Skeletal Muscle Autophagy and Protein Breakdown Following Resistance Exercise are Similar in Younger and Older Adults

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Background. The loss of skeletal muscle mass and strength during aging, sarcopenia, increases the risk for falls and dependency. Resistance exercise (RE) training is effective at improving muscle mass and strength in older adults; however, aging is associated with reduced training-induced hypertrophy. Recent research has illustrated an impaired muscle protein synthetic response following an acute bout of RE in older adults but much less is known regarding the effect of acute RE on muscle protein breakdown (MPB). We hypothesize that the ubiquitin proteasome system and the autophagosomal–lysosomal system may regulate the overall rate of MPB during postexercise recovery.

Methods. Muscle biopsies of the vastus lateralis were sampled from 16 older (age = 70 ± 2 years) and 16 younger (age = 27 ± 2 years) participants at baseline and at 3, 6, and 24 hours following an acute bout of RE. In conjunction with stable isotopic techniques to measure MPB, we utilized immunoblotting and RT-PCR to examine protein and mRNA expression for key signaling molecules in both the ubiquitin proteasome system and the autophagosomal–lysosomal system.

Results. MuRF1 mRNA expression increased, whereas GABARAP mRNA decreased after RE in both younger and older adults (p < .05). The LC3B-II/LC3B-I protein ratio decreased in both groups after RE (p < .05), but MPB was not different 24 hour post-RE in either group (p > .05).

Conclusions. Aging does not influence skeletal MPB, autophagy, or the ubiquitin proteasome system following an acute bout of RE. Therefore, targeting the muscle protein synthesis response to exercise may hold more promise in the prevention of sarcopenia.

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The loss of lean muscle mass and strength that occurs with advancing age, sarcopenia, has significant ramifications for the overall health and quality of life of older adults. Exercise is a common intervention used to attenuate the loss of lean mass and strength in older adults; however, research has illustrated an age-related impairment in the protein anabolic response to resistance exercise (RE [1–5]). Specifically, we observed a blunted increase in protein synthesis following an acute bout of RE in older adults compared with younger adults, accompanied with reduced phosphorylation of proteins in the mTOR and MAPK signaling pathways that regulate translation (5).

On the other hand, the muscle protein breakdown (MPB) response following RE is less well defined in both younger and older adults and potentially regulated through multiple cellular signaling cascades. An acute bout of eccentric RE in younger men has been shown to increase the fractional breakdown rate (FBR) of skeletal muscle proteins for 24 hours (6). The process most commonly associated with protein degradation following exercise is the ubiquitin proteasome system (UPS [7,8]). Within the UPS are two E3 ubiquitin ligases, MuRF1 (muscle specific RING finger 1) and MAFbx (muscle atrophy F-box, also known as atrogin-1), both regulated through the transcription factor Forkhead box (FoxO3a [9–11]), which is inhibited via phosphorylation by Akt or PKB (12). Protein catabolism following exercise may also be regulated through the autophagy–lysosomal system (13,14). Recent research has identified several key autophagy genes under the control of the Akt–FoxO3a signaling pathway, including light chain 3 (LC3) and GABARAP (10,15–17).

Increases in MPB (6) and the expression of atrogenes (7,8) in the UPS pathway have been shown following exercise but less is known regarding the contribution of both
the UPS and the autophagosomal–lysosomal system, especially in advancing age. In this study, our aim was to better characterize the MPB response to exercise through two key pathways; the autophagosomal–lysosomal and the UPS in both younger and older adults. We hypothesized that (a) MPB would be primarily regulated through the UPS following RE and (b) aging would alter the skeletal muscle autophagy and MPB response to exercise.

Materials and Methods

Participants
A total of 16 younger (8 males and 8 females) and 16 older (8 males and 8 females) participants were studied in the current protocol. The participants’ physical characteristics can be seen in Table 1, and their screening protocol and strength testing have been previously published (5).

