to confirm equal loading and transfer of proteins. Membranes were incubated with a blocking buffer composed of TBS (Bio-Rad, Hercules, CA), 0.1 % Tween 20 (Bio-Rad, Hercules, CA), and 5 % BSA or milk (Fisher Scientific, Hampton, NH, USA) for 2 h at room temperature before incubating with primary antibodies overnight at 4º C. Primary antibodies and dilutions are shown in Supplemental Table 1. The following day, membranes were incubated with a secondary antibody conjugated to horseradish peroxidase (Cell Signaling Technology, 7074S, RRID AB_2099233) and bands were detected with a chemiluminescent substrate from Bio-Rad (Clarity Western ECL Substrate). Images were acquired using a Bio-Rad ChemiDoc XRS and analyzed on Image Lab 8.0 (Bio-Rad, Hercules, CA). Band intensities were normalized to the total protein image. Data are presented normalized to total protein, as well as relative to CIV protein content to account for differences in mitochondrial content. Opa1-short and -long isoforms were quantified separately.

2.8. Transmission electron microscopy

Fresh muscle tissue was fixed in 100 mM cacodylate (Electron Microscopy Sciences, Hatfield, PA, USA) with 2 % glutaraldehyde (Thermo Fisher Scientific, Heysham, UK) and subsequently washed with 100 mM cacodylate and fixed a second time with 1 % osmium tetroxide (Electron Microscopy Sciences, Hatfield, PA, USA) for one hour. Samples were washed with 100 mM cacodylate and incubated with 2 % uranyl acetate (Electron Microscopy Sciences, Hatfield, PA, USA) for one hour before being dehydrated with progressively higher ethanol concentrations starting at 30 % and ending at 100 %. Equal parts Spurr resin (Electron Microscopy Sciences, Hatfield, PA, USA) and propylene oxide (Electron Microscopy Sciences, Hatfield, PA, USA) were added to samples for one hour to begin the infiltration process. An additional one-part Spurr resin was added to the mixture before leaving overnight to infiltrate (∼17 h). The following day, an additional one-part Spurr resin was added to the mixture for one hour before replacing the mixture with 100 % Spurr resin. After one hour the resin was removed and replaced a second time with 100 % Spurr resin. Samples were then cured at 70ºC for ∼20 h and sectioned using a Reichert-Jung Ultracut E (C. Reichert Optische Werke AG Wein, Austria) and Leica EM UC6 (Wetzlar, Germany). 70 nm sections were embedded on 200 hex mesh copper grids (Electron Microscopy Sciences, Hatfield, PA, USA) and stained with 2 % uranyl acetate (Electron Microscopy Sciences, Hatfield, PA, USA) and 1 % lead citrate (Electron Microscopy Sciences, Hatfield, PA, USA). Samples were imaged using a Hitachi HT7700 (Chiyoda, Tokyo, Japan) transmission electron microscope at a magnification of x8000 (Peabody, MA, USA). All incubations and washes prior to curing were done under gentle agitation.

Three fibers were randomly selected for imaging for each sample. A total of six images were taken from each fiber. Three images were acquired from the subsarcolemmal/peripheral region of the fiber, and three images were acquired from the intermyofibrillar region. Thus, for each muscle specimen, a total of nine images were taken of the peripheral region, and nine images were taken of the intermyofibrillar region. All peripheral images acquired from the same sample were analyzed and averaged together to serve as an individual data point. Intermyofibrillar images were also analyzed and averaged together as a single data point. The peripheral region was defined as the space between the sarcolemma and the first row of myofibrils. The intermyofibrillar region was defined as the area between the first and last row of myofibrils within a muscle fiber. Representative images demonstrating the analyzed portions for the peripheral and intermyofibrillar regions are shown in Fig. 1. Images were manually analyzed using ImageJ software for the following mitochondrial measures in both regions: Number: Count per micrograph, Area: Size in micrometers squared, and Fractional Area: Sum of all areas as a percentage of total micrograph area.

2.9. Statistical analysis

Statistical analyses were performed using GraphPad Prism 10. The sample size of $n = 10$/group was determined using a conservative estimate of effect size ($d = 1.2$) based on previous work showing increased Mfn2 expression after exercise training [30], $\alpha = 0.05$ and $1\text{-}\beta = 0.80$. Independent samples *t*-tests were used to compare subject characteristics and mitochondrial quality control protein expression between sarcopenic and non-sarcopenic controls at baseline. Paired samples *t*-tests were used to determine whether there were changes in characteristics or mitochondrial quality control protein expression within the sarcopenic group before and after resistance exercise training. Pearson correlation analyses were used to test for relationships between variables. All tests were two-tailed with statistical significance set at $P < 0.05$. Data are presented as means ± standard error of the mean (SEM).

