Skeletal Muscle Hypertrophy After Aerobic Exercise Training

Adam R. Konopka¹ and Matthew P. Harber²

¹Mayo Clinic College of Medicine, Endocrine Research Unit, Rochester, MN; and ²Taylor University, School of Natural and Applied Sciences, Upland, IN.

KONOPKA, A.R. and M.P. HARBER. Skeletal muscle hypertrophy after aerobic exercise training. Exerc. Sport Sci. Rev., Vol. 42, No. 2, pp. 53–61, 2014. Current dogma suggests that aerobic exercise training has minimal effects on skeletal muscle size. We and others have demonstrated that aerobic exercise acutely and chronically alters protein metabolism and induces skeletal muscle hypertrophy. These findings promote an antithesis to the status quo by providing novel perspective on skeletal muscle mass regulation and insight into exercise countermeasures for populations prone to muscle loss. Key Words: protein metabolism, endurance exercise, sarcopenia, anabolic resistance, ubiquitin proteasome pathway, myostatin, mitochondria

INTRODUCTION

Aerobic exercise training is associated with improvements in aerobic capacity, cardiovascular function, and metabolic regulation, but the primary goal of this review is to highlight the impact of aerobic exercise training on human skeletal muscle hypertrophy. The current paradigm in skeletal muscle biology and exercise physiology is that aerobic exercise has a negligible effect on skeletal muscle mass. However, during the past 40 yr, there are several precedents demonstrating the impact of aerobic exercise training on skeletal muscle growth. These studies address a novel area of skeletal muscle physiology pertinent to older adults and other clinical populations experiencing muscle loss. Age-related skeletal muscle atrophy is multifactorial but includes physical inactivity, suppressed ability to synthesize new proteins (9,34), and reduced skeletal muscle fiber size and number. Research also indicates a decline in mitochondrial function and elevated intracellular catabolic pathways in aging human skeletal muscle, which is thought to influence protein metabolism and promote the loss of skeletal muscle mass and function. Our findings suggest that aerobic exercise training is a viable exercise prescription to mitigate age-related decrements in muscle mass caused by a reduction in catabolic mRNA expression (21), induction of mitochondrial biogenesis and dynamics (22), and increased muscle protein synthesis (15,17,34) that favor myofiber and whole-muscle hypertrophy in both young and older populations (16,18). Moreover, we propose that properly performed aerobic exercise leads to skeletal muscle hypertrophy that is comparable to resistance exercise training. Therefore, the overall purpose of this review is to 1) reveal the anabolic potential of aerobic exercise training; 2) discuss subcellular mechanisms to support muscle growth after chronic aerobic exercise; and 3) revise the dogma of aerobic exercise training in relation to skeletal muscle mass. Collectively, the benefits of aerobic exercise training on skeletal muscle health are underappreciated and not completely characterized. Therefore, summarizing recent literature will further highlight the established groundwork and stimulate future research to gain valuable insight into the impact of this exercise prescription.