Study Design
Each participant was admitted to the Institute for Translational Sciences - Clinical Research Center of the University of Texas Medical Branch the day before the exercise study, and a dual-energy x-ray absorptiometry (DEXA) scan (Hologic QDR 4500W, Bedford, MA) was performed to measure body composition and lean mass. The participants were then fed a standard dinner (12 kcal/kg of body weight; 60% carbohydrate, 20% fat, and 20% protein) and a snack at 2200 hour, prepared by the Bionutrition Division of the ITS-CRC. The participants were studied following an overnight fast under basal conditions and refrained from exercise for 48 hour prior to study participation. All participants were studied during the same time of day (0400–1600: Study 1 and 0400–0900: Study 2).

Day 1.—The morning of the infusion study, at 0400, 18-gauge polyethylene catheters were inserted into the antecubital vein in both arms for tracer infusion and heated arterialized blood sampling. After drawing a background blood sample, a primed continuous infusion of l-[15N] phenylalanine (Sigma-Aldrich, St. Louis, MO) was begun and maintained at a constant rate for 3 hour (Figure 1). The priming dose for the labeled phenylalanine was 2 µmol/kg, and the infusion rate was 0.05 µmol/kg/min. Two hours following insertion of the catheter, the first muscle biopsy was obtained from the lateral portion of the vastus lateralis of the leg with the biopsy site between 15 and 25 cm from the midpatella. The biopsy was performed using a 5-mm Bergström biopsy needle under sterile procedure and local anesthesia (1% lidocaine). Muscle tissue was immediately blotted and frozen in liquid nitrogen and stored at −80°C until analysis. Two hours following the first biopsy, a second biopsy was collected from the same incision. The biopsy needle was inclined at a different angle so that the second biopsy was collected approximately 5 cm apart from the first. This method has been previously used by us (18–20) and others (7,21,22). Following the second muscle biopsy, participants were seated on the leg extension machine to begin the exercise portion of the study. Participants completed a warm up set of 10 repetitions at 45% one repetition maximum and 8 sets of 10 repetitions at 70% one repetition maximum with 3 minutes of rest in between each set. Total time for the exercise period was approximately 45 minutes. Blood was obtained at selected intervals over the next 3 hours and muscle biopsies were sampled from a new incision, approximately 5 cm proximal to the first, at 3 and 6 hour postexercise. Following collection of the fourth muscle biopsy, Day 1 of the study was concluded and participants were given a standard lunch. Participants were also fed a similar dinner and snack from the previous night prior to an overnight fast in preparation for the second infusion protocol.

Day 2.—The morning of the second infusion day, at 0400, catheters were inserted and a primed, continuous infusion of l-[15N] phenylalanine was started as in the previous infusion study. At 2 and 4 hours following the initiation of the tracer infusion, the fifth and sixth muscle biopsies were obtained from the lateral portion of the vastus lateralis of the contralateral leg from Study 1 with the biopsy site between 15 and 25 cm from the midpatella, with the sixth biopsy obtained at a time corresponding to 24 hour post RE. Following collection of the second muscle biopsy, Day 2 and the entire study was concluded.

Fractional Breakdown Rate
FBR of muscle proteins was measured for 12 younger (6 males and 6 females) and 12 older (7 males and 5 females) participants at baseline and 24 hour postexercise with the l-[15N] phenylalanine tracer using the precursor–product method (23), where the blood and muscle intracellular dilutions following cessation of tracer infusion are used to model FBR. The method requires the intracellular free phenylalanine enrichment at steady state and after 1 hour of tracer decay along with frequent arterialized blood sampling as well as the free and bound phenylalanine content

<table>
<thead>
<tr>
<th>Participants Characteristics</th>
<th>Younger Adults</th>
<th>Older Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>16 (8 males, 8 females)</td>
<td>16 (8 males, 8 females)</td>
</tr>
<tr>
<td>Age, y</td>
<td>27 ± 2</td>
<td>70 ± 2*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.2 ± 5.1</td>
<td>66.9 ± 3.0</td>
</tr>
<tr>
<td>Height, cm</td>
<td>167.2 ± 3.0</td>
<td>165.9 ± 2.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.1 ± 0.9</td>
<td>24.2 ± 0.6</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>28.3 ± 2.2</td>
<td>31.5 ± 2.0</td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>48.4 ± 3.2</td>
<td>43.7 ± 2.7</td>
</tr>
<tr>
<td>Bilateral leg extension</td>
<td>92.9 ± 9.0</td>
<td>62.4 ± 5.6*</td>
</tr>
<tr>
<td>1RM, kg</td>
<td>1.9 ± 0.1</td>
<td>1.4 ± 0.1*</td>
</tr>
</tbody>
</table>