3. Results

3.1. Participant characteristics

Participant characteristics can be found in Table 1. Mean skeletal muscle index for the sarcopenic group was 7.1 ± 0.47 kg/m^2. There were no significant differences in age, weight, BMI, or body fat percentage between the non-sarcopenic and sarcopenic participants at baseline. Sarcopenic participants at baseline had significantly lower ALM/BMI ($P = 0.038$), absolute VO_{2max} ($P = 0.037$), and relative VO_{2max} ($P = 0.020$) compared to non-sarcopenic participants.

Following 12 weeks of resistance training, sarcopenic participants' knee extensor maximal isometric force production increased 13 % (Table 1, $P = 0.017$), and ALM/BMI increased (Table 1, $P = 0.030$).

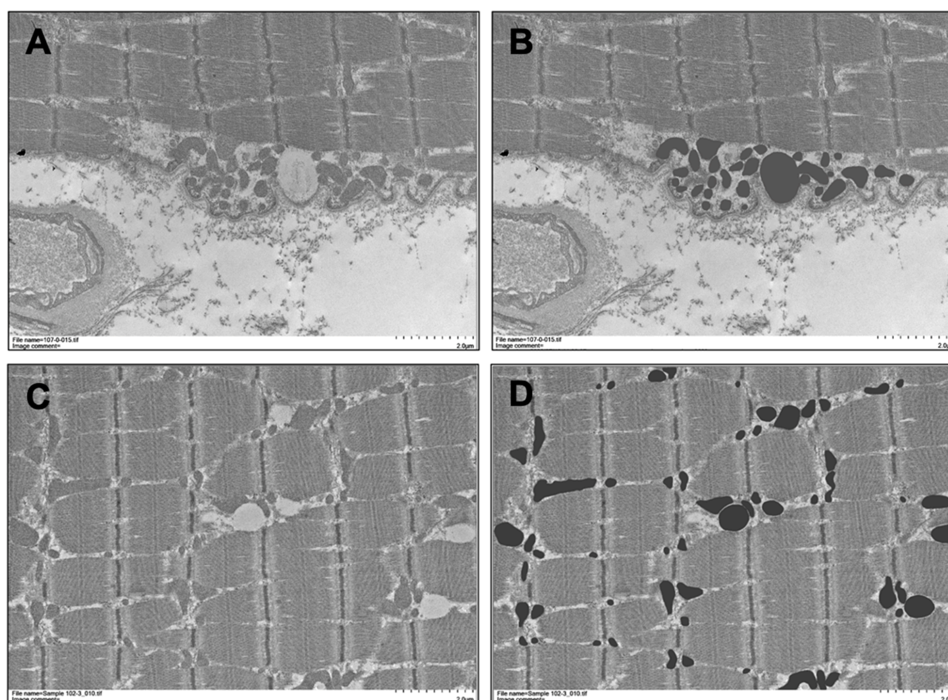

Fig. 1. Representative transmission electron micrographs of peripheral/subsarcolemmal and intermyofibrillar region. Fig. 1A depicts the peripheral/subsarcolemmal region and 1C depicts the intermyofibrillar region from a sarcopenic participant at baseline. White-gray circular structures are lipid droplets and dark gray round, and oblong shapes are mitochondria. Figs. 1B and 1D demonstrate the analyzed portions of peripherally-located and intermyofibrillar mitochondria, respectively.

Table 1
Sarcopenic and non-sarcopenic participant characteristics.

Variable	Non-Sarcopenic control	Sarcopenic baseline	Sarcopenic 12-Week resistance training
Age (years)	71.1 ± 2.5	75.9 ± 2.0	
Sex	$F = 7$; $M = 3$	$F = 7$; $M = 3$	
Height (cm)	167.7 ± 2.5	164.3 ± 3.0	
Weight (kg)	73.8 ± 3.7	74.9 ± 4.2	73.3 ± 4.2[#]
BMI (kg/m^2)	26.6 ± 1.3	27.6 ± 0.7	26.8 ± 0.6[#]
Body fat (%)	34.8 ± 2.4	36.8 ± 1.4	37.0 ± 1.4
Total Lean Mass (kg)	47.1 ± 2.3	44.0 ± 3.3	43.9 ± 3.3
Leg Lean Mass (kg)	16.30 ± 0.88	14.89 ± 1.20	14.90 ± 1.21
ALM (kg)	21.8 ± 1.3	19.9 ± 1.8	19.9 ± 1.7
ALM/BMI	0.865 ± 0.055	0.712 ± 0.055[*]	0.736 ± 0.049[#]
Absolute VO$_2$ (L/min)	1.85 ± 0.10	1.48 ± 0.15	1.52 ± 0.13
Relative VO$_2$ (mL/kg/min)	24.45 ± 1.4	19.84 ± 1.2[*]	20.53 ± 1.1
Knee Extensor Force (Nm)	n/a	111.3 ± 10.5	125.9 ± 17.7[#]

Data are means ± SEM. Legend = BMI, body mass index; ALM, appendicular lean mass.
[*] $P < 0.05$ compared with non-sarcopenic control.
[#] $P < 0.05$ compared with sarcopenic Baseline.