SKELETAL MUSCLE HYPERTROPHY

Whole-Muscle Level

Historically, it has been assumed that aerobic exercise training has minimal impact on skeletal muscle mass and therefore has received little scientific inquiry compared with resistance exercise. However, with the application of high-resolution imaging techniques (e.g., computed topography, magnetic resonance imaging), there is a growing body of evidence that aerobic exercise training can induce skeletal muscle hypertrophy in sedentary individuals aged 20 to 80 yr (Table 1). More than 20 yr ago, Schwartz et al. (33) were the first to establish that 6 months of walking/running could
<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Weight Change</th>
<th>AET Protocol</th>
<th>AET Mode</th>
<th>Analysis</th>
<th>Results</th>
<th>Comments/Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz 1991</td>
<td>13 YM (28 yr)</td>
<td>YM --</td>
<td>6 months, 5 d wk⁻¹</td>
<td>Walk/Jog</td>
<td>Thigh CSA</td>
<td>YM --</td>
<td>YM 80% adherence</td>
</tr>
<tr>
<td>PMID: 2023542</td>
<td>15 OM (68 yr)</td>
<td>OM ↓2.5 kg</td>
<td>↑Intensity/duration every 2 wk</td>
<td>CT Scan</td>
<td>OM ↑9%</td>
<td>OM 89% adherence</td>
<td></td>
</tr>
<tr>
<td>Sipila 1995</td>
<td>12 OW (76–78 yr)</td>
<td>↓1.4 kg</td>
<td>2 months, 3 d wk⁻¹</td>
<td>Quad, Ham, Lp Leg CSA</td>
<td>Quad ↔</td>
<td>Healthy adults, 87% adherence</td>
<td></td>
</tr>
<tr>
<td>PMID: 7713834</td>
<td></td>
<td>Non-Sig.</td>
<td>1 d – Step</td>
<td>CT Scan</td>
<td>Ham ↔</td>
<td>Performed 3–6 h of PA per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aerobics</td>
<td>CT Scan</td>
<td>Low. Leg ↔</td>
<td>No change in HU (i.e., quality) of muscles</td>
<td></td>
</tr>
<tr>
<td>Jubrias 2001</td>
<td>40 OM/JW (69 yr)</td>
<td>NA</td>
<td>6 months, 3 d wk⁻¹</td>
<td>1-legged press and Kayaking</td>
<td>Quad CSA, Volume</td>
<td>↔</td>
<td>CSA, VOL 94% adherence</td>
</tr>
<tr>
<td>PMID: 11299253</td>
<td>AE group (n = 10)</td>
<td></td>
<td>2 exercises for 20 min each</td>
<td>MRI</td>
<td>Thigh CSA</td>
<td>--</td>
<td>Used a primarily upper body exercise (i.e., kayak) but measured leg muscle mass</td>
</tr>
<tr>
<td>Short 2004</td>
<td>3 groups (Y, M, O), 21–87 yr</td>
<td>↓0.6 kg</td>
<td>60-80%–85% HRR</td>
<td>Cycling</td>
<td>Thigh CSA</td>
<td>--</td>
<td>Healthy adults who did not exercise more than 30 min, 2 d wk⁻¹ in past 9 months</td>
</tr>
<tr>
<td>PMID: 14506079</td>
<td>65 completed study</td>
<td></td>
<td>16 wk, 3–4 d wk⁻¹</td>
<td>CT Scan</td>
<td>--</td>
<td>No BB or tobacco, 90% adherence, 22% ↑MPS</td>
<td></td>
</tr>
<tr>
<td>Izquierdo 2004</td>
<td>10 OM (68 yr)</td>
<td>--</td>
<td>16 wk, 2 d wk⁻¹</td>
<td>Cycling</td>
<td>Quad. CSA</td>
<td>Non-sig.</td>
<td>Healthy adults who had not regularly exercised in 5 yr</td>
</tr>
<tr>
<td>PMID: 15076785</td>
<td></td>
<td></td>
<td>30–40 min</td>
<td>Ultrasound</td>
<td>14%</td>
<td>90% exercise adherence</td>
<td></td>
</tr>
<tr>
<td>Izquierdo 2005</td>
<td>11 MM (43 yr)</td>
<td>--</td>
<td>16 wk, 2 d wk⁻¹</td>
<td>Cycling</td>
<td>Quad. CSA</td>
<td>MM↑10%</td>
<td>Same training as 2005 study</td>
</tr>
<tr>
<td>PMID: 15616847</td>
<td></td>
<td></td>
<td>30–40 min</td>
<td>Ultrasound</td>
<td></td>
<td>90% exercise adherence</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70%–90% HRmax</td>
<td></td>
<td></td>
<td>Training was based off blood lactate levels, some INT was performed</td>
<td></td>
</tr>
<tr>
<td>Harper 2009</td>
<td>7 OW (71 yr)</td>
<td>--</td>
<td>12 wk, 3–4 d wk⁻¹</td>
<td>Cycling</td>
<td>Quad. VOL</td>
<td>OW↑12%</td>
<td>Healthy adults, nonexercisers, nonsmokers, No BB or statins</td>
</tr>
<tr>
<td>PMID: 19692660</td>
<td></td>
<td></td>