Notes: Values are means ± SE. 1RM = 1 repetition maximum.
*Significantly different from younger adults (p < .05).
of the muscle. Biopsies 1 and 5 were used to establish intracellular free phenylalanine enrichment at steady state for Day 1 and Day 2, respectively, and biopsies 2 and 6 were used to assess intracellular free phenylalanine enrichment after 1 hour of tracer decay for Day 1 and Day 2, respectively. Arterialized blood was frequently sampled during the 1 hour of tracer decay for both Day 1 and Day 2. The assumption that arterial blood is the only source of tracer entering the muscle intracellular free pool, such that there is no tracer recycling was made as well (23).

FBR was calculated using the formula:

$$\text{FBR} = \frac{\Delta E_M}{p \int E_A(t) \, dt - (1 + p) \int E_M(t) \, dt} \frac{Q_M}{T},$$

where $E_A$ and $E_M$ are the arterialized and muscle free enrichments, $p = E_A/(E_A - E_M)$ at plateau, and $Q_M/T$ is the ratio of free to bound phenylalanine in muscle.

**SODIUM DODECYL SULFATE–POLYACRYLAMIDE GEL ELECTROPHORESIS AND WESTERN BLOT ANALYSIS**

Details of the immunoblotting procedures have been previously published (18). Briefly, 50 µg of total protein was loaded into each lane, samples were separated by electrophoresis, transferred to a polyvinylidene difluoride membrane (Bio-Rad, Hercules, CA) and then incubated in a single primary antibody overnight at 4°C. Chemiluminescent optical density measurements were obtained with a phosphoimager (Bio-Rad) and densitometric analysis was performed using Quantity One software (version 4.5.2; Bio-Rad). Membranes containing phospho-detected proteins were stripped of primary and secondary antibodies then re-probed for total protein. Total protein was determined for each blot and did not change from baseline over the course of the experiment (Figure 6). An internal loading control (α-tubulin) was also assessed to ensure that a traditional housekeeping protein was not changing over time (Figure 6). However, data are presented as phosphorylation status relative to a standard loading control that was loaded on every gel and then expressed as a fold change from baseline to remain consistent with previous publications for comparison (13,18,24,25).

**Antibodies**

The following primary antibodies used were purchased from Cell Signaling (Beverly, MA): phospho-Akt (protein kinase B) (Thr308), phospho-AMP-activated protein kinase (Thr172), phospho-FoxO3a (Forkhead Box O3a) (Ser253), Akt, AMP-activated protein kinase, FoxO3a, LC3B, Atg7 (autophagy-related protein 7), beclin-1, and α-tubulin. All antibodies were used in a dilution of 1:1000 except for phospho-FoxO3a (1:250), FoxO3a (1:500), and α-Tubulin (1:30000). Anti-rabbit IgG horseradish peroxidase-conjugated secondary antibody (1:2000) was purchased from Amersham Biosciences (Piscataway, NJ).