Weight, body fat percentage, appendicular lean mass, leg lean mass, and absolute and relative VO_{2max} were not significantly affected by the resistance exercise intervention; however, BMI was lower after training (Table 1, $P = 0.003$).

3.2. Mitochondrial content

Mitochondrial content, as measured by complex IV (CIV) protein content, did not differ between the non-sarcopenic and sarcopenic adults prior to training and did not increase in the sarcopenic participants after training (Fig. 2A). Similar results were found for expression of PGC-1α, a marker of mitochondrial biogenesis (Fig. 2B). Skeletal muscle peripherally-located (PL) and intermyofibrillar (IMF) mitochondrial content were also assessed by TEM analysis (Fig. 2C—H). Consistent with CIV expression, PL and IMF mitochondrial number, average size, and fractional area were all unaffected by 12 weeks of resistance exercise training. As there were no significant differences, but some numeric differences, in mitochondrial content between groups, mitochondrial quality control protein expression is presented independently and relative to CIV protein expression below for full interpretation.

3.3. Mitochondrial fusion, fission, and mitophagy

For all fusion proteins (Mfn2, Opa1-S, and Opa1-L), expression did not differ between non-sarcopenic and sarcopenic older adults at baseline (Fig. 3A–F). In sarcopenic participants, there was a tendency for Mfn2 protein to increase after resistance training ($P = 0.054$; Fig. 3A) when expressed relative total protein, but not when expressed relative to CIV expression (Fig. 3D). Similarly, the expression of fission proteins Drp1 and Fis1 did not differ based on sarcopenia status and was unaffected by training (Fig. 3G and 3H, respectively). When expressed relative to CIV expression, there remained no differences in Drp1 or Fis1 between groups (Fig. 3J and 3K, respectively). Likewise, expression of the mitophagy protein Pink1, did not differ between groups, nor after resistance exercise training in the sarcopenic group (Fig. 3I and 3L).

3.4. Relationships between quality control protein expression, muscle mass, and function

While there were no differences in protein expression between groups at baseline when ALM/BMI was treated as a dichotomous variable, bivariate correlation analyses were also used to determine if relationships existed between expression of quality control proteins, ALM/BMI, and other metrics of muscle mass. In these analyses, ALM/BMI was