<td>20–45 min</td>
<td>MRI</td>
<td></td>
<td>100% Adherence</td>
<td></td>
</tr>
<tr>
<td>Silvanpas 2009</td>
<td>15 MW (52 yr)</td>
<td>↓1.0 kg</td>
<td>21 wk, 2 d wk⁻¹</td>
<td>Cycling</td>
<td>Lean Leg Mass</td>
<td>MW↑–2.5%</td>
<td>Healthy subjects, 1 on BP Med, 2 on estrogen replacement</td>
</tr>
<tr>
<td>PMID: 7713834</td>
<td>wk 1–7: 30 min wk 8–14: 45 min wk 15–21: 60–90 min</td>
<td></td>
<td>60–90 min</td>
<td>DXA</td>
<td></td>
<td>100% adherence</td>
<td></td>
</tr>
<tr>
<td>Konopka 2010</td>
<td>9 OW (70 yr)</td>
<td>--</td>
<td>12 wk, 3–4 d wk⁻¹</td>
<td>Cycling</td>
<td>Quad. CSA</td>
<td>OW↑11%</td>
<td>Alternated INT greater or less than anaerobic threshold</td>
</tr>
<tr>
<td>PMID: 20566734</td>
<td></td>
<td></td>
<td>20–45 min</td>
<td>MRI</td>
<td></td>
<td>Healthy adults, nonexercisers, nonsmokers, no BB or statins</td>
<td></td>
</tr>
<tr>
<td>Lovell 2010</td>
<td>12 OM (75 yr)</td>
<td>↓2.0 kg</td>
<td>16 wk, 3 d wk⁻¹</td>
<td>Cycling</td>
<td>ULM/ MM</td>
<td>OM↑4%</td>
<td>100% adherence</td>
</tr>
<tr>
<td>PMID: 20181991</td>
<td></td>
<td></td>
<td>30–45 min</td>
<td>DXA</td>
<td></td>
<td>Healthy adults, nonexercisers, regularly participated in walking/gardening activities</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR corresponding to 50–70% VO₂max</td>
<td></td>
<td></td>
<td>98% adherence</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Group</td>
<td>Age</td>
<td>Gender</td>
<td>Intervention</td>
<td>Exercise Details</td>
<td>Outcome Measures</td>
<td>Adherence</td>
</tr>
<tr>
<td>---------------</td>
<td>-------</td>
<td>-----</td>
<td>--------</td>
<td>--------------</td>
<td>------------------</td>
<td>------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Hudelmaier 2010</td>
<td>19 MW (51 yr)</td>
<td>--</td>
<td>Cycling</td>
<td>Quad and Ham</td>
<td>CSA ↑4% Quad Ham ↑5% Sartorius MRI</td>
<td>Perimenopausal women completed 1 h wk⁻¹ of PA ~93% adherence</td>
<td></td>
</tr>
<tr>
<td>PMID: 20665894</td>
<td>6</td>
<td>wk 1: 75% HRmax 20 min; wk 2-6: 4-5× 30 min 75%-90%</td>
<td>MRI</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McPhee 2010</td>
<td>28 YW (21 yr)</td>
<td>NA</td>
<td>Cycling</td>
<td>Quad. VOL</td>
<td>YW↑7%</td>
<td>Inactive young women Greater CV capacity associated with greater in muscle volume</td>
<td></td>
</tr>
<tr>
<td>PMID: 20369366</td>
<td>6 wk, 3 d wk⁻¹ Cycling Quad. and Ham MRI</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fanup 2012</td>
<td>7 YM (23 yr)</td>
<td>--</td>
<td>Cycling</td>
<td>Thigh, Quad</td>
<td>MRI ↑7%</td>
<td>Untrained subjects</td>
<td></td>
</tr>
<tr>
<td>PMID: 22266546</td>
<td>10 wk, 3 d wk⁻¹ Cycling 40 min at 55-90 RPM</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harber 2012</td>
<td>6 OM (74 yr)</td>
<td>OM --</td>
<td>Cycling</td>
<td>Quad. Volume</td>
<td>OM↑6% YM↑7%</td>
<td>100% adherence, nonexercisers, nonsmokers and no BB use OM: 4 on statins, 5 on prostate med, and/or 3 on BP med</td>
<td></td>
</tr>
<tr>
<td>PMID: 22984247</td>
<td>7 YM (20 yr)</td>
<td>YM --</td>
<td>Cycling</td>
<td>Quad. Volume</td>
<td>OM↑54 cm³ YM↑49 cm³</td>
<td>OM had greater hypertrophy (cm³⁻¹) per work completed (MJ) than YM</td>
<td></td>
</tr>
<tr>
<td>No. contractions = 118,640</td>
<td>YM: Work = 16.4 MJ;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. contractions = 138,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These investigations have used fan beam dual x-ray absorptiometry (DXA), ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) to measure the muscle group(s) used during training. No crude indices of mass such as circumference, skin fold, underwater weighing, or pencil beam DXA were included.