**mRNA Expression**

Details of the RNA extraction, cDNA synthesis, PCR primers, and semiquantitative real-time PCR procedures have been published previously (26). Briefly, RNA concentration and integrity was assessed using the Agilent 2100 BioAnalyzer (Agilent Technologies, Palo Alto, CA). RNA was isolated from 13 younger (8 males and 5 females) and 13 older (8 males and 5 females) participants at baseline and at 3, 6, and 24 hour postexercise. The average RNA integrity number for 104 total isolated RNA samples was 8.40 ± 0.03
(1–10 scale; 10 highest) and a 1.30 ± 0.01 28S to 18S ratio. Primer pairs were customized using Beacon Designer 5.0 software (Premier Biosoft Int., Palo Alto, CA) in which they were designed to avoid homology (BLAST analysis) and secondary structures. Primers were purchased from Invitrogen (Carlsbad, CA) or Sigma Aldrich (St. Louis, MO). Human β2M (beta 2 microglobulin), MuRF1 (muscle RING finger 1), and MAFbx (muscle atrophy F box, also known as atrogin-1) primer sets have been published previously (27). Real-time PCR (iQ5 Multicolor Real-Time PCR cycler, Bio-Rad, Hercules, CA) was performed on diluted cDNA using SYBR green fluorescence on custom (β2-microglobulin, Sigma Aldrich and MuRF1 and MAFbx, Invitrogen) and predesigned Taqman (LC3 and GABARAP, Applied Biosystems) primers. To account for any starting difference in the amount of total RNA, gene expression levels were normalized to β2-microglobulin. Relative fold changes were determined from the Ct values using the $2^{-\Delta\Delta Ct}$ method (28).

**Statistical Analysis**

All values are expressed as means ± SE. Comparisons were performed using analysis of variance with repeated measures, the effects being group (young, old) and time (baseline and 3, 6, and 24 hour postexercise). Post hoc testing was performed using Bonferroni when appropriate. If a test of normality and/or equal variance failed, simple transformations were performed. Significance was set at $p \leq .05$. All analyses were performed with SigmaStat 11.0 (Systat Software Inc, San Jose, CA).

**RESULTS**

**Upstream Regulators of Protein Breakdown**

Akt phosphorylation at Thr308 increased significantly in both groups at 3 hour postexercise ($p < .05$; Figure 2A) and returned to basal values at 6 and 24 hours following exercise ($p > .05$).

There was a main effect for time with FoxO3a phosphorylation at Ser253 decreased at all time points following exercise in both groups ($p < .05$; Figure 2B). No differences between groups were observed ($p > .05$). Phosphorylation of AMP-activated protein kinase at Thr172 did not change across time in either group ($p > .05$; data not shown). The phosphorylation of AMP-activated protein kinase was significantly greater in the older adults than the younger adults throughout the duration of the study ($p < .05$).

**mRNA Expression of E3 Ubiquitin Ligases and Autophagy Markers**

mRNA expression of MuRF1 was similar at rest between young and old. Following exercise, there was an approximate three- to fourfold increase in expression of MuRF1 at 3 hour postexercise ($p < .05$; Figure 3A).

Expression of MuRF1 was also significantly elevated above rest at 6 hour postexercise in both groups ($p < .05$) but had returned to basal values by 24 hour post-exercise ($p > .05$).

Expression of the MAFbx transcript did not change over time or between groups following exercise ($p > .05$; Figure 4B). mRNA expression of LC3 was similar in both younger and older adults at baseline and across all time points following exercise with no significant changes over time ($p > .05$; Figure 4C).

Expression of GABARAP mRNA was similar at rest between young and old ($p > .05$). Following exercise, both groups had a significant decrease in mRNA expression at 3 hour postexercise ($p < .05$; Figure 4D). mRNA expression trended to be lower at 6 hour postexercise in both groups compared with baseline ($p = .09$) but returned to basal levels at 24 hour postexercise ($p > .05$).

**Regulation of Autophagy Induction**

Total protein expression of LC3B-I was similar in both groups throughout the duration of the study and did not change over time ($p > .05$; Figure 4A). Expression of
LC3B-II protein was similar in both groups at baseline ($p > .05$; Figure 4B), but following exercise, the protein content of LC3B-II decreased significantly at 3, 6, and 24 hour postexercise in the older participants ($p < .05$) and at 6 and 24 hour postexercise in the younger participants ($p < .05$), with no differences between groups ($p > .05$). The LC3B-II/LC3B-I ratio was similar in both young and old at baseline, and following exercise, there was a significant decrease in the LC3B-II/LC3B-I ratio in both groups at 3, 6, and 24 hour post-exercise ($p < .05$; Figure 4C).