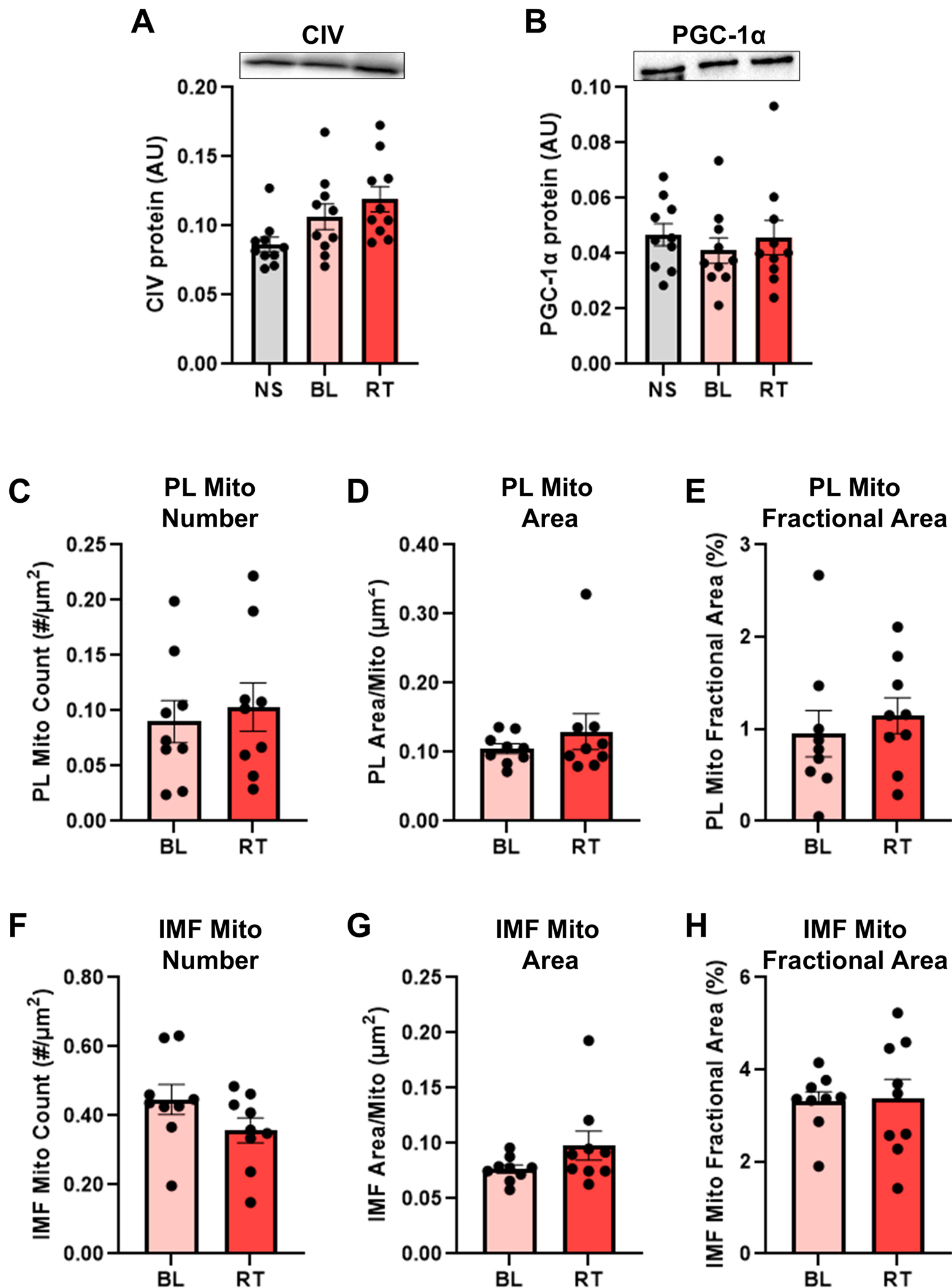

Fig. 2. CIV (A) and PGC-1α (B) protein expression do not differ between sarcopenic and non-sarcopenic skeletal muscle before or after exercise training, while peripherally-located (C,D,E) and intermyofibrillar (F,G,H) mitochondria content are unaffected by resistance exercise training. Legend = AU, arbitrary units; PL, peripherally-located; IMF, intermyofibrillar; NS, non-sarcopenic control; BL, baseline; RT, post resistance exercise training. Data are presented as means ± SEM, n = 9–10 per group.

inversely related to Mfn2 expression and CIV expression (Fig. 4A&B, $r = -0.55$, $P = 0.013$ and $r = -0.61$, $P = 0.004$, respectively). Lean body mass and ALM correlated inversely with both Mfn2 and Opa1-S expression (Fig. 4C–F, r = −0.55 - −0.51, $P \leq 0.022$). As 70 % of the sample were women, subsequent analyses were performed in only female participants to confirm that associations were not attributable solely to sex, as the six men had higher values for all muscle mass variables. In women, CIV expression correlated inversely with ALM/BMI ($r = -0.63$, $P = 0.016$), and Opa1-S expression correlated inversely with both lean body mass ($r = -0.54$, $P = 0.044$) and ALM ($r = -0.59$, $P =$