YW, young women; YM, young men; MW, middle-aged women; MM, middle-aged men; OW, old women; OM, old men; NA, not available; CSA, cross-sectional area; VOL, volume; ULMM, upper leg muscle mass; Quad, quadriceps; Ham, hamstrings; VL, vastus lateralis; HRR, heart rate reserve; INT, interval training; AE, aerobic exercise; PA, physical activity; HU, Hounsfield units; BB, beta blockers; CV, cardiovascular; SED, sedentary; → = progressively increased to; ↑ = Increase; ↓ = Decrease; ↔ = No Change; No. = number.
elicit a 9% increase in thigh cross-sectional area (CSA) of old men (68 yr). Within this study, old and young men performed walking or jogging five times per week. Exercise intensity and duration were increased progressively in 2-wk segments, where the last 2 months consisted of exercise at 85% of heart rate reserve (HRR) for 45 min. Although the old men experienced a robust increase in skeletal muscle size, no changes in the young men were observed. The reason for the discrepancy between groups is not completely known, but the young men attended significantly less exercise sessions than the old men. Therefore, these data suggest that exercise frequency may play an important role in stimulating muscle growth with aerobic exercise.

As with any exercise training program in humans, adaptations are highly variable (19), which could be why some studies have not observed increased muscle size. Although skeletal muscle hypertrophy after aerobic exercise training is not ubiquitous, nearly all studies examining muscle mass since 2005 (eight of nine) have reported skeletal muscle hypertrophy in the muscle group(s) most used during exercise. Also, more than 70% of all investigations using cycle ergometry as the mode of exercise have observed an increase in skeletal muscle mass in cohorts of apparently healthy younger, middle- and older-aged men and women (Table 1). A recent cross-sectional investigation reported that young, middle, and older-aged individuals who are highly aerobically active have greater knee extensor power and associated leg lean mass compared with sedentary counterparts (8). Collectively, these investigations provide convincing evidence that aerobic exercise training is an anabolic stimulus in physically inactive subject populations.

The effectiveness of aerobic exercise training to induce skeletal muscle hypertrophy most likely depends on obtaining sufficient exercise intensity (70%–80% HRR), duration (30–45 min), and frequency (4–5 d wk⁻¹) to achieve a large number of muscle contractions that place a high-volume, low-load on skeletal muscle compared with traditional hypertrophic resistance exercise programs. In our investigations (16,18,21–23), participants performed cycle ergometry for 12 wk where exercise duration, intensity, and frequency were progressively increased so the last 5 wk consisted of 45 min per session, 80% HRR, four times per week, with a 100% exercise attendance (23). Our participants completed approximately 118,000 to 145,000 contractions per leg, inducing similar quadriceps femoris muscle growth in both young and older individuals and concomitantly resulting in the well-accepted improvements in aerobic capacity and peak workload (16,18,21–23). It has been modeled that cycling at approximately 75% of peak aerobic capacity, an intensity similar to our studies and others, creates an external load of approximately 38% of maximal dynamic muscle force (32). The concept of high-volume low-external loading stimulating muscle growth is supported by emerging evidence that greater external loading during resistance exercise does not result in greater gains of muscle mass (25). This study (25) compared the effects of three different leg extension protocols (three sets of 30% 1RM, three sets of 80% 1 RM, and one set of 80% 1RM) to voluntary fatigue and found there were no differences between the protocols in terms of muscle growth. Both three sets of 30% and 80% 1RM elicited an increase of 7%, which is similar to the hypertrophy observed with several aerobic exercise training protocols. Therefore, it seems that high volume but low external loading exercise (30%–40% of maximum) can elicit significant gains in skeletal muscle mass.

Aerobic exercise training can also improve muscle function and exercise capacity (8,16,23). Skeletal muscle power production has been correlated with the ability to perform tasks of daily living whereas exercise capacity is inversely related to the prognosis of disease and death. These relationships suggest that regular aerobic exercise can enhance the quality of life by improving the functional capacity and reducing the risk of morbidity in adults. Collectively, these observations provide impetus for clinicians and scientists to incorporate aerobic exercise training as an efficient prescription to increase skeletal muscle mass and functional capacity.