Total protein content of Atg7 did not change over time in the younger participants ($p > .05$; Figure 5A) but was
significantly lower in the younger participants compared with the older at all time points \((p < .05)\). Protein levels of Atg7 increased from baseline in the older participants at 24 hour postexercise \((p < .05)\).

Total protein content of beclin-1 did not change over time in the younger and older participants \((p > .05; \text{Figure } 5B)\) but was significantly lower in the younger participants compared with the older participants at all time points \((p < .05)\).

### Total Protein Content

Total protein content did not change across time in either group for Akt, FoxO3a, or α-tubulin \((p > .05; \text{data not shown})\), and representative images can be seen in Figure 6.

### Fractional Breakdown Rate

Skeletal muscle protein FBR did not change across time in either group \((p > .05; \text{Figure } 7)\). FBR was not different between groups at baseline or 24 hour postexercise \((p > .05)\).

### Discussion

In this study, the regulation of skeletal MPB following an acute bout of RE was assessed in younger and older adults. The expression of markers in two key muscle protein degradation pathways was measured; the UPS and the autophagosomal–lysosomal system, in addition to the FBR of muscle proteins. Following exercise, an increased expression of markers in the UPS was observed in both younger and older adults, indicative of an increase in MPB, whereas the expression of two key regulators of autophagy induction decreased following exercise in both age groups, signifying a potential downregulation of muscle autophagy. Although there were no significant increases in FBR 24 hour postexercise, it is likely that peak increases in MPB were potentially missed \((6)\) due to this study design. The primary and novel findings from this study are that markers of protein breakdown were elevated and autophagy was depressed in both younger and older adults following an acute bout of RE.

A few recent studies have illustrated a blunted protein anabolic response to RE in older persons \((1,2,5)\) but less is known regarding the effect of advancing age on MPB following exercise. A slight increase in Akt phosphorylation following exercise was observed in both age groups; however, this increase in Akt phosphorylation was inadequate to induce phosphorylation of FoxO3a at the time points examined in this study. In fact, following exercise, the phosphorylation of FoxO3a decreased in both the younger and older participants, which is indicative of increased nuclear translocation of the transcription factor \((29)\). This finding

![Figure 5](https://example.com/figure5.png)  
**Figure 5.** Regulation of autophagy induction. Data represent total protein content of Atg7 (A) and beclin-1 (B) at baseline, 3, 6, and 24 hour post-exercise. Representative immunoblot images are shown. *Significantly different from baseline \((p < .05)\). #Significantly different from older participants \((p < .05)\).

![Figure 6](https://example.com/figure6.png)  
**Figure 6.** Representative total protein images. Representative immunoblot images from, Akt, FoxO3a, and α-tubulin.
is supportive of the increase in Muf1 mRNA expression observed in both the younger and older adults and an increase in protein degradation through the UPS. The mRNA expression of MAFbx/atrogin-1 did not vary over time or between groups, which has also been previously demonstrated following exercise (30). The increase in phosphorylation of Akt at Thr308 was similar in magnitude to that previously reported by our lab in the same study at the Ser473 phosphorylation site (5). Although the increase in Akt phosphorylation was significant at 3 hours postexercise in both younger and older participants in this study, the decrease in FoxO3a phosphorylation is indicative of decreased Akt kinase activity. The postexercise increase in Akt phosphorylation might have been inadequate to increase the activity of the kinase, or perhaps the shorter activation of Akt was insufficient to induce changes in downstream effectors, such as FoxO3a, over the extended postexercise recovery period.