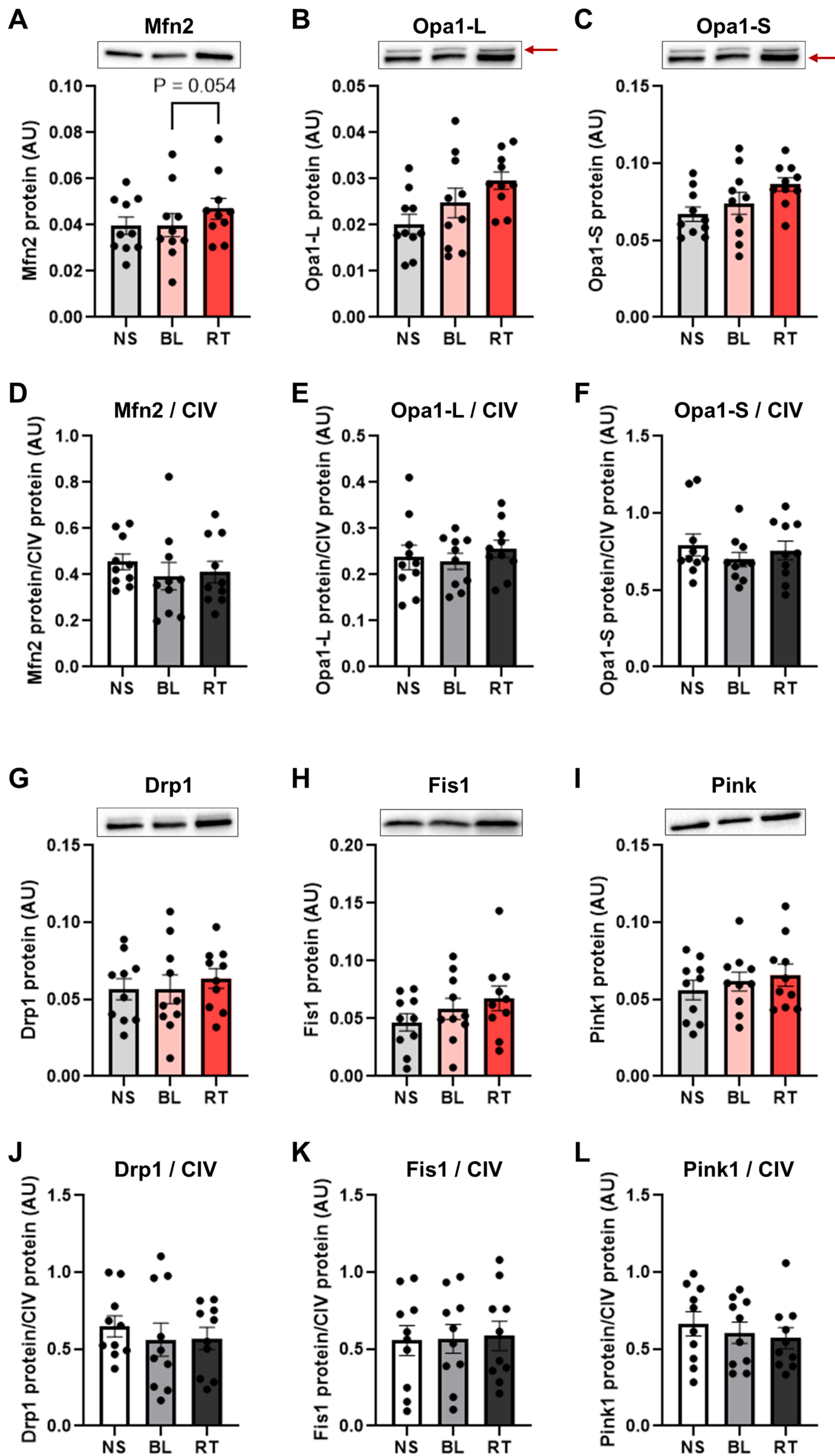

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Fig. 3. Protein expression of mitochondrial fusion, fission, and mitophagy proteins. Fusion proteins mitofusin 2 (Mfn2), and optic atrophy type 1 long and short (Opa1-L and Opa1-S) does not differ between sarcopenic and non-sarcopenic skeletal muscle, but expression of Mfn2 may increase after resistance training in sarcopenic older adults. Expression of fission proteins dynamin-related protein 1 (Drp1) and fission 1 (Fis1), and mitophagy protein Pink1 are not impacted by sarcopenia or resistance exercise training. Data in panels A, B, C, G, H, and I are normalized to total protein, while panels D, E, F, J, K, and L are normalized to total protein and subsequently expressed relative to complex IV (CIV) expression. Legend = AU, arbitrary units; BL, baseline; RT, post resistance exercise training; NS, non-sarcopenic control. Data are presented as means ± SEM, $n = 10$ per group.