Comparison of Aerobic- With Resistance Training-Induced Skeletal Muscle Hypertrophy

Resistance exercise training is a conventional exercise prescription to induce skeletal muscle growth. Therefore, to confirm the efficacy of aerobic exercise training in eliciting skeletal muscle hypertrophy, we compared our findings with a traditional resistance exercise program that was conducted within the same laboratory (37). Therefore, the same methods were used to analyze skeletal muscle size after 12 wk of either resistance or aerobic exercise. A study conducted by Trappe et al. (37) implemented 12 wk of knee extension exercise (three sets of 10 repetitions at 70% of 1RM) in 67 ± 2-yr-old men (n = 8) and women (n = 4). For the purpose of this review, we will focus on the placebo group (i.e., those who did not consume acetaminophen or ibuprofen), which demonstrated an approximately 9% increase in quadriceps femoris muscle volume after resistance exercise training (37). The gains in skeletal muscle volume after resistance exercise training are similar to 12 wk of aerobic exercise training (the last 5 wk consisting of 4 d wk⁻¹, 45 min d⁻¹, 80% HRR). In a series of studies with old women (70 ± 2 yr, n = 9), old men (74 ± 3 yr, n = 6), and young men (20 ± 1 yr, n = 7), the mean increase in skeletal muscle volume from all subjects is approximately 8% (16,18). Therefore, from investigations implementing 12 wk of either resistance or aerobic exercise training, both modes of exercise have elicited a similar increase in quadriceps femoris muscle volume, suggesting that both modes of exercise are equally effective at stimulating hypertrophy in the muscles used for 12 wk. These findings are supported by Hudelmaier et al. (20) and remain consistent with exercise programs of 6 months’ duration (29,33). Collectively, studies observing skeletal muscle growth after aerobic exercise training observe an average increase of more than 7% (Table 1), which is comparable to the hypertrophy after resistance exercise training (23,29,37).

Myofiber Level

When comparing aerobically trained to inactive individuals, trained individuals have larger slow-twitch myosin heavy-chain (MHC) I fibers (7,13) and fast-twitch MHC IIA fibers (14) that seem to be an advantageous characteristic for superior performance. In addition, older endurance trained
runners have larger MHC I fibers than either age-matched untrained subjects (26) or younger adults matched for fitness (4). Therefore, cross-sectional study designs indicate that long-term endurance exercise may promote myofiber hypertrophy and could contribute to the enhanced functional capacity observed in lifelong endurance exercisers.

These data are supported by Coggan et al. (5) who observed increased MHC I and MHC IIa CSA in the gastrocnemius after 9 to 12 months of walk/run protocol (45 min d⁻¹, 4 d wk⁻¹, 80% heart rate max) in older men and women (64 yr). Our studies also reveal that 12 wk of aerobic cycle ergometer training increased MHC I fiber CSA in the vastus lateralis by 16% in older women (16) and approximately 20% in young and old men, collectively (18), whereas no changes in CSA were observed for MHC IIa fibers. Additional studies have reported increased CSA of MHC I (12), MHC IIa (1,3) or both fiber types (5), whereas some investigations have not (6). Collectively, it seems that observations of whole-muscle hypertrophy with aerobic exercise are reinforced by reports of increased myofiber size in the majority of relevant studies.

MUSCLE PROTEIN METABOLISM

Muscle Protein Synthesis

The dynamic balance between the rate of muscle protein synthesis (MPS) and breakdown (MPB) is a pertinent topic because of its impact on skeletal muscle hypertrophy and atrophy. Much debate within the literature has been centered on observations that older adults (younger than 80 yr) may have a blunted increase in MPS after anabolic stimuli (i.e., anabolic resistance). The reduced ability to synthesize muscle proteins after insulin, nutrition, and/or resistance exercise may contribute to age-related skeletal muscle atrophy, but these findings are equivocal ((9) see for review). Pertinent to this review is the notion that implementation of aerobic exercise may overcome limitations to stimulating MPS or muscle growth in older individuals.