Although an increase in the expression of markers of protein breakdown through the UPS was observed following RE, several markers of autophagy decreased in expression. The conversion of LC3B-I to LC3B-II decreased, as did the mRNA expression of GABARAP, both of which illustrate a decrease in autophagy induction (15–17). The conversion of cytosolic microtubule-associated protein 1 LC3B-I to the autophagosomal membrane-associated form, LC3B-II, is a marker of enhanced autophagy (31–33). With an increase in autophagic flux, protein levels of these two markers will decrease as they are degraded upon autophagosomal–lysosomal fusion, and an increase in autophagy would require transcriptional control to replenish these two components (17,34). There was no decrease in the mRNA expression of LC3, which corresponds with the stable total protein levels of LC3B-I observed in both groups following exercise. The extent of autophagy induction is commonly indicated with the LC3B-II/LC3B-I ratio, and in this study, a decrease in the LC3B-II/LC3B-I ratio was observed following exercise in both younger and older participants. A decrease in the LC3B-II/LC3B-I ratio, along with the decreased mRNA expression of GABARAP following exercise indicates a decrease in autophagic flux through skeletal muscle that occurs independently of age. Furthermore, recent work has also illustrated a potential downregulation of autophagy following RE in both rats and humans (13,35), although numerous differences exist in the aforementioned study designs that makes comparison with this difficult.

Several additional proteins are involved in the regulation of autophagy induction, including Atg7 and beclin-1. Beclin-1 is involved in the early steps of induction with nucleation of the autophagosomal membrane, and Atg7 is crucial in several steps including the conversion of LC3B-I to LC3B-II. In this study, no drastic changes in protein expression of these two markers was observed following exercise; however, the expression of both Atg7 and beclin-1 was significantly greater across all time points in the older adults compared with the younger adults. The differences in the expression of Atg7 and beclin-1 may indicate a greater autophagic capacity in the older participants. Recent research has highlighted a potential role of autophagy in sarcopenia (36,37). When autophagy was ameliorated in older mice, lean muscle mass was preserved (36). Wohlgemuth and colleagues (37) recently reported an increased expression of beclin-1 in the skeletal muscle of older rats, similar to what was observed in this study. Although other markers of autophagy were not different in the older animals (Atg7), the authors did observe impairment in LC3B-I to LC3B-II processing, which may explain why upstream regulators like beclin-1 were upregulated (37).

Although it did not quite reach statistical significance, we did observe an approximate 16% increase in FBR at 24 hour postexercise in both groups, which is similar to the 18% increase in FBR 24 hour following acute eccentric RE in younger men (6). There were no differences between the younger and older adults at either baseline or 24 hour postexercise. Due to limitations in the biopsy time course and FBR measurements, it is likely that we missed peak increases in MPB after exercise. We report for the first time, the FBR of muscle proteins after RE in older adults, and we also show no differences in FBR between younger and older adults before and after exercise. Signaling and gene expression values had returned to basal levels by 24 hours, supportive of our FBR findings.

Older and younger participants in this study shared similarities in physical characteristics in regards to body mass index and percent body fat. Lean mass was slightly, but not statistically, reduced in the older participants, and older participants also had a 33% lower one repetition maximum on the bilateral leg extension. The decreased strength cannot be explained solely by the slightly reduced lean mass of the older participants (38). In this study, the older participants also may have reduced muscle quality and poorer control at the neuromuscular level, preventing them from generating strength similar to the younger participants. With lean mass in the older participants similar to that of...
the younger participants, we may not have been able to capture maximum age-related differences in the response of the UPS and autophagosomal–lysosomal system to RE. This limiting factor makes the translation of the findings of this study to a much older population (>85 years) challenging. Recent literature has demonstrated differences in the protein breakdown response to exercise in very old women (>80 years [8]), which we did not observe in this study. The relative health of the participants in this study (body mass index ~25) also presents a challenge in translating these results to an aging population with a body mass index greater than 30.

In summary, the MPB response to an acute bout of RE was similar in both younger and older adults. Although recent literature has suggested an impairment in the muscle protein synthetic response to exercise with aging, the regulation of muscle protein catabolism through two key signaling cascades following exercise appears to be unchanged with increasing age. Protein breakdown following exercise seems to be largely regulated through the UPS, with a potential downregulation of skeletal muscle autophagy. Aging may be associated with an increased capacity for muscle autophagy; however, more research is needed to explore the regulation of skeletal MPB through autophagy. From the results of this study, it appears that components regulating MPB in skeletal muscle respond similarly in younger and older adults following a bout of RE. From these findings, it appears that targeting the protein anabolic response to exercise may hold more promise in the prevention of sarcopenia.

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References