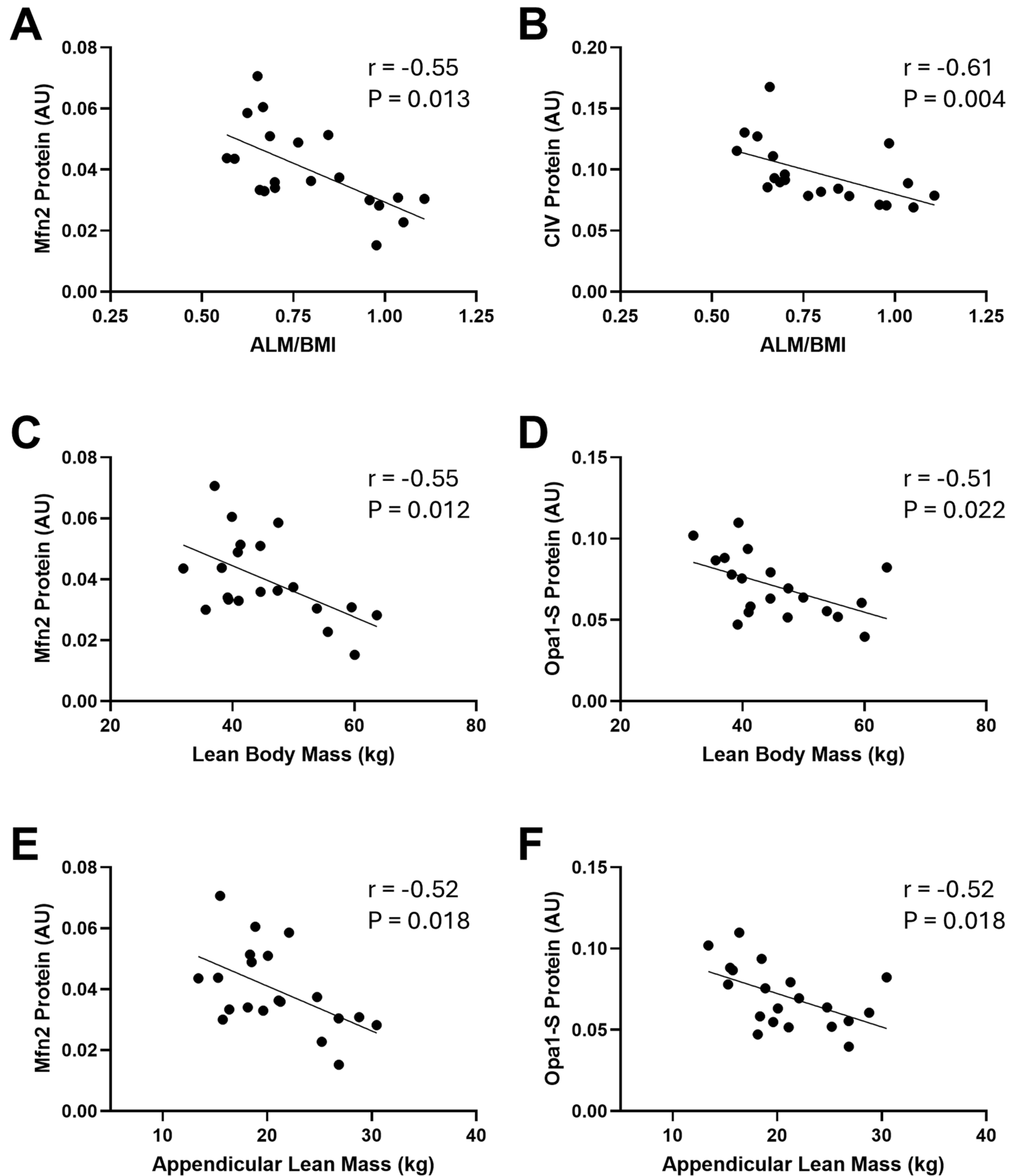

Fig. 4. Higher sarcopenic index and lean mass are associated with lower expression of mitochondrial content and fusion proteins. Mfn2: mitofusin 2, CIV: Complex IV, Opa1-S: optic atrophy type 1-short, ALM: appendicular lean mass; BMI: body mass index.

0.025). Despite these relationships, there were no significant relationships between expression of these proteins and functional indices related to sarcopenia such as grip strength or VO_{2max} in analyses accounting for sex ($P = 0.22$–0.80). No other protein expression levels correlated with any muscle mass variables at baseline.

4. Discussion

In vastus lateralis muscle, markers of mitochondrial biogenesis, fusion, fission, and mitophagy were not different between age-, sex-, and BMI-matched sarcopenic and non-sarcopenic older adults grouped by ALM/BMI. There were inverse correlations between CIV and fusion protein Opa1-S expression and muscle mass variables when treating

these as continuous variables; surprisingly, individuals with lower muscle mass or sarcopenic index had higher CIV and Opa1-S expression. In response to resistance training, the sarcopenic participants did increase skeletal muscle strength, although this did not occur in tandem with increases in mitochondrial content, muscle mass, or alterations in quality control protein expression aside from a potential increase in fusion protein Mfn2 expression after training. While the sarcopenic participants in this study did have low ALM/BMI at baseline, it is possible that these participants simply had lower muscle mass – and not less functional muscle – then their non-sarcopenic counterparts. In this case, one might not expect major differences in the expression of mitochondrial quality control proteins between groups. Conversely, the present data could support the notion that there are no substantial alterations in mitochondrial content and quality control protein expression in older adults with mild-moderate sarcopenia defined by ALM/BMI.

4.1. Sarcopenic versus non-sarcopenic mitochondrial content and quality control proteins

The protein expression findings were contrary to our hypothesis that sarcopenic individuals would have lower mitochondrial content, concomitant with greater quantities of proteins regulating fission and lower quantities of proteins regulating fusion compared with non-sarcopenic controls. With regard to mitochondrial content, one previous study found that CIV expression and CS activity were both lower in sarcopenic men compared to non-sarcopenic men[21]; however, that study used more stringent Asian Working Group for Sarcopenia (AWGS) criteria to define the presence of sarcopenia in their Chinese population [21]. This included ALM relative to height (ALM/h^2) along with low handgrip strength or gait speed to classify their participants as sarcopenic. Male participants in that study had an $ALM/h^2 < 7.0$ kg/m^2, while our male participants' ALM/h^2 was 8.9 kg/m^2. Similarly, the women in our study ($ALM/h^2 = 6.5$ kg/m^2) were also above the sarcopenic cut off value set forth by the AWGS ($ALM/h^2 < 5.7$ kg/m^2) [31]; therefore, we may not have observed declines in mitochondrial content in our study due to our participants not being severely sarcopenic. In addition, the functional component of the AWGS criteria could represent an important distinction between the former and present studies. It is possible that the sarcopenic participants in the present study simply had less muscle of similar function or quality to the non-sarcopenic participants and therefore no differences in mitochondrial content. This notion is supported by the inverse correlation between CIV expression and ALM/BMI in our participants, suggesting even higher mitochondrial content in those with lower sarcopenic index values.