Specifically, acute aerobic exercise has the ability to restore anabolic sensitivity to insulin in older adults, stimulating intracellular anabolic signaling pathways and generating a positive protein balance not apparent in sedentary individuals (11). Similarly, performing aerobic exercise the evening before consuming essential amino acids (AA) and carbohydrates increased MPS and induced a net positive protein balance in older adults, whereas sedentary subjects remained in a net negative protein balance (35). It seems that aerobic exercise improved leg blood flow and AA delivery to skeletal muscle, overcoming age-related anabolic impairments to hyperaminoacidemia and hyperinsulinemia during sedentary conditions.

When comparing age-specific MPS after acute and chronic aerobic exercise, both young (15,17,24,38) and older adults (10,28,34) increase MPS without any apparent age-related differences (10,34) (Fig. 1). One study (10) has proposed acute anabolic resistance in older adults after a practical bout of aerobic exercise with AA infusion; however, the MPS and mTOR signaling response was not different between age groups. The authors of this study speculate that, because older individuals have elevated intracellular AA flux and concentrations, they do not have the same MPS efficiency (i.e., MPS/intracellular AA rate of appearance). These findings require further investigation because this hypothesis suggests that older adults should have a greater increase in MPS relative to their younger counterparts during recovery from acute aerobic exercise with AA infusion. Most importantly, the equivalent anabolic response after the same stimulus suggests that there may not be an overall anabolic limitation in older individuals after aerobic exercise. Studies exploring the possibility of acute anabolic resistance with age should implement long-term exercise training to determine the temporal and mechanistic relationships that overcome this potential impairment. Aerobic exercise training studies revealed 1) basal, mixed MPS increased by 22%, independent of age (34) and 2) similar skeletal muscle mass accretion assessed via magnetic resonance imaging in young and old individuals (22) (Fig. 1). Together, these investigations indicate that any proposed acute anabolic

Figure 1. Anabolic responses to acute and chronic aerobic exercise in young and old subjects. (A) The increase in muscle protein synthesis (MPS) was similar between young and old participants after acute aerobic exercise with amino acid infusion (10). Data reported as the difference between means before and after exercise. (B) The increase in basal MPS (~22%) after 16 wk of aerobic exercise training in young and old subjects was not different (34). Data reported as mean ± SD. (C) Similar increase in quadriceps femoris cross-sectional area (~4 cm²) after 12 wk of aerobic exercise training in young and old men (22). Data reported as mean ± SE.
resistance is overcome with chronic exercise and further highlight the need to perform aerobic exercise training for the improvement of skeletal muscle health.

An interesting observation in our study comparing young (n = 7; 20 yr) and old men (n = 6; 74 yr) was that, despite working at the same relative exercise intensity, old men self-selected a lower cadence (70 vs. 81 RPM) resulting in approximately 19,000 less muscle contractions and completed nearly half the total mechanical work. However, the old men garnered the same absolute increase in skeletal muscle volume (~50 cm³), as the young men (18), suggesting that old men may be more sensitive at translating mechanical work into skeletal muscle growth (i.e., muscle hypertrophy per work completed; Fig. 2) and can reverse 15 to 20 yr of age-related muscle loss in a 12-wk duration. These findings indicate that older men may be more sensitive to regular anabolic stimuli (i.e., aerobic exercise) than young men (Fig. 2).

Although mixed MPS acutely and chronically responds to aerobic exercise, there may be a reason to speculate that alterations in protein metabolism of specific protein fractions are explicit to the mode of exercise. An eloquent study reported that an acute bout of aerobic exercise stimulates MPS in crude fractions of mitochondrial but not myofibrillar proteins before and after 10 wk of aerobic training in young adults (38). Unfortunately, muscle size, composition, and/or function were not presented, and thus the relationship between assessments of myofibrillar, mitochondrial, and sarcoplasmic protein synthesis rates and skeletal muscle health after exercise training remains unknown. Therefore, future research is warranted to determine MPS in distinctive subfractions, specific fiber types, or isolated proteins in both young and older adults, and these data should be accompanied with skeletal muscle size, composition, and function to provide a direct and comprehensive understanding of the impact of aerobic exercise training on skeletal muscle protein quality. Identifying novel areas in protein metabolism research provides new opportunities for future study and improves our knowledge of skeletal muscle physiology. Collectively, research revolving around protein metabolism suggests that aerobic exercise acutely and chronically stimulates skeletal muscle protein synthesis, creating a myocellular milieu that coincides with increased myofiber and whole-muscle size after training.

Muscle Protein Breakdown

Because of the lack of an accepted methodology to accurately measure MPB in humans, the literature is unclear and even equivocal within the same laboratory. Research has suggested that postabsorptive protein breakdown is diminished, unaltered, or elevated in older adults. Because of various methodologies representing different protein pools (i.e., whole body, mixed muscle, and myofibrillar muscle fraction), it is important to acknowledge that various protein reservoirs and methodologies may yield dissimilar rates of protein turnover and thus affect data interpretation.

A previous investigation found elevated levels of 3-methylhistidine in the interstitial fluid of skeletal muscle from older adults, which represents increased actin and myosin proteolysis (36). These data are supported by increased mRNA expression of enzymes involved in the ubiquitin proteasome pathway (UPP) as well as myostatin (27). The UPP is responsible for the majority of intracellular protein degradation, with strong associations between static makers of the UPP (e.g., FOXO3a, MuRF-1, Atrogin-1) and skeletal muscle atrophy. In addition, myostatin is a potent inhibitor of muscle growth because of its role in satellite cell regulation and MPS as well as potentially augmenting MPB. Therefore, reducing these catabolic components creates plausible mechanisms to improve skeletal muscle mass with exercise (Fig. 3).

Acute bouts of aerobic exercise increase UPP mRNA, representing an increased drive for MPB while reducing myostatin mRNA expression, one potential mechanism leading to increased MPS in young individuals (15,17). These data likely indicate key molecular components stimulating protein turnover and myocellular remodeling after acute exercise-induced cellular stress. Conversely, after repeated bouts of aerobic exercise (i.e., 12 wk), we observed significant

**Figure 2.** Comparison of skeletal muscle hypertrophy in relation to mechanical work completed during a 12-wk aerobic exercise training program (18). (A) Aerobic exercise training induced similar hypertrophy of the quadriceps femoris in weight-stable young (n = 7; 20 ± 1 yr) and older men (n = 6; 74 ± 3 yr). (B) Young men completed nearly twice the mechanical work during the aerobic training program. (C) When skeletal muscle hypertrophy is expressed relative to the anabolic stimulus (i.e., work performed (MJ)), it seems that old men were more sensitive at converting mechanical work into skeletal muscle mass accretion (i.e., anabolic sensitivity). MJ = Mega joules. *difference between groups; †training effect, P < 0.05.

---

**Figure 2.** Comparison of skeletal muscle hypertrophy in relation to mechanical work completed during a 12-wk aerobic exercise training program (18). (A) Aerobic exercise training induced similar hypertrophy of the quadriceps femoris in weight-stable young (n = 7; 20 ± 1 yr) and older men (n = 6; 74 ± 3 yr). (B) Young men completed nearly twice the mechanical work during the aerobic training program. (C) When skeletal muscle hypertrophy is expressed relative to the anabolic stimulus (i.e., work performed (MJ)), it seems that old men were more sensitive at converting mechanical work into skeletal muscle mass accretion (i.e., anabolic sensitivity). MJ = Mega joules. *difference between groups; †training effect, P < 0.05.
reductions in basal FOXO3a (-24%) and myostatin (-49%) mRNA expression in older women, with concomitant myofiber and whole-muscle hypertrophy (21). The decrease in catabolic factors after aerobic exercise training is supported by reductions in UPP and/or myostatin mRNA after resistance training in young (30,39) and older adults (<80 yr) (30). Interestingly, in one group of women older than 80 yr, resistance training did not reduce basal UPP or myostatin mRNA expression (39) nor confer myofiber or whole-muscle hypertrophy, demonstrating clear associations between the reduction in UPP and myostatin with skeletal muscle hypertrophy after exercise training (Fig. 3). Advancements in accepted methodologies to study MPB are needed to quantify the impact of exercise on skeletal muscle health and propel our knowledge beyond static markers (e.g., mRNA, protein content) associated with the regulation of skeletal muscle protein metabolism. Most importantly, aerobic exercise training results in reduced catabolic factors and skeletal muscle hypertrophy.