Expression of mitochondrial biogenesis, fusion, fission, and mitophagy proteins did not differ between non-sarcopenic and sarcopenic groups in the present study. These results are in partial agreement with previous reports. One study reported no differences in PGC-1 α, Opa1, or Fis1 protein content between physically frail sarcopenic older adults and non-sarcopenic age-matched controls [20]. Those sarcopenic participants did, however, have lower expression of Mfn2 and microtubule-associated protein 1 light chain 3 beta (LC3B), an autophagy-related protein [20], while we observed no differences in Mfn2 nor our mitophagy markers. This difference in findings could be attributed to participant characteristics between studies. All participants recruited in the previous study had fall-induced hip fractures, while our participants were independently living and free of mobility issues. This suggests that otherwise healthy sarcopenic older adults may not exhibit altered mitochondrial quality control. Our participants were, on average, less sarcopenic than those in the previous report (skeletal muscle mass index 7.1 vs. 5.9 kg/m^2, respectively), and the previous study included older adults with congestive heart failure, coronary heart disease, and diabetes mellitus [20] which are known to impact mitochondrial quality control [32,33], and could contribute to differences between the former and present studies. The previously discussed study by Miglivacca et al. [21], which showed lower CIV content and CS activity in sarcopenic compared to non-sarcopenic men, also reported lower Fis1 and Opa1 gene expression, but it is unclear whether these findings translated to protein abundance. Finally, our findings are consistent with a mouse model of sarcopenia that showed no differences in Mfn2, Opa1, Drp1, or LC3B protein content between wild type and mitochondrial DNA (mtDNA) proofreading deficient mice [34]. The proofreading deficient mice have previously been shown to exhibit premature aging and muscle wasting, thus making them an animal proxy for sarcopenia [35].

Despite a lack of differences in protein expression between our sarcopenic and non-sarcopenic older adults grouped by ALM/BMI, we did find that Mfn2 and Opa1-S protein content were both inversely correlated with measures of muscle mass. The correlations between Mfn2 and ALM, ALM/BMI and lean body mass appeared to be driven by sex as men had higher muscle mass and generally lower Mfn2 expression; however, the correlations between Opa1-S expression, ALM and lean body mass persisted when women were analyzed independently. It is possible that this reflects compensatory fusion in older participants with lower muscle mass, in which dysfunctional mitochondria can fuse with healthy mitochondria in response to stress as an attempt to rescue membrane potential and preserve function [36–38]. In addition, mtDNA deletion mutation frequency increases with age [39] but the mixing of mtDNA via fusion is thought to reduce the likelihood of mutated mtDNA reaching pathogenic threshold by diluting the relative proportion of mutated to normal mtDNA [40,41]. Conversely, the disruption of membrane potential can also cleave inner mitochondrial membrane fusion protein Opa1 into its short isoforms, which some have suggested inhibits inner mitochondrial membrane fusion and in turn, the sharing of membrane potential and matrix components [12,42,43]. While this would suggest that the associations with Opa1-S are an artifact of disrupted membrane potential in those with low ALM/BMI, these relationships require further causal investigation.

4.2. Effects of resistance exercise training on mitochondrial quality control proteins

The resistance training intervention in this study elicited a ~13 % increase in knee extensor force production, which is consistent with other resistance training studies in older adults that have reported 10–15 % increases in force production [30,44,45]. Participants in the present study also reduced their body weight and BMI, while increasing sarcopenic index (ALM/BMI). ALM and leg lean mass were unaltered after the intervention which would suggest the increase in sarcopenic index was due to the lower BMI after training. While the participants with mild-moderate sarcopenia increased strength, increases in muscle mass were not detected. While we cannot rule out that some degree of muscle fiber hypertrophy occurred in the sarcopenic participants after resistance training, the lack of increase in muscle mass suggests that a substantial proportion of the strength gains could be attributable to neural factors and enhanced recruitment of motor units, as opposed to muscle hypertrophy.

To the best of our knowledge, the present study is the first to assess changes in mitochondrial content and quality control proteins in response to resistance exercise in individuals with sarcopenia. Despite seeing similar changes in muscular strength as previous resistance training studies with similar durations in older individuals, we did not observe any significant changes in skeletal muscle mitochondrial content following resistance training in individuals with sarcopenia. This was somewhat surprising considering studies have reported increases in mitochondrial content following resistance training in older adults, though results vary. Six to fourteen weeks of resistance exercise increased electron transport chain complex protein content in middle to older adults [45], increased citrate synthase (CS) activity, a marker of mitochondrial content, in middle-aged adults [30,46], and increased CIV activity in older adults [24]. Despite this, the data are not conclusive

for all markers: Despite higher CIV activity, resistance training did not increase CS activity in one study [24]. Further, Ruple et al [46]. found no increases in CS activity or expression of mitochondrial electron transport chain protein content following 6 weeks resistance exercise training, and Irving et al [47]. found that 8 weeks of resistance training did not increase total electron transport chain protein content in older men and women. In addition, 12 weeks of resistance training did not impact CS activity in older men [48,49]. These results demonstrate the impact of resistance training on mitochondrial content in older adults are inconsistent, varying by population studied, intervention duration, and methods of measurement. Our findings from protein expression and TEM analyses support studies showing no increase in mitochondrial content after resistance training in sarcopenic individuals, highlighting the variability in aging muscle and the limited understanding of mitochondrial changes in response to resistance training in sarcopenia.

Resistance training in individuals with sarcopenia did not alter the expression of markers of mitochondrial biogenesis, fusion, fission, and mitophagy, with the exception of a tendency for Mfn2 expression to increase ~18 % after resistance training. While this is the first investigation specifically assessing protein expression following resistance training in individuals with sarcopenia, Mesquita et al [30]. found that Mfn1, Mfn2, Opa1, and Drp1 protein content increased in middle-aged to older adults following 10 weeks of resistance exercise and Zampieri et al [50]. demonstrated 9 weeks of leg press exercise decreased Opa1 protein content in older adults with no effect on Mfn2 protein content. These limited investigations demonstrate mixed results but do indicate resistance training is capable of altering mitochondrial quality control protein content. While our baseline protein expression did not differ between individuals with and without sarcopenia, we anticipated seeing training-induced changes. However, our data may indicate that while mitochondria from the sarcopenic adults do not demonstrate severe baseline alterations in quality control protein expression, they may not be as responsive to a training stimulus, indicating some deficit. This is supported by the fact that in the present study CIV and PGC1 protein expression, as well as mitochondrial area, were numerically higher but not statistically significant. This could suggest that in sarcopenia, mitochondrial quality control processes are not as responsive to resistance exercise and may require a greater stimulus to achieve more than a modest effect. While our training intervention was longer than some of the aforementioned studies, a 2021 meta-analysis on resistance training and sarcopenia suggest longer interventions may be needed as greater improvements in muscle mass was noted in studies lasting more than 12 weeks [51]. Further, previous reports have suggested mitochondrial biogenesis may occur at a slower rate than muscular hypertrophy following resistance exercise training [52]; thus, a longer intervention could be needed to observe alterations in muscle mass and mitochondrial quality control in sarcopenic individuals.

4.3. Limitations

For our study, CIV was used as a marker for mitochondrial content as its expression correlates with mitochondrial content determined by EM, but several other mitochondrial content markers exist, including CS activity and cardiolipin content [53] which were not measured in this study. Additionally, there are Pink1/Parkin-independent mitophagy pathways that could be differentially regulated in sarcopenia that were not investigated in this study. Future studies are needed on how other mitochondrial degradation pathways may differ between sarcopenic individual and healthy age matched controls. The lack of differences in mitophagy and other mitochondrial quality control proteins between sarcopenic and non-sarcopenic older adults in our study may be partially explained by our sarcopenia criteria. As previously mentioned, our classification of sarcopenia resulted in a group who were mild-moderately sarcopenic. Incorporating an element of physical function or a more stringent muscle mass criteria (i.e., more severe sarcopenia) may have yielded different results. Finally, while including both male and female participants could be viewed as a strength of the study, the numbers of male and female participants were insufficient to test for sex-specific effects on protein expression.

4.4. Conclusions

Mitochondrial dysfunction has been implicated as a contributing factor to sarcopenia; however, our results suggest markers of mitochondrial content and quality control do not differ between non-sarcopenic older adults and those with mild-moderate sarcopenia when dichotomous groups were established using ALM/BMI. This could indicate that mitochondrial content and quality control proteins may not be substantially altered in mild-moderate sarcopenia; however, contrary to our hypothesis, individuals with lower muscle mass or ALM/BMI values had higher expression of CIV and Opa1-S expression in analyses treating metrics of muscle mass as continuous variables. Additional work is required to determine whether the Opa1-S results reflect the potential for higher fusion to maintain content, or whether this is an artifact of higher content with disrupted membrane potential which would be consistent with mitochondrial dysfunction in the sarcopenic individuals. Finally, short-term (12 weeks) resistance training in sarcopenic older adults did not affect mitochondrial quality control protein expression with the possible exception of Mfn2. Future studies may need to include individuals with more severe sarcopenia and functional deficits, as well as a longer or higher intensity intervention to elicit mitochondrial adaptations.

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CRediT authorship contribution statement

Catherine B. Springer-Sapp: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Olayinka O. Ogbara:** Writing – review & editing, Investigation, Formal analysis. **Odessa Addison:** Writing – review & editing, Project administration, Investigation, Data curation. **Sarah Kuzmiak-Glancy:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Steven J. Prior:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

Steven J. Prior reports financial support was provided by National Institute on Aging. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjfa.2025.100090.

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