**MITOCHONDRIA**

Mitochondria are organelles within tissues that consume oxygen to convert substrates (i.e., lipids, carbohydrates) into adenosine triphosphate for energetically demanding processes. Muscle protein synthesis is a costly process contributing to the high utilization of ATP by muscle cells during basal conditions and can account for approximately 20% of resting energy expenditure. In addition to energy provision, mitochondria also may be an important regulator of intracellular signaling cascades that modulate skeletal muscle size and function. PGC-1α is a key protein associated with mitochondrial biogenesis; however, emerging evidence suggests that PGC-1α regulates many pathways including mitochondrial dynamics and protein metabolism.

Mitochondria continually interact through dynamic processes of membrane fusion and fission that regulate mitochondrial morphology (40). With long periods of physical inactivity, as experienced with sedentary aging, excess mitochondrial oxidative stress can create mutations to mtDNA and mitochondrial proteins. The fusion and fission of mitochondria stabilize mtDNA by adjusting mitochondrial morphology and therefore regulate function accordingly. In animals (i.e., knockout) and humans (i.e., mutations) that lack mitofusion genes Mfn2 and Opal, there seems to be increased accumulation of damaged mtDNA, impaired mitochondrial respiration, as well as skeletal muscle atrophy. However, aerobic exercise training increases PGC-1α and proteins related to mitochondrial fusion and fission in young and older adults (22). Increased mitochondrial dynamics may improve mitochondrial function by reducing oxidant emissions and catabolic pathways, therefore, lowering MPB while improving mitochondrial ATP production, creating sufficient energy for charging aminoacyl-tRNA for protein translation. Collectively, improvements in mitochondrial morphology and function may contribute to skeletal muscle anabolism after aerobic exercise training (Fig. 3).

Furthermore, PGC-1α also has been linked to inhibiting FOXO3a intracellular signaling, protein breakdown, and skeletal muscle atrophy in cell culture and animal models (2), providing another mechanistic link on how aerobic exercise training may prevent the decline in mitochondrial abundance and skeletal muscle mass with age. Additional work in vitro and in vivo revealed there are multiple isoforms of PGC-1α that induce divergent adaptations and are regulated by two different promoter regions. PGC-1αL, what is typically discussed within the literature as PGC-1α, stimulated mitochondrial alterations, leading to improved oxidative capacity, whereas PGC-1α4 induced skeletal muscle cell growth (31). After 8 wk of resistance exercise, PGC-1α4 was increased 1.5-fold, whereas a combined training program of both aerobic and resistance exercise increased PGC-1α4 twice that of the resistance group alone (i.e., threefold) (31). These findings suggest that aerobic exercise may potentiate the response to resistance exercise but surprisingly did not increase PGC-1α4 alone. These
data are intriguing because, along with the increased expression of PGC-1α, there were concomitant reductions in catabolic mRNA expression (FOXO3a, MuRF-1, myostatin) and increased insulin-like growth factor. As discussed previously, reductions in these catabolic factors are similar to the reductions we observe after 12 wk of aerobic exercise training when there is marked skeletal muscle hypertrophy (21). These promising mechanisms begin to unlock clues on how chronic aerobic exercise could stimulate both mitochondrial and myocellular growth (Fig. 3), but further work is needed to clarify these potential connections.

CONCLUSIONS

This review provides considerable evidence to support that aerobic exercise training can produce skeletal muscle hypertrophy. Multiple investigations demonstrate alterations in skeletal muscle molecular regulation and protein metabolism that are conducive for increased myofiber and whole-muscle size after aerobic exercise training in sedentary individuals (Fig. 4). Cross-talk between pathways regulating mitochondrial homeostasis and skeletal muscle protein metabolism may play a role in the ability of aerobic exercise to stimulate skeletal muscle hypertrophy. Collectively, these data warrant that aerobic exercise training should be acknowledged to increase skeletal muscle mass and be considered an effective countermeasure for muscle loss with advancing age. More research is needed to understand the complete influence of aerobic exercise as well as adjunct therapies (i.e., diet, nutriceuticals, and nontraditional exercise) on skeletal muscle size, function, and quality across various age groups and clinical populations.

Acknowledgments

This work was funded by the National Institutes of Health (Grant AG032127), the Gatorade Sports Science Institute, and the National Aeronautics and Space Administration (Grant NNX06HF59G). The authors recognize that other pertinent research could not be included within this article because of reference restrictions.

The authors have no conflicts of interest to declare.

References


Figure 4. Aerobic exercise training (AET) has an effect on many mechanisms that may collectively promote skeletal muscle hypertrophy.